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REVISITING THE CONTENT OF NON-SPECIFIC INFLAMMATORY PROCESS MARKERS AND 25-HYDROXYVITAMIN D IN THE BLOOD OF PREGNANT WOMEN OF HIGH INFECTIOUS RISK

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Intrauterine infection continues to have a negative impact on perinatal indicators. The aim of the study was to compare the concentration of some markers of the inflammatory process and vitamin D in the blood of pregnant women with placental dysfunction against the background of high infection risk (56 women – a group I), as well as in healthy pregnant women (40 women – group II). Blood levels of procalcitonin, lactate, C-reactive protein and vitamin D were determined by ELISA. More than 60 % of pregnant women from the I-st group were carriers of CMV, HSV, and toxoplasmosis. The violation of the vaginal ecosystem was determined in them 5 times more often than in group II. The level of vitamin D in the I-st group was lower than in the comparison group (31.73 ± 8.6 ng/ml and 43.38 ± 11.20 ng/ml; $U=502.5$, $P=0.00001$), and the content of C-reactive protein (15 times), procalcitonin (3 times) and lactate (2.2 times) was greater than in the control group. Low blood levels of calcidiol are associated with high levels of inflammatory markers. It is possible that the correction of vitamin D status in the pre-gravid stage and from the early stages of pregnancy in women at high infectious risk can contribute to the improvement of perinatal outcomes.

Key words: pregnancy, intrauterine infection, vitamin D, procalcitonin, lactate, C-reactive protein

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ДО ПИТАННЯ ПРО ЗМІСТ НЕСПЕЦИФІЧНИХ МАРКЕРІВ ЗАПАЛЬНОГО ПРОЦЕСУ І КАЛЬЦИТРИОЛУ В КРОВІ У ВАГІТНИХ ВИСОКОГО ІНФЕКЦІЙНОГО РИЗИКУ

Внутрішньоутробне інфікування продовжує негативно впливати на перинатальні показники. Метою роботи стало порівняльне визначення концентрації деяких маркерів запального процесу і вітаміну D в крові у вагітних з плацентарною дисфункцією на тлі високого інфекційного ризику (56 жінок – I група), а також у здорових вагітних (40 жінок – II група). Рівні в крові прокальцитоніну, лактату, С-реактивного білка і вітаміну D визначали методом ІФА. Більше 60 % вагітних з I групи були носіями CMV, HSV і токсоплазмозу і порушення вагінальної екосистеми визначалося у них в 5 разів частіше, ніж в II групі. Рівень вітаміну D в I групі був нижчим, ніж в групі порівняння (31.73 ± 8.6 нг/мл і 43.38 ± 11.20 нг/мл; $U=502.5$, $P=0.00001$), а вміст С-реактивного білка (в 15 разів), прокальцитоніну (в 3) і лактату (в 2,2 рази) був більшим, ніж в групі контролю. Низький рівень кальцидіолу в крові асоціюється із підвищеним рівнем маркерів запалення. Можливо, корекція вітаміну D статусу на догравідарному етапі і з ранніх термінів вагітності у жінок високого інфекційного ризику може сприяти покращенню перинатальних результатів.

Ключові слова: вагітність, внутрішньоутробне інфікування, кальцитріол, прокальцитонін, лактат, С-реактивний білок.

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According to modern data, the true frequency of intrauterine infection has not established yet. The prevalence of this pathology in the human population can reach 10–32 %. Intrauterine infection (IUI) largely determines the indicators of perinatal and infant morbidity and mortality, and this determines the urgency of this problem. Infection of a pregnant woman requires solving the question of whether it is necessary to treat the woman herself in the event of a primary infection or existing chronic foci sanitation, as well as the prevention or treatment of fetus' and newborn's clinical manifestations of infection [8].

Despite IUI asymptomatic course directly during pregnancy, some of them are associated with long-term consequences in later life. The implementation of some congenital infections can be successfully prevented with adequate preventive and therapeutic measures are realized [11].

The cause of IUI can be both pathogenic and conditionally pathogenic microorganisms and viruses. In the vast majority of cases, pathogens are representatives of the normal microflora of a woman's various biotopes – vagina, intestines, oral cavity and respiratory tract. The implementation of pathogenic infectious effects is possible by directly influencing on the uterine-placental-fetal system (ascending way) or indirectly through the activation of cytokines. The majority of microorganisms detected during infection belong to the normal microbiota of a woman [1].

According to modern data, one of the ways to implement IUI is the disruption of local vaginal microbiocenosis during colonization with opportunistic flora (*Streptococcus agalactiae*, *Staphylococcus aureus*, *Bacteroides* sp., *Escherichia coli*, etc.) with the formation of a clinic of so-called aerobic vaginitis, which is characterized by a pronounced inflammatory response of vaginal mucosa and its atrophic changes. It is assumed that most cases of purulent-septic diseases of the mother, fetus and newborn are associated with these microbial associations [4, 9].

Vulvovaginal candidiasis is associated with 15 % to 40 % of infectious lesions of vulva and vagina. In 10–20 % of women, carriage is asymptomatic, but the result of a long-persisting, recurring process may be an immunodeficiency state, recurrent urinary tract infections, miscarriage, placental dysfunction with intrauterine growth retardation of fetus, premature rupture of fetal membranes, spontaneous preterm birth and also purulent-septic complications in the postpartum period [2, 3, 12–14].

Currently, a large amount of research has shown that vitamin D (VD) is a powerful hormone with its own receptors presented in many organs and tissues, the effects of which are realized through genomic and non-genomic pathways. VD receptors (VDR) encode more than 3 % of a human genome and realize the classical skeletal and pleiotropic effects of calcitriol, one of which is its participation in the formation of immunopathology and systemic inflammatory response syndrome (SIRS) in a number of chronic pathologies, and specifically during pregnancy [6, 7].

The complexity of IUI diagnosis is due to similar epidemiological data when exposed to various infectious agents and the same type of nonspecific clinical manifestations [10]. In most cases, the clinical manifestations of a systemic inflammatory response in a pregnant woman may be absent: under these conditions, detection of nonspecific markers of the inflammatory process becomes significant.

The purpose of the study was to determine the concentration of some nonspecific markers of the inflammatory process and calcitriol in the blood of pregnant women of high infectious risk and assess their clinical significance and relationships in the ability to predict a systemic inflammatory response.

Materials and methods. During 2018–2019 a prospective examination of 96 women was conducted at the conditions of the Communal Institution “Maternity Hospital No. 1” (Odessa), the clinical base of the Odessa National Medical University. Examination of women was carried out after obtaining written informed consent (Order of the Ministry of Health of Ukraine dated 21.01.2016 No. 29) and a positive decision of the bioethics commission of the Odesa National Medical University (protocol No. 124 dated 2.02.2018) in compliance with the moral and ethical principles of the Helsinki Declaration of the WHO association for biomedical research (World Medical Association Helsinki 1994, 2000, 2008).

The studies were conducted on a “case-control” basis. The main group included 56 pregnant women with high infectious risk (HIR) and verified diagnosis of placental dysfunction (PD); 40 conditionally healthy patients with physiological pregnancy formed the control group. The criteria for inclusion of pregnant women in the main group were the presence of IUI factor – verified infection by a group of TORCH infections, presence of ultrasound signs of infection of the feto-placental complex and chronic inflammatory diseases with latent course. The groups were formed in the second trimester of pregnancy (22–26 weeks).

A general clinical examination of pregnant women, clinical and laboratory studies to assess the condition of the intrauterine fetus and the utero-placental-fetal circulation (ultrasound, dopplerometry, hormonal and other methods) were carried out in accordance with the requirements of regulatory documents in the prescribed terms of pregnancy and according to indications.

The diagnosis of PD was based on a combination of the data from an ultrasound examination with feto- and placentometry, Doppler-assessment of blood flow, cardiotocography, assessment of the fetus’s biophysical profile, study of the placenta hormonal function. Ultrasound was carried out on the Samsung Medison UGEOWS80A (Samsung Medison CO, LTD, 2014, Korea). Cardiotocographic studies of the fetus were performed using Sonicade fetal cardiomonitors in compliance with Dose-Redman’s criteria.

For verification of IUI, the methods of bacterioscopic, bacteriological, enzyme immunoassay (ELISA) and polymerase chain reaction (PCR) were used. When specific immunoglobulins (Ig) were detected in the blood of pregnant women in a diagnostically significant titer, in dynamics a second study of “paired sera” was carried out with the determination of the avidity and affinity of antibodies, followed by consultation with an infectious disease specialist. All pregnant women were offered a bacteriological study with an antibioticogram.

Levels of non-specific markers of the inflammatory process in the blood of pregnant women, namely procalcitonin (PCT), lactate (lactic acid – 2-hydroxypropanoic acid) and C-reactive protein (CRP), as well as the level of total vitamin D – (25(OH)D) were determined by enzyme immunoassay on Cobas Integra 400 Plus analyzer (Roche Diagnostics, Switzerland). Blood samples were taken from a vein on an empty stomach (8 hours without eating), without a tourniquet in order to exclude a possible effect on the level of lactate.

Statistical calculations were carried out using MS Excel software and the online resource www.socscistatistics.com. With the help of the Shapiro-Wilk test, it was determined that in this work the quantitative indicators of the variation series have a non-normal distribution, in the comparison of two independent samples of quantitative indicators, the non-parametric Mann-Whitney test (U) was used. Mean values are calculated as median and quartile deviation ($Me \pm Q$). Correlation analysis was performed using a Spearman's rank correlation coefficient.

Results of the study and their discussion. By age and anthropometric data, the groups were homogeneous. The average age in the control group was 30.35 ± 3.12 years, in the main group patients – 29.21 ± 4.3 years ($U=958$, $P=0.11507$). The body mass index (BMI) in patients of the main group corresponded to (22.2 ± 1.7) kg/m² and in the control group – (22.8 ± 1.93) kg/m², ($U=1066$, $P>0.34458$). In the main group of 56 women, 40 (71.43 %) women were primiparous, in the control group – 22 (55.00 %; $F=0.028$; $P=0.028029$); multiparous, respectively 16 (28.57 %) and 18 (45 %; $F=0.028$; $P=0.028029$).

The presence of a high infectious risk was by the results of a survey for TORCH-infections evidenced. So, specific antibodies to *Toxoplasma gondii* – group G immunoglobulins (IgG) were detected in 10 (17.85 %) pregnant women, 11 (19.64 %) for cytomegalovirus (CMV) infections, and herpes virus (HSV) infections were presented in 23 (41.07 %) women. Upon repeated examination, the dynamics of low-avidity antibodies were determined in 3 (5.36 %) with toxoplasmosis, in 6 (10.71 %) with HSV, and in 2 (3.57 %) with CMV; in addition, class M Ig were detected in 2 (3.57 %) pregnant women with herpetic infection.

In the control group, 6 (15 %) pregnant women showed highly avid IgG for *Toxoplasma gondii*; 3 (7.50 %) also had highly avid anti-HSV antibodies.

At bacteriological and bacterioscopic examination of the urogenital discharge, the following pathogenic and conditionally pathogenic microorganisms were isolated (fig. 1). The most frequently allocated flora in pregnant women with IUI (56 persons) were fungi of the genus *Candida albicans* (15 women – 26.79 %) and *Gardnerella vag.* (13 women – 23.21 %).

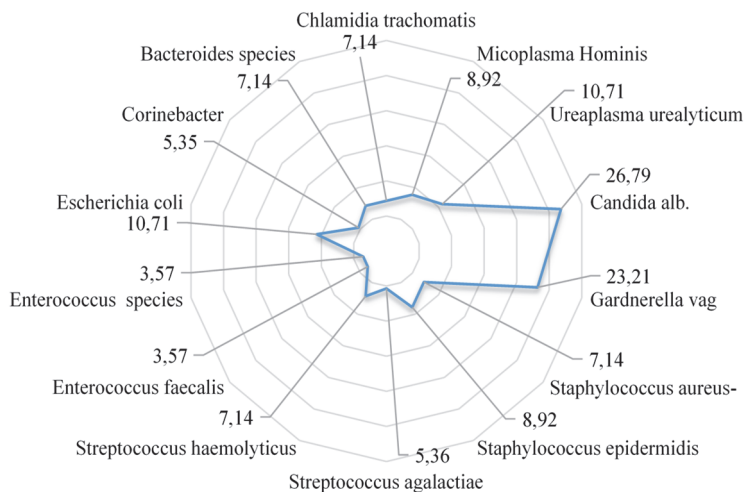


Fig. 1. The species composition of urogenital microflora in pregnant women with placental dysfunction and high infectious risk (n=56; %).

Ureaplasma urealyticum (6 people – 10.71 %), *Micoplasma hominis* (5 patients, 8.92 %) and *Chlamidia trach* (4 patients, 7.14 %) were isolated in almost every tenth pregnant woman – 4 (7.14 %).

They were *Streptococcus agalactiae* (3 persons, 5.36 %), *Staphylococcus sepid.* (6 persons, 10.71 %), *Escherichia coli* (6 persons, 10.71 %); 4 women each (7.14 %) were carriers of *Staphylococcus aureus*, *Bacteroides species*, *Streptococcus haemolyticus*. In 12.50 % (5 persons) of 40 relatively healthy pregnant women, bacteria *Streptococcus spp.*, *E. colli*, *Enterococc. sp.*, *Gardnerella vaginalis*, yeast-like fungi of the genus *Candida* were isolated during bacteriological examination of the urogenital discharge in titers less than 10^3 . In addition, *Lactobacillus cr.* were isolated in 7.5 % (3 persons) of control group in titers 10^3 – 10^4 . The indicated carriage was not by any clinical manifestations accompanied.

Women in both groups had chronic inflammatory diseases in their history that could have a definite effect on the course of pregnancy.

Chronic pyelonephritis was diagnosed in 37.5 % (21 persons) of 56 pregnant women of the main group and in 15 % (6 out of 40 persons) of the control group ($F=0.0006$; $P=0.000424$); 5 women (23.80 %) of 21 with chronic pyelonephritis during pregnancy exacerbated the disease. The presence of chronic diseases of the gastrointestinal tract (gastritis, cholecystic-pancreatitis) was indicated by 5.36 % (3 persons out of 56) of pregnant women from the main group and 2.5 % (1 person out of 40) from the control group, ($F=0.44$; $P=0.718216$). In the group of high infectious risk, chronic tonsillitis (16.07 % – 9 persons out of 56) was significantly more often; in the control group, 5.00 % (2 persons out of 40), ($F=0.0096$; $P=0.021075$). It should be noted that in the main group 30.36 % (17 persons out of 56) women had acute respiratory viral infection (ARVI) during pregnancy, in the control group – 7.5 % (3 persons out of 40), ($F=0.00004$; $P=0.000154$), which is significantly less.

IUI was verified and its clinical features were confirmed by such indirect ultrasound criteria of a systemic inflammatory response in the uteroplacental-fetal system as qualitative and quantitative changes in amniotic fluid, changes in the structure of the placenta and fetus's internal organs.

Low placentation was significantly more often diagnosed in PD pregnant women (15 persons out of 56 or 26.79 %) than in the control group (3 persons out of 40 or 7.5 %), ($F=0.0006$; $P=0.000809$); placental hypertrophy was observed in 10.71 % (6 persons) and 2.5 % (1 person), respectively ($F=0.0245$; $P=0.026517$). Polyhydramnios (12 persons, i.e. 21.43 % in the main group and 3 persons or 7.5 % in the control group;

$F=0.015$; $P=0.015957$), oligohydramnios (22 patients out of 56) showed inflammatory changes in the amniotic membrane or 39.29 % in the main group; 2 patients out of 40 or 5.00 % in the control group; $F=0.00001$; $P=0.00001$). The frequency of polyhydramnios was significantly, thrice, and oligohydramnios was 7 times greater in pregnant women with PD. Ventriculomegaly, known as one of the indirect signs of IUI, was in 10.71 % (6 persons out of 56) intrauterine fetuses in the main group detected. In 6 out of 56 pregnant women (10.71 %) in the main group, was intrauterine growth retardation syndrome (IFGR) diagnosed.

The level of CRP, procalcitonin and lactate in the blood of pregnant women with IUI was higher than that in the control group (Table 1).

Table 1

The content of non-specific markers of the inflammatory response in the blood of pregnant women with IUI and in healthy pregnant women

Index	Pregnant with high infectious risk, n=56	Conditionally healthy pregnant women, n=40	Confidence, P value
C-reactive protein, mg/l	66.61±9.43	4.40±1.98	$U_{\text{test}}=351$; $P=0.00001$
Procalcitonin, ng/ml	0.25±0.17	0.08±0.02	$U_{\text{test}}=390$; $P=0.00001$
Lactate, mmol/L	2.79±0.83	1.25±0.63	$U_{\text{test}}=236$; $P=0.00001$

Elevated levels of SIRS markers determined in pregnant women with IUI correlated with a low blood level of 25-hydroxyvitamin D: at high infectious risk, its concentration was significantly lower than in healthy pregnant women (31.73 ± 8.6 ng/ml and 43.38 ± 11.20 ng/ml; $U_{\text{test}}=2097$; $U_{\text{test}}=502.5$, $P=0.00001$), (Fig. 2).

Only in 13 out of 56 (23.21 %) pregnant women with a HIR, VD status corresponded to the optimal one (above 30 ng/ml), and in the group of apparently healthy women, the VD level was below normal in 15 % (6 women), ($F=0.0258$; $p<0.01$). A negative reliable dependence of the average strength between the VD and procalcitonin indices ($r_s=-0.715$; $P=0.00001$), as well as the VD and CRP ($r_s=-0.56419$; $P=0.00001$) is indicated by the correlation analysis (Fig. 3).

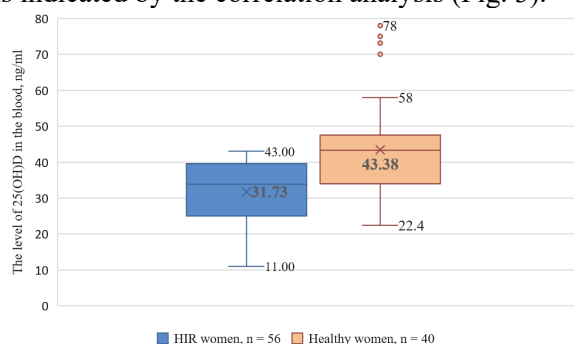


Fig. 2. The level of 25-hydroxyvitamin D (ng/ml) in the blood of high infectious risk pregnant women (n=56) and in healthy pregnant women (n=40).

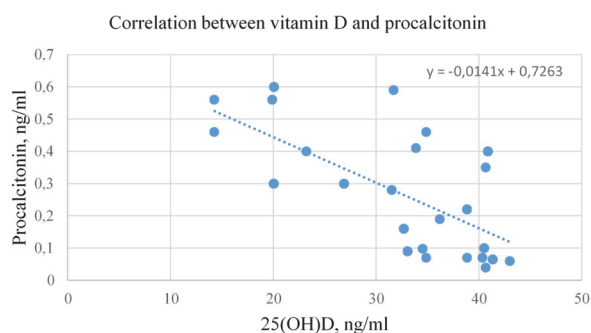


Fig. 3. The correlation between the level of vitamin D and procalcitonin in the blood of pregnant women of high infectious risk.

The relationship between the lactate content and the VD level is weak ($r_s=-0.47$; $P=0.000257$)

The homogeneity of groups in terms of age and anthropometric data excludes the influence of these data on the results of the study. The revealed difference in the number of nulliparous women between groups may possibly be an indirect indication of insufficiently developed adaptive-compensatory mechanisms in the hormonal system, hemodynamics during the first experience of pregnancy.

With a high frequency (64.3 %), bacterial associations were detected in patients of the main group, known for their pathogenic potential in conditions of activation of nonspecific immunity during pregnancy and supporting the clinic of aerobic vaginitis and bacterial vaginosis, which corresponds to the data of literature [1, 3, 4, 9]. In general, pregnant women at HIR have a violation of the vaginal ecosystem 5 times more often compared with conditionally healthy pregnant women (64.29 % VS 12.5 %; $F=0.0001$; $P=0.0001$). The most common etiological factor of the pathology are urogenital infections in the mixed form; in many cases, a disease has an asymptomatic course and characterized by the absence of inflammation specific clinic.

The known ability of anaerobic bacteria to form a structured biofilm under the conditions of the vaginal ecosystem violation causes a recurrent course of bacterial vaginosis and is accompanied by pregnancy complications. In particular, *Ureaplasma urealyticum* and *Mycoplasma hominis/genitalium*, which were identified by us in almost every 10 women, participate in the formation of biofilms, and the inflammation caused by them is associated with miscarriages, premature births and bronchopulmonary diseases in premature newborns [5].

The VD may play an important role in controlling placental responses to infection by the synthesis of some an antimicrobial peptide in trophoblast, decidual cells and placental macrophages. On the other hand, calcitriol inhibits the synthesis of cytokines, including tumor necrosis factor, granulocyte-macrophage colony-stimulating factor, and interleukin-6 in the decidua. There is evidence that maternal vitamin D deficiency is associated with bacterial vaginosis [7].

According to our data, the level of VD in pregnant women with HIR was 1.4 times less than in healthy women, which suggests that a decrease in vitamin D is associated with the risk of perinatal infection in pregnant women. The level of CRP in blood was 15 times higher ($P=0.00001$), procalcitonin concentration was thrice higher than its level in conditionally healthy pregnant ($P=0.00001$), which may confirm the significance of a bacterial infection in the genesis of an inflammatory process in the system “mother-placenta-fetus” confirmed by ultrasound. It is likely that under conditions of prolonged infectious exposure, a persistent increase in baseline CRP concentrations is observed, which supports SIRS.

The level of lactate in the blood of HIR pregnant women was 2.2 times higher than in healthy pregnant women, ($P=0.00001$). Probably, significant hyperlactatemia with IUI can be, on the one side, a sign of the inflammation and overproduction, on the other side, it can indicate to metabolic stress and tissue hypoperfusion. It is also possible to admit a violation of its elimination from the body, in particular, by the kidneys. The correlations between the blood levels of vitamin D in HIR pregnant and inflammation markers that we have identified, are consistent with the literature data [6].

Thus, it can be assumed that in conditions of insufficiency or deficiency of calcitriol in pregnant women with HIR, the likelihood of intrauterine infection increases. The implementation mechanism suggests the direct involvement of the VD/VD receptor system in the formation of endothelial dysfunction and inflammatory response syndrome through the pleiotropic effects of VD. The results of the study allow us to draw some conclusions.

Conclusions

1. A high infectious risk in pregnant women is due to the presence of chronic inflammatory extragenital diseases (2–2.5 more often, $P=0.0001$), a violation of the vaginal microbiocenosis (5 times more often, $P=0.0001$) and viral-bacterial conditionally pathogenic agents of the TORCH group. The most common etiological factor is urogenital infections in the mixed form and the disease is asymptomatic and characterized by the absence of a specific inflammation clinic.

2. The status of vitamin D corresponded to the optimal only in 23.21 % of pregnant women with a HIR, while in the group of healthy pregnant women, the level of VD was normal in 85 % ($F=0.0258$; $p<0.001$).

3. In pregnant women with a high infectious risk compared with healthy women an increase of some markers of the inflammatory process was found. Vitamin D deficiency or its lack is associated with an increase in the level of this markers (C-reactive protein – 15 times; $r_s=-0.56419$; $P=0.00001$, procalcitonin – 3 times; $r_s=-0.715$; $P=0.00001$; lactate – 2.2 times; $r_s=-0.47$; $P=0.000257$).

Further studies in women of high infectious risk with calcitriol deficiency syndrome, in order to predict possible pregnancy complications and improve perinatal outcomes are seen as a promising direction.

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DIAGNOSTIC AND TREATMENT APPROACHES TO ACUTE PANCREATITIS IN PREGNANT WOMEN

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The frequency of acute pancreatitis is from 1:1500 to 1:10000 pregnancies. The purpose of the study was to improve diagnostic and treatment approaches for acute pancreatitis in pregnant women. 21 pregnant women who were diagnosed with acute pancreatitis were under supervision. The diagnosis of acute pancreatitis in pregnant women was based on the Atlanta classification criteria (2013). Complex conservative treatment of acute pancreatitis in pregnant women consisted of prescribed octreotide, proton pump inhibitors, in the II trimester – protease inhibitor semi-synthetic penicillins, cephalosporins of the III-IV generations. It is necessary to correct the water-electrolyte balance, compensate for plasma loss, microcirculation disorders, fight against edema of the pancreas and peripancreatic tissue. The course of acute pancreatitis in pregnant women in 52.4 % of cases was characterized by an average and severe degree of severity, which was accompanied by distress and the threat of fetal death. There were no fatalities. The implementation of the diagnostic and treatment approaches used by us in acute pancreatitis in pregnant women made it possible to avoid mortality, surgical and obstetric-perinatal complications. Management of pregnant women with acute pancreatitis is an extremely difficult task and primarily depends on the severity of acute pancreatitis in pregnant women. The management of pregnant women suffering from acute pancreatitis requires a multidisciplinary approach to predict the course of pancreatitis, determine the tactics of managing pregnancy and acute pancreatitis in pregnant women, the method and timing of delivery.

Key words: management of pregnant women, acute pancreatitis, multidisciplinary approach.

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ДІАГНОСТИЧНІ ТА ЛІКУВАЛЬНІ ПІДХОДИ ДО ГОСТРОГО ПАНКРЕАТИТУ У ВАГІТНИХ

Частота виникнення гострого панкреатиту складає від 1:1500 до 1:10000 вагітностей. Мета дослідження полягала у вдосконаленні діагностичних та лікувальних підходів при гострому панкреатиті у вагітних. Під наглядом була 21 вагітна жінка з гострим панкреатитом. Постановка діагнозу гострого панкреатиту у вагітних ґрунтувалась на критеріях класифікації Atlanta (2013). Комплексне консервативне лікування гострого панкреатиту у вагітних полягало у призначенні октреотиду, інгібіторів протонної помпи, у II триместрі – інгібіторів протеаз, напівсинтетичних пеніцилінів, цефалоспоринів III–IV поколінь. Слід проводити корекцію водно-електролітного балансу, відшкодування втрати плазми, порушень мікроциркуляції, боротьбу з набряком підшлункової залози та парапанкреатичної клітковини. Перебіг гострого панкреатиту у вагітних у 52,4 % випадків характеризувався середнім та тяжким ступенем тяжкості, що супроводжувалось дистресом плода. Летальних випадків не було. Впровадження застосованих нами діагностичних та лікувальних підходів при гострому панкреатиті у вагітних дозволило уникнути летальності, хірургічних та акушерсько-перинатальних ускладнень. Ведення вагітних із гострим панкреатитом є вкрай складним завданням і в першу чергу залежить від ступеня тяжкості гострого панкреатиту у таких хворих. Ведення вагітних, які хворіють на гострий панкреатит, вимагає мультидисциплінарного підходу для прогнозування перебігу панкреатиту, визначення тактики ведення вагітності при цьому, способу і термінів розродження.

Ключові слова: ведення вагітних, гострий панкреатит, мультидисциплінарний підхід.

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According to various authors, the frequency of acute pancreatitis in pregnant women (APP) ranges from 1:1,500 to 1:10,000 pregnancies [1, 2, 9]. As a result of certain difficulties in diagnosis and imperfection in the choice of treatment tactics, management of pregnancy and the timing of delivery, APP significantly threaten the health of the mother and fetus and testify to the lack of specific recommendations [4, 5, 6].