UNIVERSITY OF MEDICINE AND PHARMACY OF CRAIOVA

PhD SCHOOL

DOCTORAL THESIS

Mother-to-child transmission of HIV

ABSTRACT

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Contents

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1. INTRODUCTION

Human immunodeficiency virus (HIV) is responsible for causing acquired immunodeficiency syndrome (AIDS) and it was first found in 1983 (1). HIV/AIDS continues to be one of the world's most serious pandemics (2).

Women living with HIV, who become pregnant or who acquire the virus during pregnancy are at risk of both maternal and perinatal morbidity and mortality mainly if the infection is poorly controlled (1). Preventing mother-to-child transmission of HIV is the main goal in the care of pregnant women living with HIV (3).

During pregnancy, an appropriate antiretroviral therapy (ART) should be administered, with very close monitoring of HIV viral load (VL-HIV) (1).

The objectives of this study are: to determine the rate of mother-to-child transmission of HIV infection among pregnant women living with HIV registered in Craiova Regional Center for Monitoring and Evaluation of HIV / AIDS (CRC); to identify some correlations between certain risk factors and maternal-fetal transmission of HIV infection; to establish the correlation between the mother's adherence to ART and the serological status of the newborn to highlight the importance of ART in reducing the risk of mother-to-child transmission of HIV; to identify the characteristics of children perinatally exposed to HIV and to make a comparison of characteristics of HIV-infected and HIV-uninfected infants.

2. CURRENT STATE OF KNOWLEDGE

2.1. Etiology

HIV is grouped to the genus Lentivirus within Retroviridae family, Lentivirinae subfamily.Two types of lentiviruses are known: HIV-1 and HIV-2, with similar structure and life cycle but different origin, clinical and epidemiological features (4) (5).

2.2. Pathogenesis

In the last two decades, it has been suggested that there are several receptors that play an important role in the penetration of HIV into target cells. There is a general consensus that the CD4 molecule and a co-receptor for chemokines, either CCR5 or CXCR4, are essential for the virus to enter target cells, while other receptors can only serve to facilitate HIV transmission (6) (7).

2.3. Epidemiology of HIV/AIDS

2.3.1. Incidence

According to the World Health Organization, there were 37.7 milion people living with HIV by the end of 2020, of whom 19.3 million were women (8). In Romania, in december 2021, of the 17.271 people living with HIV, 6655 were women (9).

2.3.1. Transmission

Sexual Transmission: factors that increase the risk of heterosexual HIV transmission include: high VL-HIV or advanced stage of HIV infection of the infected partner, acute HIV infection, genital lesions, bleeding and trauma during intercourse, other sexually transmitted infections (10).

Parenteral transmission: by intravenous drug use, contaminated blood transfusion, organ and tissue transplantation, contaminated syringes, needles, non-sterile medical devices (11).

Mother-to-child transmission may occur antenatal, during labor or delivery, or postpartum by breast-feeding (12); this can be prevented by performing prenatal screening, using ART in pregnant women, and post-exposure prophylaxis of the newborn, scheduled cesarean section, and infant formula feeding (13).

2.4. Clinical manifestations of HIV infection

1. **Acute retroviral syndrome:** it is the first stage of the infection and develops as early as 2 to 4 weeks after infection (14) (15).
2. **Asymptomatic infection:** may last 8 years (15).
3. **Symptomatic infection:** the early stage is characterized by the persistance of enlarged lymph nodes. As VL-HIV increases and the number of CD4 cells decreases, the risk of opportunistic infections, malignancies, cachexia, neurological complications and death increases substantially (16).

2.5. Diagnosis of HIV infection

Laboratory diagnosis is performed by serological and virological tests.

1. Detection of HIV RNA in serum – using polymerase chain reaction (PCR) (17) (18).
2. p24 antigen – using enzyme immunoassay (ELISA) (19).
3. Viral culture
4. Detection anti-HIV antibodies – using ELISA. Two ELISA tests and one confirmatory test are required to confirm HIV infection (15).

2.6. Treatment of HIV infection

ART has dramatically reduced the morbidity and mortality associated with HIV infection. ART should be introduced regardless of the number of CD4 + T cells and the level of HIV viremia (20). A genotypic resistance test should be performed before the initiation of ART, at the time of diagnosis or before the introduction of ART (21). Adherence to ART involves the correct participation of patients in the treatment plan, and creating a collaboration between doctor and patient (22).

2.7. HIV infection in pregnant women and management of newborns with perinatal HIV exposure

The rate of mother-to-child transmission of HIV in the absence of complete prophylaxis measures is between 15% and 45% (23). Prenatal screening is of great importance for the diagnosis of HIV infection (24).

ART should be initiated as soon as a pregnant woman is diagnosed with HIV infection or the pregnancy is confirmed in an HIV-positive woman, who is not being treated. Scheduled cesarean section for week 38 is recommended for pregnant women with VL-HIV> 1000 copies / ml. They are given intravenous Zidovuine 3 hours before the scheduled cesarean section, in addition to the oral treatment (3).

ART should be continued postpartum. Breastfeeding is not recommended for women living with HIV (25) (26).

All newborns perinatally exposed to HIV must receive prophylactic ART within 6 to 12 hours of birth (27). It is necessary to determine VL-HIV by PCR in the first 2 days of life, at 2 weeks, 2 months and 4-6 months. ELISA and Western Blot tests are indicated in newborns at 12 months, 18 months (27).

Seroreverted children are those who become seronegative between 6-18 months of age (4).

3. OWN CONTRIBUTIONS

3.1. Working hypothesis and general objectives

HIV infection is still associated with increased maternal-fetal morbidity, and a high rate of perinatal transmission of the infection in the absence of prevention strategies in the prenatal period, birth and postpartum period (28) .

The study aims to determine the rate of mother-to-child transmission of HIV infection among pregnant women living with HIV registered in CRC, to identify some correlations between certain risk factors and maternal-fetal transmission of HIV infection, to establish the correlation between the mother's adherence to ART and the serological status of the newborn to highlight the importance of ART in reducing the risk of mother-to-child transmission of HIV and to identify the characteristics of children perinatally exposed to HIV and to make a comparison of characteristics of HIV-infected and HIV-uninfected infants.

I considered useful to approach this subject because an effective care strategy of pregnant women living with HIV can reduce the risk of mother-to-child transmission of HIV and can improve the maternal prognosis.

3.2. Research methodology

3.2.1. Material and method

The study was performed between 1 January 2008 and 31 December 2020 and included pregnant women diagnosed with HIV infection before pregnancy,

during pregnancy and intrapartum, recorded in the CRC, as well as their newborns.

We collected data using medical records and electronic database. For statistical data analysis, we used Microsoft Excel, EPI 2000 software packages. For descriptive statistics we used Microsoft Excel, measuring the central tendency and dispersion parameters such as: median, mean, standard deviation, modal value. For the univariate analysis we used statistical tests such as Fisher, Chi^2, Cramer, Mann-Whitney, t-Student. For statistical correlations, we used Pearson correlation coefficient r (significance threshold $p < 0.05$). The obtained results were synthesized in tables and figures.

3.3. Results

Substudy I - aimed to determine the mother-to-child transmission rate of HIV and to identify the correlations between it and certain risk factors among pregnant women with known HIV status, compared to those diagnosed with HIV infection during pregnancy and birth.

The study group included 182 pregnant women and it was divided into two other groups, depending on the time of diagnosis of HIV infection: group A, which included 159 pregnant women with known HIV status and group B, which included 23 pregnant women diagnosed with HIV infection during pregnancy and at delivery.

From the data analysis, we found that mother-to-child transmission rate was 6.04% in the general group, higher in group B. For pregnant women to whom all prophylaxis measures were applied, the maternal-fetal transmission rate was of 2.8%. The incidence of mother-to-child transmission of HIV was 2.3%.

The mean age of the patients at the time of diagnosis was 16.69 ± 7.58 years old, and at birth it was 25.33 ± 4.6 years old, in the general group. Most patients (71.62%) were parenterally infected with HIV.

The immunological evaluation during pregnancy showed a moderate degree of immunodepression in the general group, and the mean VL-HIV in the third trimester of pregnancy was 2.60 ± 1.20 $\log_{10}$ copies / ml, with a statistically significant difference between the two groups ($p < 0.00001$). We found a statistically significant difference between the two groups regarding the clinical and immunological classification for HIV infection at birth: 75.5% of patients belonging to group A vs 26% patients from group B, were in the AIDS stage ($p < 0.00001$). The proportion of women who gave birth by caesarean section was significantly higher in group A compared to group B ($p = 0.000336$).

Mother-to-child transmission of HIV was correlated with the absence of screening for HIV infection among pregnant women, low adherence to ART during pregnancy, and detectable VL-HIV. The factors associated with non-adherence to ART were low educational level, poor socioeconomic status, and the presence of ART side effects.

Substudy II - focused on identifying the characteristics of newborns perinatally exposed to HIV and making a comparison between HIV-infected and uninfected newborns.

The study group included 182 newborns and it was divided into two other subgroups: subgroup P, which included 11 HIV-infected newborns, and subgroup N, which included 171 uninfected newborns.

The proportion of premature infants was higher among those vertically infected with HIV (63.64% vs 18.13%), and the average birth weight was significantly different between the two subgroups, lower among HIV-positive infants ($p = 0.0408$).

Length at birth and head circumference below the 10th percentile were found in similar percentages within the two subgroups. Preterm delivery and low birth weight were associated with mother-to-child transmission of HIV infection. Low maternal CD4 count and preterm birth were associated with low birth weight.

All uninfected newborns and 10 infected newborns received prophylactic ART for 6 weeks. Perinatal infections occured in 48 newborns, being significantly more common in subgroup P, as compared to subgroup N ($p = 0.0012$). The proportion of infants who were breastfed was higher in the subgroup P ($p = 0.0001$).

4. DISCUSSIONS

Pregnancy in women living with HIV remains a challenge, and requires a multidisciplinary team in order to ensure adequate care.

A number of studies have shown that the risk of mother-to-child transmission of HIV can be reduced by applying all prophylactic measures (29) (30).

In the current study, the mother-to-child transmission rate of HIV was 6.04%. Approximately 50% of women who transmitted the infection to their children were diagnosed at delivery due to the absence of prenatal screening and the late diagnosis. This led to a lack of ART, which is one of the main determinants of perinatal HIV transmission.

Adherence to ART plays an important role in preventing mother-to-child transmission of HIV. In this study, perinatal HIV transmission was associated with poor adherence to ART and detectable HIV viremia during pregnancy, similar to data from two other studies perforrmed in our center (22) (31).

Factors that may influence the adherence to ART have been described in the literature, some of them being evaluated in the study we conducted. We identified a correlation between non-adherence to ART and the following factors: low educational level, poor socioeconomic status and the presence of ART adverse effects, these factors being found in another study conducted at CRC, between 2014 and 2019(22). Good adherence to ART is associated with undetectable VL-HIV, like we saw in the first substudy.

In the second substudy, the proportion of premature infants and those with low birth weight was higher among those vertically infected with HIV. Preterm birth and low maternal CD4 count (<200 cells / mm^3) were associated with low birth weight, similar to data from other studies (32).

Early diagnosis of HIV infection during pregnancy and good adherence to ART are the main factors in preventing mother-to-child transmission of HIV infection.

5. CONCLUSIONS

- The rate of mother-to-child transmission of HIV was high in the studied period (6.04%) due to the incomplete application of prophylactic measures.
- Mother-to-child transmission of HIV was correlated with the absence of screening for HIV infection among pregnant women, low adherence to ART during pregnancy, and detectable HIV viremia.
- The main factors associated with non-adherence to ART were low educational level, poor socioeconomic status, and the presence of ART side effects.
- The correlation between the level of adherence to ART and VL-HIV was statistically significant (p Chi^2<0.0001).

- Preterm birth and low birth weight were associated with mother-to-child transmission of HIV infection.
- Perinatal infections were significantly more common in HIV-infected infants, as compared to HIV-uninfected infants.
- Breastfeeding was identified as a possible risk factor for perinatal HIV transmission.
- The results of this study showed that there were deficiencies in the care and monitoring of pregnant women living with HIV, despite the national strategy to prevent mother-to-child transmission of HIV.

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