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# Specific features of pregnancy and delivery in HIV-infected women

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HIV-infected women have a higher risk of complications during pregnancy and delivery (chronic placental insufficiency, anemia, placental abruption, preterm birth) compared with HIV-negative women, especially in case of opportunistic infections, immunodeficiency and a high viral load in the blood. The obstetrical pathologies are hard to study in these women because the above conditions are associated with a range of confounding factors that are not directly related to HIV infection but are often present, such as drug addiction, weight deficit, and chronic viral hepatitis coinfection. The literature review provides data from domestic and international studies on the correlation between HIV infection and the frequency of complications during pregnancy, delivery and the postpartum period, as well as the effect of the infection on the condition of newborns. The article cites current recommendations on the choice of delivery types for HIV-infected women.

**Keywords:** HIV-infected pregnant women; rates for pregnancy and childbirth complications; mother-to-child HIV transmission prevention.

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## Особенности течения беременности и родов у ВИЧ-инфицированных женщин

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ВИЧ-инфицированные женщины подвергаются значительно большему риску развития осложнений беременности и родов (хроническая плацентарная недостаточность, анемия беременных, отслойка нормально расположенной плаценты, преждевременные роды) по сравнению с неинфицированными ВИЧ беременными, особенно при присоединении оппортунистических инфекций, наличии иммунодефицита и высокой вирусной нагрузки в крови. Сложность изучения акушерской патологии у пациенток данной группы обусловлена широким спектром отягощающих факторов, непосредственно не связанных с ВИЧ-инфекцией, но часто ее сопровождающих: активным потреблением наркотических средств, дефицитом массы тела, коинфицированием хроническими вирусными гепатитами. В обзоре литературы приведены данные российских и международных исследований о влиянии ВИЧ-инфекции на частоту осложнений беременности, родов, послеродового периода и состояние новорожденных. Представлены современные рекомендации по выбору метода родоразрешения у ВИЧ-инфицированных женщин.

**Ключевые слова:** ВИЧ-инфицированные беременные; частота осложнений беременности и родов; профилактика перинатальной передачи ВИЧ.

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## Aspects of obstetric pathology in women with human immunodeficiency virus infection

While antiretroviral therapy (ARVT) was not yet used in pregnant women with HIV infection, these patients had a high incidence of complications during pregnancy, childbirth, and postpartum compared with the general population [1]. Since the introduction of highly active antiretroviral therapy (HAART) in pregnancy, the incidence of complications has decreased but remains above that of the general population. Several studies have demonstrated that even the use of HAART in pregnant women with HIV infection does not rule out an increased risk of adverse pregnancy and childbirth outcomes, although this pattern has been noted not many researchers [2–4]. Several authors believe that the incidence of complications of pregnancy and childbirth in women with HIV infection is higher in countries with a low standard of living, where HAART is less available [5]. In general, markers of more advanced stages of HIV infection, such as a low level of CD4 lymphocytes, and presence of opportunistic infections in pregnant women can increase the incidence of obstetric complications [6].

Most studies have shown that the incidence of sexually transmitted diseases (STDs) is higher in pregnant women with HIV infection than in the general population. STDs during pregnancy are often accompanied by inflammatory changes in the placenta and increase the risk of pregnancy termination, preterm delivery, and perinatal HIV transmission by disrupting the protective mechanisms of the fetoplacental complex [7, 8]. A study published in 2012 performed a comparative analysis of two groups of pregnant women with HIV infection, namely, those who had perinatal HIV transmission and those who gave birth to children without HIV infection. The authors revealed that a combination of bacterial–viral lesions in the placenta with signs of chronic placental insufficiency and acute decompensation developed in patients with STDs who infected their children with HIV during pregnancy [7].

The incidence of various STDs is higher in pregnant women with HIV infection than in HIV-seronegative women [8]. Since a significant proportion of the group of pregnant women with HIV infection is represented by patients characterized by a low adherence to monitoring in medical institutions, as well as social maladjustment, having several sexual partners, active consumption of alcohol and drugs, and disinterest in the health of the unborn child, the diagnostics and treatment of STDs in this group are complicated. In turn, untreated infections of the urogenital tract can cause damage to the placenta with the development of chorioamnionitis, chronic placental insufficiency, and antenatal HIV transmission to the fetus [9].

STDs such as herpes, cytomegalovirus, and *Candida* infections are detected more often in pregnant women with

advanced stage of HIV infection who did not receive ARVT or had late initiation of therapy because of immunodeficiency than in the general population, and they can also be regarded as opportunistic infections, that is, conditions affecting negatively the course of HIV infection [10].

Herpes is one of the most frequent opportunistic diseases; its prevalence in pregnant women with HIV infection is steadily increasing owing to an emerging HIV pandemic and the increasing role of the heterosexual transmission route. A study revealed that the prevalence of herpetic infection in the general population of pregnant women varies from 7% to 40% [11], while it can reach 50%–90% in women with HIV infection [12]. An exacerbation of herpetic infection in early pregnancy leads to miscarriage due to infectious embryopathies and chronic endometritis caused by long-term persistence of the virus in the endometrium [13]. When the fetus passes the infected birth canal of the mother, the risk of neonatal herpes is high because of the direct contact with the infected mucous membranes of the birth canal. To prevent this complication, delivery by a well-planned cesarean section is recommended [14]. In addition, the presence of herpetic infection can greatly increase the risk of perinatal transmission of HIV during labor [12, 15].

Vulvovaginal candidiasis is one of the most common diseases during pregnancy. In the general population, *Candida* infection is detected in 30%–40% of pregnancies and can reach 45%–50% by the third trimester [16], and in women with HIV infection, it is detected in 70% of pregnancy cases [17]. In pregnant women with HIV infection, vulvovaginal candidiasis can also be regarded as an opportunistic infection. In a study conducted in India, no direct correlation was found between the levels of CD4 lymphocytes and HIV RNA in the blood plasma and the incidence of vulvovaginal candidiasis in pregnant women with HIV infection [18]. This suggests that screening for the presence of fungi of the genus *Candida* should be performed in all pregnant women with HIV infection, regardless of the term, and if vaginal candidiasis is detected, timely treatment should be prescribed according to the current recommendations. Untreated vaginal candidiasis during pregnancy may be associated with an increased risk of spontaneous miscarriage, premature rupture of membrane, premature delivery, and low birth weight [19].

Anemia is a common complication of pregnancy. The frequency of anemia in pregnant women without HIV infection ranges from 15% to 50%, with an average of 32% in Russia [20]. Anemia is registered in pregnant women with HIV infection 1.5 times more often than that in the general population [21]. Iron deficiency affects adversely the course of pregnancy, childbirth, and postpartum, as it increases the frequency of preterm delivery and weak uterine contraction. Since preterm delivery and weak uterine contraction increase the risk of perinatal HIV transmission, reducing the

incidence of anemia in pregnant women with HIV infection may reduce the risk of infection in infants born from infected mothers [22]. The main causes of anemia during pregnancy include a decrease in iron intake; deficiencies in folic acid, B vitamins, and proteins; chronic gastrointestinal diseases; a burdened obstetric history (i.e., frequent childbirth, history of spontaneous miscarriages, bleeding in previous births, and depletion iron reserve); and complications of the current pregnancy (i.e., multifetal pregnancy, bleeding during pregnancy of various localizations, and placenta previa). In pregnant women with HIV infection, these factors may be associated with chronic viral inflammation of the bone marrow, and intake of antiretroviral drugs such as zidovudine and phosphazide. During pregnancy, patients with HIV infection are prone to malabsorption, which appears to be caused by HIV infection [23]. To diagnose anemia in pregnant women with HIV infection, a comprehensive examination is necessary to identify the cause of anemia.

Thrombocytopenia in pregnant women with HIV infection occurs at all stages of the disease, and its incidence ranged from 10% to 15%, with a tendency to increase in case of progressive immunodeficiency [24]. During pregnancy, childbirth, and postpartum, thrombocytopenia is associated with a risk of bleeding. Thrombocytopenia that develops in HIV infection is referred to as secondary immune-acquired thrombocytopenia. The immune response underlying the development of thrombocytopenias is a complex multistep cyclic process involving B-lymphocytes, T-lymphocytes, natural killer cells, macrophages, and cytokines. Antiplatelet antibodies accelerate the clearance of platelets from the circulation. The binding of antibodies to platelets leads to Fc $\gamma$  receptor (Fc $\gamma$ R)-mediated destruction of platelets by phagocytes [25]. In HIV infection, impaired production of platelets also occurs. Given the damaging effect of HIV in the bone marrow, the production of megakaryocytes, which are precursors of platelets, is reduced, and their differentiation is impaired. Thrombocytopenia can be an indicator of advanced progressive liver disease, such as chronic viral hepatitis, often associated with HIV infection. In this case, increased destruction of platelets is associated, in addition to the autoimmune mechanism, with hypersplenism syndrome and portal hypertension, resulting in a delay and destruction of the formed elements in the hypertrophied spleen [26]. Some studies have confirmed the effect of certain antiretroviral drugs on lowering platelet levels. Thus, in the initial weeks of taking non-nucleoside reverse transcriptase inhibitors, owing to their toxic effect on the liver, fibrinolysis is activated, and the production of antiplasmin decreases [27].

Given the significant proportion of the parenteral transmission of HIV infection, the frequency of coinfection with chronic viral hepatitis B and C in pregnant women with HIV infection remains high. In total, 61.9 thousand

cases of hepatitis B and C were registered in the Russian Federation (with 65.1 and 68.1 thousand cases in 2017 and 2016, respectively). The incidence rates of chronic hepatitis B differ sharply across the constituent entities of the Russian Federation, so the prevalence ranges from 1.85 to 128.69 per 100 thousand populations. This value depends to a certain extent on the quality of diagnostics and completeness of registration of these diseases as well as on the geographical aspects of the region with rampant narcotic drug trafficking [28]. The prevalence of chronic viral hepatitis B among pregnant women in the Russian Federation reaches 0.5% [29]. However, data on the prevalence of chronic viral hepatitis C in pregnant women in Russia are insufficient. Several authors claim that the incidence rate ranges from 8% to 15% [30]. In pregnant women with HIV infection, the prevalence of chronic hepatitis C reached 60% by the end of 2016 [31]. Threatened miscarriage is one of the most common obstetric complications in patients with both hepatitis B and HIV. The frequency of its development is higher with an increase in the activity of hepatic transaminases; therefore, the dynamic determination of alanine aminotransferase activity during pregnancy can be a criterion for predicting the risk of threatened miscarriage [32].

A study conducted in St. Petersburg in 2013 reported that the most common complications in pregnant women with HIV infection were chronic placental insufficiency in 35.5% of the cases (10%–24% in the general population), preeclampsia of varying severities in 27.5% (12%–22% in the general population), and premature rupture of membranes in 24.2% (up to 18% in the general population) [33–36]. Threatened miscarriage, polyhydramnios, and abnormal placenta location were diagnosed less commonly. Every third pregnant woman (33.4%) had a combination of these complications of pregnancy [33].

### **Selection of delivery method in pregnant women with HIV infection**

Choosing the delivery method in pregnant women with HIV infection is important in terms of reducing the risk of perinatal transmission of HIV and resolving the emerging obstetric situations. In 1999, the American Congress of Obstetricians and Gynecologists recommended elective cesarian section at week 38 of gestation for all women with HIV infection and plasma viral load higher than 1000 copies/ml. These recommendations were based on the results of a meta-analysis that included 15 studies from six European countries [37]. These studies analyzed the frequency of perinatal HIV transmission in women with different methods of delivery. HIV infection was diagnosed in 8.8% of children born by a cesarean section performed after rupture of the membranes, in 10.2% of cases during vaginal delivery, and in 2.4% of cases with elective caesarian

section. Thus, researchers concluded that elective cesarean section can reduce the risk of fetal HIV infection by 50% [38].

Currently, the preferred method of delivery in women with HIV infection is based on the presence or absence of epidemiological indications for a cesarean section as well as obstetric and/or somatic indications for surgical delivery. The presence of HIV infection in a pregnant woman is not an indication for a cesarean section. Surgical delivery in pregnant women with HIV infection is preferable only in cases when it objectively reduces the risk of intrapartum transmission of infection (in a planned manner, before the onset of labor while maintaining the integrity of the fetal bladder) in women with a high or unknown HIV viral load or in the presence of obstetric and somatic indications. The frequency of surgical delivery in both pregnant women with and without HIV infection varies among countries, as it is 25% of the total number of births in the UK, 30% in the USA, up to 70% in Brazil, and  $\geq 20\%$  in Russia [39, 40]. The proportion of surgical delivery in pregnant women with HIV infection remains higher than that in the general population, which is most likely due to the higher incidence of pathology in pregnancy and childbirth, as well as the higher incidence of somatic pathology in these patients. In the Russian Federation, the frequency of cesarean section reaches 45% in pregnant women with HIV infection [33].

### **Complications during delivery and postpartum period in women with HIV infection**

Several researchers have revealed that the incidence of preterm delivery in patients with HIV infection is significantly higher than that in the general population, regardless of the presence or absence of ARVT during pregnancy [5, 41]. This is primarily due to the presence of a chronic viral infection as well as the greater prevalence of genital tract infections and other risk factors for preterm delivery (such as low social and economic status, smoking, and drug addiction) [42]. Scientists have different opinions about the effect of ARVT on the rate of preterm delivery in women with HIV infection; the prescription of HAART at the stage of pregnancy planning can reduce the level of HIV RNA in the blood, reduce the systemic inflammatory process, and restore the immune system, which in turn should lead to a reduction in the frequency of preterm delivery. By contrast, several authors have indicated an even greater proportion of preterm deliveries among patients with HIV infection who received ARVT for a long time and with persistent suppression of viremia [2, 3, 43]. In a Swiss study of HIV infection in mothers and children, women who received HAART before pregnancy had an almost two times higher risk of preterm delivery than patients who received zidovudine monotherapy from the third trimester of pregnancy [44]. Researchers suggested that ARVT during pregnancy can cause an imbalance

in the Th1/Th2 immune response, induce chronic placental insufficiency, and reduce progesterone levels, which is the trigger for early delivery [45]. A recent study revealed a relationship between long-term intake of protease inhibitors (saquinavir/ritonavir, lopinavir/ritonavir) and increased incidence of preterm delivery [43]. In another study, the authors believe that these drugs lead to a decrease in the level of interleukin-10, an anti-inflammatory cytokine produced by monocytes and macrophages, which plays an important role in pregnancy maintenance [46].

Many studies have noted a number of complications, and the frequency of which is higher in pregnant women with HIV infection and puerperas, including preterm discharge of amniotic fluid, labor abnormalities with a predominance of weak uterine contraction, chronic and acute intrauterine fetal hypoxia, and significantly greater blood loss during childbirth [42, 47]. However, the relationship between these obstetric complications and the course of HIV infection, viral load, and immune status during pregnancy has not been investigated. According to Russian researchers, preeclampsia and chronic placental insufficiency are diagnosed three times more often and 1.5 times more often in pregnant women with HIV infection than in the general population [48]. The causes of the increased incidence of preeclampsia are not fully understood. The suggestion was that the rate of migration of trophoblasts decreased and that the uterine vessels retained the same structure as in the absence of pregnancy, which resulted in the rapid development of endotheliosis [49, 50].

The incidence of postpartum complications is higher in puerperas with HIV infection than in the general population [51, 52]. The causes of the increase in the incidence of complications are multifactorial and are associated with social and behavioral characteristics, presence of concomitant infections of the urogenital tract, and a high frequency of delivery by cesarean section. Many authors reported that HIV infection in combination with a low social status increased the risk of uterine subinvolution twofold [53].

Women with HIV infection have an increased risk of postoperative complications (such as endometritis, infiltration, and suppuration of the postoperative scar, perineal suture infections, and sepsis) compared with women without HIV infection. Probably, the frequency of complications correlates with the degree of immunosuppression [54]. The influence of the level of viremia in postpartum women on the incidence of postpartum complications has not been established.

### **Conditions of newborns born to mothers with HIV infection**

When the placental tissue is infected with HIV, signs of chronic placental insufficiency with pronounced nonspecific involutive-dystrophic changes and acute circulatory disorders are evident [55]. Functional inconsistency of the

placenta is the main cause of intrauterine hypoxia, fetal growth retardation, and its damage during childbirth [56].

Among pathologies of children born to mothers with HIV infection, the most frequent are perinatal lesions of the central nervous system (37.3%), varying degrees of undernutrition (26.1%), and asphyxia at birth (28.4%) [22]. Neonatal abstinence syndrome is often observed, which severity depends directly on the time of the mother's last intake of psychotropic substances [47].

Studies of the effect of antiretroviral drugs taken during pregnancy on the condition of the newborn have shown that HAART does not affect significantly the fetus, but there may be toxic effects on the hematopoietic system (zidovudine) or hyperbilirubinemia (atazanavir). In exceptional cases, liver damage (hepatotoxic effect of nevirapine), kidney damage (nephrotoxic effect of tenofovir), or hyperlipidemia associated with ritonavir-boosted lopinavir are diagnosed [57]. Babies whose mothers received HAART throughout their pregnancy are usually born with a lower weight than the population and gain weight more slowly during the neonatal period. Subsequently, no significant differences were found in the physical development of children [58]. Several studies in Africa have shown that children born to mothers with HIV infection are at increased risk of neonatal and infant mortality. Most likely, this is due to availability of ARV both for prophylaxis during pregnancy and for the treatment of a child with perinatal HIV transmission [6].

## CONCLUSIONS

The course of pregnancy, childbirth, and postpartum in women with HIV infection is accompanied by a higher frequency of complications and adverse outcomes than in the general population. The most common obstetric complications in these patients are bacterial–viral lesions of the placenta with the formation of chronic placental insufficiency, preterm delivery, high frequency of surgical delivery, and birth of newborns with body weight inappropriate for the gestational age. The main risk factors for the pathological course of pregnancy and childbirth in patients with HIV infection are the high prevalence of STDs, chronic hepatitis, anemia, thrombocytopenia and, in some cases, intake of antiretroviral drugs with proven toxic effects. A high level of HIV RNA in the mother's blood and a low level of CD4 lymphocytes can be associated with several comorbidities associated with HIV, complicating pregnancy, childbirth, and postpartum.

The social and behavioral characteristics of pregnant women with HIV infection, such as active use of psychoactive drugs and/or alcohol, unsafe sexual behaviors contributing to STD infection, chronic viral hepatitis, as well as low adherence to monitoring and chemoprophylaxis, have a significant effect on the course of pregnancy. The causes of the increased incidence of obstetric complications in women with HIV infection are multifactorial.

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