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ANALYSIS OF THE TIMING AND DELIVERY METHODS, CLINICAL AND LABORATORY INDICATORS OF HIV-INFECTED PREGNANT WOMEN IN SAINT PETERSBURG

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▪ Assessing the timing and delivery methods, clinical and laboratory indicators of HIV-infected pregnant women is important for organizing effective care for this group of patients and further reducing the frequency of perinatal transmission of HIV infection. In 2014–2017, in Saint Petersburg, there were 2,524 childbirths in HIV-infected women, who were observed during pregnancy mainly in the Center for the Prevention and Control of AIDS and Infectious Diseases (AIDS Center). The average frequency of perinatal HIV transmission in the city over the study period was 1.3%, which is lower than the average for Russia (2.5%). A retrospective and prospective analysis of 1,858 medical records of HIV-infected women observed during pregnancy at the AIDS Center in 2014–2017 was performed. An annual decrease in the proportion of chronic viral hepatitis C coinfection was found, which was proportional to a decrease in parenteral HIV transmission in the study group. Due to the increase in HIV testing coverage, the frequency of detection of infections in pregnant women in antenatal clinics during registration was reduced. This allows conducting a thorough examination, counseling and a timely initiation of antiretroviral therapy (ART) during pregnancy planning. The vast majority of HIV-infected women are committed to follow-up in medical facilities during pregnancy, to receive antiretroviral prophylaxis (ARP) and, as a result, to give birth to a healthy child. The rate of preterm birth among HIV-infected women is higher than in HIV-seronegative women. This determines the timely initiation of ARP/ART during pregnancy for prevention of preterm delivery. The proportion of births through the birth canal increases annually, but the operative delivery rate remains above the population.

▪ **Keywords:** HIV-infected pregnant woman; perinatal transmission of HIV; childbirth in HIV-infected women; HIV RNA and CD4-lymphocyte levels during pregnancy.

АНАЛИЗ СРОКОВ И МЕТОДОВ РОДОРАЗРЕШЕНИЯ, КЛИНИКО-ЛАБОРАТОРНЫХ ПОКАЗАТЕЛЕЙ БЕРЕМЕННЫХ, ИНФИЦИРОВАННЫХ ВИРУСОМ ИММУНОДЕФИЦИТА ЧЕЛОВЕКА, В САНКТ-ПЕТЕРБУРГЕ

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▪ Оценка сроков и методов родоразрешения, клинико-лабораторных показателей беременных, инфицированных вирусом иммунодефицита человека (ВИЧ), важна для организации им эффективной помощи и дальнейшего снижения частоты передачи инфекции от матери ребенку. В Санкт-Петербурге в 2014–2017 гг. произошло 2524 родов у ВИЧ-инфицированных женщин, наблюдавшихся при беременности преимущественно в СПбГБУЗ «Центр по профилактике и борьбе со СПИД и инфекционными заболеваниями» (Центр СПИД). Средняя частота пери-

натальной передачи ВИЧ за исследуемый период в городе составила 1,3 %, что ниже, чем в среднем по России. Проведен ретроспективно-проспективный анализ 1858 карт ВИЧ-инфицированных женщин, наблюдавшихся при беременности в Центре СПИД в 2014–2017 гг. Зафиксировано ежегодное уменьшение доли коинфекции хронического вирусного гепатита С, что пропорционально снижению парентерального пути передачи ВИЧ. За счет увеличения охвата населения тестированием снижается частота первичного выявления ВИЧ в женских консультациях при постановке на учет по беременности. Это позволяет тщательно обследовать, проконсультировать и начать антиретровирусную терапию на этапе планирования беременности. Подавляющее число ВИЧ-инфицированных женщин наблюдаются в медицинских учреждениях при беременности, получают антиретровирусную профилактику, и, как следствие, у них рождаются здоровые дети. Частота преждевременных родов среди ВИЧ-инфицированных женщин выше, чем у ВИЧ-серонегативных. Важной частью профилактики досрочного родоразрешения является своевременное начало антиретровирусной профилактики/антиретровирусной терапии. Ежегодно увеличивается доля родов через естественные родовые пути, однако уровень оперативного родоразрешения все еще остается выше популяционного.

▪ **Ключевые слова:** ВИЧ-инфицированная беременная; перинатальная передача ВИЧ; сроки и методы родоразрешения ВИЧ-инфицированных беременных; наблюдение ВИЧ-инфицированных беременных.

Introduction

In accordance with the decrees of the President of the Russian Federation (No. 761 "On the National Strategy of Actions in the Interests of Children for 2012–2017" dated 01.06.2012, No. 240 "On the Declaration of the Decade of Childhood in the Russian Federation" dated 29.05.2017, and the Decree of the Government of the Russian Federation No. 2203-r "On approval of the State strategy for combating HIV infection in the Russian Federation for the period up to 2020 and the future perspective" dated 20.10.2016), the elimination of perinatal transmission of human immunodeficiency virus (HIV) is a priority for the government and the medical community [1–3]. Currently, the World Health Organization has confirmed the elimination of mother-to-child transmission of HIV infection in former USSR countries, such as Armenia, Belarus, and the Republic of Moldova [4, 5]. According to preliminary data, the frequency of perinatal transmission of HIV in 2018 in the Russian Federation was 1.5% [6] and in St. Petersburg was 1.2%. During the monitoring period as of 31.12.2018, 191,074 children were born to HIV-infected mothers in Russia, and of these, HIV infection was confirmed in 9,529 women. Every year, approximately 15,000 births are registered to HIV-infected women in Russia [6]. Over the past few years, the number of births to HIV-infected mothers in St. Petersburg has remained steadily high at 500–700 per year [7, 8]. Despite the large number of births in the city, mother-to-child transmission of HIV in St. Petersburg is less frequent than the national average [7, 9]. These data were contributed by organizations that interface with the city healthcare institutions that provide assistance to pregnant women, including HIV-infected women. This work is regulated by regional bylaws, namely, Decrees of the Health Committee of the Government of St. Petersburg No. 692-r "On Prevention of Mother-to-Child Transmission of HIV Infection" and No. 145-r "On Amendments to the Decree" dated 20.12.2011 No. 692-r" dated 16.04.2013 [10, 11]. A study on the epidemiological, obstetric, somatic, and laboratory parameters of HIV-infected women who have given birth to children in St. Petersburg is of interest in order to determine new approaches for reducing the frequency of perinatal HIV transmission in the city.

Materials and Methods

A retrospective analysis of 1,858 medical records of HIV-infected pregnant women who gave birth to children in St. Petersburg from 2014 to 2017 was performed. Data were collected on the age of the pregnant women, the timing of registration at a women's care clinic (WCC) and the AIDS Center (AC) during pregnancy, clinical and laboratory indicators, information on the delivery time, growth, and weight indicators of newborns. Laboratory studies were conducted in the laboratory of the St. Petersburg Center for the Prevention and Control of Infectious Diseases. HIV RNA was quantified using the Abbott m2000 RealTime System automated complex by in vitro reverse transcriptase polymerase chain reaction (RT-PCR) to determine

HIV-1 RNA levels in the range of 20–10 million copies/ml. The study was conducted using Abbott RealTime HIV-1 test systems. Immunological examination included quantification of cellular immunity, namely, that of T-helper cells/inducers (CD4). The blood serum of patients obtained by a standard method served as the research material. Studies were performed using Behring monoclonal antibodies in a lymphocytotoxicity test (NIH USA). Statistical analysis of the data was performed using the STATISTICA for Windows system (version 8) at a significance level of $p \leq 0.05$.

Results

The age of women in the study group ranged from 15 to 47 years ($M \pm m$ 31.4 ± 4.3). The age of the pregnant women tended to increase over time, and as noted in 2014, the average age was 29.9 ± 4.1 years, while in 2015, the average age was 30.9 ± 4.2. In 2016, the average age was 31.9 ± 4.2, while in 2017, the average age was 32.7 ± 4.4 years. Most pregnancies (96%) were wanted but were not always planned.

The time when HIV-infected women visited a WCC for registration of their pregnancy varied from 3 to 36 weeks ($M \pm m$ 10.8 ± 5.2) and from 4 to 39 weeks in cases of visits to the AC ($M \pm m$ 13.2 ± 7.8). During monitoring, a twofold decrease in new cases of HIV infection was noted when women registered at a WCC during pregnancy, and in 2014, more than one-third of pregnant women learned about their HIV status during the initial examination (34.8%), and in 2017, this number was 16.3% ($p < 0.001$).

The rate of co-infection with chronic viral hepatitis C (HVHC) in HIV-infected pregnant women was 42.5%. A decrease from 50.5% in 2014 to 36.8% in 2017 in the number of cases of HVHC co-infection during the monitoring period was noted ($p < 0.001$). Anemia was diagnosed in 66.7% of pregnant women in 2014, but by 2017, its prevalence decreased to 60% ($p < 0.05$). Table 1 shows the prevalence of HVHC and anemia in HIV-infected pregnant women.

Approximately 2% of HIV-infected pregnant women in St. Petersburg each year do not receive antiretroviral prophylaxis (ARVP) or antiretroviral therapy (ARVT) for various reasons. Moreover, 31.9% ($n = 592$) of the HIV-infected pregnant women who received ARVP took antiretroviral drugs before pregnancy, and their pregnancy began with an undetectable blood RNA level. The remaining 66.1% of patients started prophylaxis for perinatal HIV transmission during pregnancy, namely, 17.6% ($n = 328$) started it in trimester I according to clinical and laboratory indications, 41.6% ($n = 772$) in trimester II at the scheduled time in accordance with national clinical guidelines [12, 13], and 6.9% ($n = 128$) in trimester III of pregnancy.

An annual increase was observed in HIV-infected pregnant women who started receiving ARVT before pregnancy (an average of 7.5% per year ($p < 0.001$) in 2014 compared with 2017). Thus, in 2014, 21.4% ($n = 101$) of women were treated with antiretroviral drugs before pregnancy, while in 2015, 27.8% ($n = 128$) received these drugs; in 2016 and 2017, 35.4% ($n = 156$) and 42.6% ($n = 207$), respectively, received these drugs. The onset of pregnancy in cases where the level of HIV viral load was undetectable indicates the extremely low probability of fetal infection during pregnancy and delivery. Data on the blood level of HIV RNA and the level of CD4 lymphocytes during registration for pregnancy at the AC and at weeks 34–36 of gestation are presented in Table 2.

During ARVT treatment in pregnant women, a significant increase in the level of CD4 lymphocytes ($p < 0.001$) and decrease in the level of HIV RNA ($p < 0.001$) were noted. HIV-infected women became pregnant with a higher level of HIV viral load in 2014 than in 2017 ($p < 0.05$), and the average immunogram values during the follow-up period were significantly increased ($p < 0.05$).

Table 1 / Таблица 1

Prevalence of HCV and anemia in HIV-infected pregnant women (*n* = 1,858)

Распространенность хронического вирусного гепатита С и анемии у ВИЧ-инфицированных беременных (*n* = 1858)

Indicator	Year			
	2014	2015	2016	2017
HIV infection, *n*	471	460	471	486
Chronic viral hepatitis C, *n* (%)	238 (50.5 %)	202 (43.9 %)	77 (40.1 %)	179 (36.8 %)*
Anemia, *n* (%)	314 (66.7 %)	327 (71.1 %)	248 (56.2 %)	291 (59.9 %)**

Note * $p < 0.001$ compared with 2014; ** $p < 0.005$ compared with 2014

Table 2 / Таблица 2

Changes in HIV RNA and CD4-lymphocytes in HIV-infected pregnant women during ARP/ART (*n* = 1,858)
Изменение показателей РНК ВИЧ и CD4-лимфоцитов у ВИЧ-инфицированных беременных на фоне антиретровирусной терапии (*n* = 1858)

Indicator	Year			
	2014	2015	2016	2017
CD4 lymphocytes at the first visit to a gynecologist at the AIDS Center during pregnancy, n (%)	404.3 (25.4)*	422.3 (24.6)*	487.3 (26.4)*	536.8 (27.1)*
CD4 lymphocytes at weeks 34–36 of gestation, n (%)	535.5 (30.2)	579.8 (30.2)	611.8 (30.7)	625.1 (30.2)**
HIV RNA at the first visit to a gynecologist at the AIDS Center during pregnancy, copies/ml	55709.5*	92967.7*	46562.7*	32137.5*
HIV RNA at weeks 34–36 of gestation, copies/ml	6532.5	4546.5	409.1	153.8**

N o t e. * $p < 0.001$ compared with the indicator before delivery; **$p < 0.05$ compared with

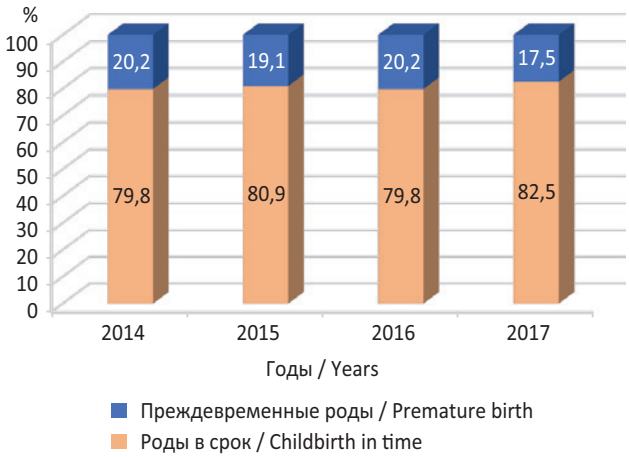

Fig. 1. Rate of preterm birth among HIV-infected women (*n* = 1.858)

Рис. 1. Доля преждевременных родов у родильниц с ВИЧ-инфекцией (*n* = 1858)

Fig. 2. Delivery methods for HIV-infected pregnant women (*n* = 1.858)

Рис. 2. Способы родоразрешения ВИЧ-инфицированных беременных (*n* = 1858)

One in five HIV-infected pregnant women had a preterm delivery (19.2%); in 16 women, delivery occurred at weeks 22–27 of gestation (4.5% of the total number of preterm births), 108 (30.2%) patients had a preterm delivery at weeks 28–33, and in 233 (65.3%) women, preterm delivery occurred at weeks 34–36. However, the proportion of preterm deliveries was decreased in 2017 than in 2014 (Fig. 1).

The main method of delivery in HIV-infected pregnant women is vaginal delivery (68.8%, *n* = 1279); cesarean section for obstetric indications was performed in 1 in 3 pregnant women (29.1%, *n* = 541), while cesarean section for epidemiological indications was performed in 2.1% (*n* = 38) of cases. Approximately one-third of HIV-infected pregnant women give birth to a child every year by cesarean section according to obstetric indications (signs of uterine scar failure after various surgical interventions, such as previous cesarean section, chronic, or intrauterine fetal hypoxia, placental abruption, and extragenital diseases requiring exclusion of an active pushing phase). Cesarean section for epidemiological indications (high or unknown viral load of HIV at the time of delivery, late initiation of ARVP, and detection of HIV infection in late pregnancy) was performed in 2% of cases on average (Fig. 2).

The length of newborns ranged from 25 to 58 cm ($M \pm m$ 49.84 ± 4.7 cm), and their weight ranged from 390 to 5580 g ($M \pm m$ 3001.8 ± 688.27 g).

From 2014 to 2017, 27 HIV-infected women registered abandonment of their children in maternity hospitals (1.5% of the total number of puerperas), while 11 women in 2014 (2.3% of the number of births for the current year), 3 (0.7%) in 2015, 7 (1.6%) in 2016, and 6 (1.2%) in 2017 registered abandonment of their children (Fig. 3).

Discussion

During monitoring of the HIV epidemic, an annual increase in the age of HIV-infected pregnant women was noted both in the Russian Federation and in St. Petersburg. From 2005 to 2010, the average age of HIV-infected pregnant women was 24.2 years, while from 2011 to 2013, the average age was 28.2 ± 1.2 years, and from 2014 to 2017, it was 31.4 years. These differences may be associated with an increase in the average age of HIV-infected women in general and an increase in the number of repeated births in patients in this group [12, 14–16].

Most HIV-infected pregnant women entered the dispensary registration at a WCC in the first trimester of pregnancy due to an increase in the proportion of socially adapted women in the group of HIV-infected patients who were sexually infected and motivated to give birth to a healthy child. A small proportion of patients visited the WCC in the second and third trimesters due to the late diagnostics of pregnancy and HIV infection, lower social status, active intake of psychoactive drugs, and, as a result, a lack of interest in giving birth to a healthy child. Some of the pregnant women delayed their visit to a WCC and AC, as they were afraid of disclosure of HIV status or because they denied its presence.

During the monitoring period, the number of new cases of HIV infection diagnosed in pregnant women during registration at a WCC decreased by half, and in 2011, the proportion of pregnant women in whom HIV was detected for the first time at a WCC was 51.8% [17]; in 2014, this number was 34.8%, and in 2017, this number was 16.3% ($p < 0.001$). This is most likely due to the annual increase in the coverage of the city population that underwent HIV testing, since in 2014, 761,859 people (15.1% of the population of St. Petersburg) were tested, whereas in 2017, 1,492,650 people (22.2% of the population) were tested [18–20].

The wide coverage of the monitoring of HIV-infected pregnant women (98.5%) by a dispensary can be explained by AC doctors who provide counseling on the prevention of perinatal transmission of HIV at the pregnancy planning stage, as well as the high-quality counseling by WCC obstetrician-gynecologists, which explains the need and importance of prompt visits to the AC to receive ARVP. Nevertheless, each year, a small portion of HIV-infected pregnant women visit the AC only in the third trimester. The reasons for these late visits to the AC obstetrician-gynecologist by women who were aware of their diagnosis before

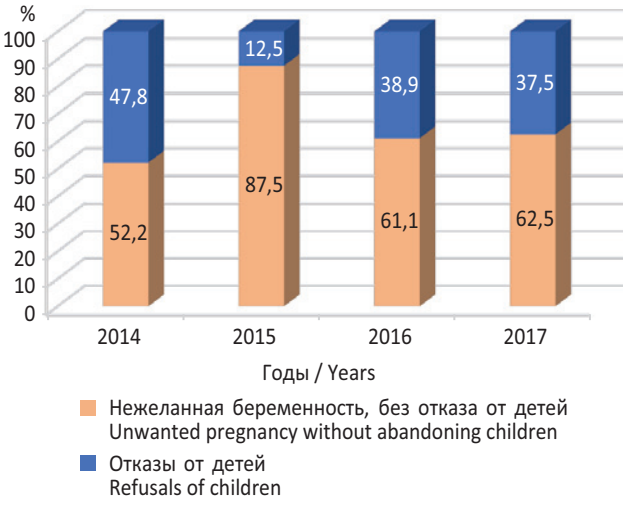

Fig. 3. Newborn abandonment by HIV-infected women with unwanted pregnancy in maternity hospitals ($n = 27$; 1.5% of the total number of newborns during the study)

Рис. 3. Отказы от новорожденных в родильных домах ВИЧ-инфицированных женщин с нежеланной беременностью ($n = 27$; 1,5 % общего количества новорожденных за время исследования)

pregnancy were low adherence to follow-up and ARVT, substance abuse, and denial of the diagnosis and the need for treatment.

An insignificant percentage of women become infected with HIV during pregnancy from their HIV-infected partner, who either does not know about his HIV infection or conceals the diagnosis. In this case, HIV infection can be diagnosed in a woman late in her pregnancy or after childbirth, and consequently, the fetus can be infected during delivery or when breastfed by the mother. At the St. Petersburg AC, 15% ($n = 53$) of children with an established HIV diagnosis were infected through breastfeeding [21]. Thus, it is very important to motivate partners of all pregnant women to be tested for HIV [22].

Timely visits to an AC gynecologist by pregnant women with an HIV-positive test result enable initiation of ARVP in a timely manner (early second trimester), which may lead to an undetectable level of HIV RNA in the blood as early as possible, thereby reducing the risk of perinatal virus transmission to less than 1% [14, 23–25].

The proportion of HIV-infected pregnant women with HVHC co-infection decreased significantly during the monitoring period (from 50.5% in 2014 to 36.8% in 2017, $p < 0.001$), which may be due to the predominance of the sexual route of HIV infection in St. Petersburg since 2014 [15, 26]. From 2011 to 2013, in St. Petersburg, the

proportion of HVHC co-infection was 48.9–52.5% due to the large number of drug users in the population of HIV-infected individuals [27].

Anemia is a common complication during pregnancy in both HIV-infected patients and women without HIV infection. In HIV-infected pregnant women, anemia can be a symptom of HIV infection progression or can be indicative of opportunistic infections. Anemia is an adverse event that may occur during ARVT treatment [28]. In previous studies, the prevalence of anemia during pregnancy in HIV-infected women reached 30–40.2% [27, 29].

During the monitoring period, the blood level of HIV RNA in patients at the time of registration for pregnancy at the AC significantly decreased ($p < 0.05$), which can be explained by an increase in the proportion of HIV-infected women who became pregnant while undergoing treatment with ARVT and who already had a suppressed viral load.

The decrease in the level of HIV RNA by the time of childbirth in women undergoing ARVT or ARVP also positively changed over time, since in 2014, the viral load by the time of childbirth decreased on average 8.5 times (average of 6,532 copies/ml); in 2017, the load decreased by more than 200 times and amounted to 153 copies/ml, while 87% of women had an undetectable viral load at weeks 34–36 of pregnancy.

At present, the management of labor in HIV-infected women is individualized and based on the amount of viral load in the blood plasma, adherence to ARVT during pregnancy, duration without amniotic fluid, course of labor, and other clinical factors. It was previously believed that all HIV-infected women should deliver a child by cesarean section to reduce the level of perinatal transmission of HIV infection. In 2000 and 2010, a cohort study reported a decrease in the proportion of cesarean sections in HIV-infected women from 75% to 47% [30]. In St. Petersburg, from 2011 to 2013, the proportion of cesarean sections in HIV-positive women was 32.7% [27]. According to epidemiological indications, the proportion of cesarean sections during the HIV epidemic can be reduced by increasing the availability of antiretroviral drugs. However, despite all efforts, the frequency of surgical delivery in HIV-infected women is higher than that in the general population [31]. Currently, cesarean section for epidemiological indications is performed according to national clinical guidelines. In St. Petersburg, the proportion of surgical deliveries in HIV-infected women is approximately 2% of the total number of births, but due to the variety of comorbid somatic conditions and obstetric complications, one-third of HIV-infected pregnant women require surgical delivery [28].

According to the Federal State Statistics Service, the proportion of preterm deliveries in St. Petersburg from 2014 to 2017 amounted to 4.2% [34]. HIV-infected pregnant women are at risk for preterm birth [27, 33–35]. From 2011 to 2013, in St. Petersburg, the preterm birth rate was 23.5% [27]. Every year, one-fifth of pregnant women who register at the AC (19.2%) experience preterm childbirth. These patients are at risk for perinatal transmission of HIV infection [25, 36]. Considering this, it is extremely important to reduce the level of HIV RNA in pregnant women receiving ARVT as early as possible and no later than the second trimester of pregnancy.

The proportion of abandonment of newborns in maternity hospitals among HIV-infected women was and remains higher than that among HIV-seronegative women [37]. The primary reasons for abandoning newborns were the active use of substances by HIV-infected women and their low social status.

Conclusions

It has been established that most HIV-infected pregnant women visit a WCC and AC in trimester I of pregnancy. From 2014 to 2017, the number of new HIV-infected women who registered at the WCC during their first visit due to pregnancy decreased by half. The proportion of women who were co-infected with chronic viral hepatitis C is gradually decreasing due to a decrease in the number of cases of infection by the parenteral route. By 2017, a decrease in the incidence of anemia in HIV-infected pregnant women was noted. Every year, the number of women who become pregnant while under ARVT treatment and who have an undetectable level of HIV viral load increases by 7.5%, which has led to a decrease in the probability of perinatal infection to a minimum level. The initiation of ARVT before pregnancy favorably affects the average level of CD4 lymphocytes and HIV RNA at the initial examination during pregnancy and before childbirth. The main method of delivery for HIV-infected pregnant women is vaginal delivery. Cesarean section for various indications is performed in one-third of cases, which is higher than that performed at the population level. The frequency of preterm births in HIV-

infected women, which is one of the factors that increases the risk of perinatal transmission of HIV, is 4–5 times higher than that in the general population.

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