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The obstetrical management of HIV-positive pregnancy

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The obstetrical management of HIV-positive pregnancy

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ABSTRACT



The human immunodeficiency virus (HIV) infection is a real public health problem in both developing and developed countries. HIV infection has not been treated efficiently for a long time, with HIV-positive women at increased risk of transmitting the infection to their newborns. Without the appropriate treatment, the evolution of the infection is relatively fast. Due to the antiretroviral treatment, the progression of the disease is blocked during the period of asymptomatic infection, and the risk of neonatal transmission is very low. HIV-positive patients undergoing antiretroviral therapy develop undetectable viremia and, in such situations, patients no longer have a risk of transmitting the infection. The antiretroviral medication is a combination of several classes of drugs (protease inhibitors, nucleoside and non-nucleoside reverse transcriptase inhibitors, integrase inhibitors and CCR5 inhibitors) whose aim is to stop the viral replication at different stages. The infection is most often transmitted in the perinatal period, so it is very important that we know the maternal viremia and choose the type of birth with the lowest risk of transmitting the infection to the fetus. For this reason, any HIV-positive patient with detectable viremia at childbirth should receive treatment during labor and delivery, with a nucleoside or non-nucleoside reverse transcriptase inhibitor that crosses the fetal-placental barrier.

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Introduction

HIV (human immunodeficiency virus) is a single-stranded RNA virus that infects CD4-positive T lymphocytes (dendritic cells) through CCR5 and CXCR4 cell membrane receptors. In human DNA, there may be mutations (heterozygous or homozygous delta 32 mutation) that cause the deletion of the CCR5 receptor, thus giving the human body resistance to infection, especially in the case of the homozygous mutation. The most common route of infection is through unprotected sexual intercourse with an HIV-positive person with detectable viremia [1-4].

The virus can be detected 2 days after the infection in the vaginal mucosa or gastrointestinal tract, and within 5-30 days after the infection, the patient's viremia can be determined. As the virus replicates inside CD4-positive cells, the viremia increases exponentially and peaks with seroconversion [5,6]. After the onset of the specific immune response to HIV, the value of viremia expressed

in logarithmic form decreases by 2.3 logarithms until it stabilizes at 6 months after the infection [7].

During the acute retroviral syndrome, symptoms vary widely from asymptomatic to aseptic meningitis or encephalitis. The most common symptoms are fever, myalgia, arthralgia and lymphadenopathy [8,9].

Maternal-fetal transmission is one of the world's public health problems. In the absence of antiretroviral treatment, the risk of transmission is 15-45% and it depends on several factors (breastfeeding, the delivery route, the mother's immune status and maternal viremia). The transmission of the infection occurs through the passage of virions into the maternal plasma and breast milk, so that 90% of the positive newborns became infected in the perinatal period [10].

Discussion

Before giving birth, all patients should be tested for HIV through an antibody-HIV1/2 test. In case of a positive result, another ELISA test must be performed to test for

anti-HIV1/2 antibodies, and if the result is also positive, a Western-Blot or Immuno-Blot confirmation test will be performed. If the confirmatory test is positive, the next step is to perform the viremia, the number of positive CD4 cells and the antiretroviral resistance profile. If any of the three tests is negative, the result is considered negative and the testing process is stopped. Patients may have a false negative result, up to the time of seroconversion, when antibodies appear (it can take between 6 weeks and 12 months). The treatment should be initiated immediately after diagnosis [11,12].

Patients diagnosed with HIV need to start the antiretroviral therapy (ART) regardless of the value of CD4-positive T lymphocytes or the stage of the infection to reduce the risk of neonatal transmission, targeting virology success (undetectable viremia) and immunological success (higher positive CD4 T lymphocytes) of 250 cells/ mm³ [13,14].

A study by Hoffman showed that the early initiation of antiretroviral therapy was associated with decreased rates of neonatal infection. The study was performed on a group of 1,142 HIV-positive pregnant patients in South Africa, and vertical transmission was 0.7% among patients receiving ART therapy, compared to 5.7% for patients without therapy [15-18].

Tenofovir, Lamivudine (or Emtricitabine) and Dolutegravir are recommended as first-line treatments in adults and adolescents [19,20]. An observational study from Botswana conducted by Zash R & co. demonstrated that there is an association between the treatment with Dolutegravir and neural tube defects [21]. However, the risk of intrauterine death, small for age and premature birth did not have an increased incidence in people treated with Dolutegravir [22,23]. An alternative to this treatment is Tenofovir, Lamivudine or Emtricitabine and Efavirenz [19,20].

A randomized study by Fowler, which included 4,000 HIV-positive pregnant patients with a CD4-positive T cell level above 350/ microL, compared therapies containing two protease inhibitors (Zidovudine, Lamivudine and Lopinavir-Ritonavir or Tenofovir, Emtricitabine) and Lopinavir-Ritonavir) with single-dose administration of Zidovudine and Nevirapine in combination with nucleoside reverse transcriptase inhibitor therapy. The rate of neonatal transmission was shown to be significantly lower in patients receiving two protease inhibitors (0.5% vs. 1.8%) [24].

Treatment resistance is another public health problem. Most resistant strains undergo genomic mutations, so they acquire resistance to non-nucleoside reverse transcriptase inhibitors and nucleoside reverse transcriptase inhibitors [25-27]. This resistance is also transmitted to the newborn, especially in cases of low adherence to the treatment [19,20]. There are several studies that have shown an

increased risk of premature birth or small for age after the ART treatment, but these also occur as a result of untreated HIV infection, to which the neonatal complications are added [28-30].

The choice of birth method depends on maternal viremia. If the patient has a viremia of fewer than 1,000 copies/ ml of blood and is undergoing ART therapy, the incidence of HIV transmission is low, regardless of the route of delivery and it is independent from the time of ruptured membranes, no caesarean section being required to reduce the risk of transmitting the HIV infection [31-36]. The meta-analysis conducted by Kennedy CE & co. which included HIV-positive patients treated with antiretroviral who underwent elective cesarean section at 38 weeks of amenorrhea, did not show a decreased risk of transmitting the infection to the fetus compared to patients who gave birth vaginally [37,38].

In patients with viremia greater than 1,000 copies/ ml, at 34 weeks of amenorrhea, it is recommended to extract the fetus by cesarean section at 38 weeks, before the onset of labor or before the spontaneous rupture of the membranes. This category includes patients without antiretroviral therapy, patients diagnosed with HIV infections during pregnancy, patients with acute retroviral syndrome and patients infected with a strain resistant to antiretroviral therapy [39,40]. In these situations, the caesarean section reduced the risk of vertical transmission of the infection to the fetus. This conclusion is also supported by the meta-analysis performed by the Lancet which included 15 cohort studies performed before the existence of ART therapy and which revealed that the neonatal infection rate was 8.4% in the case of cesarean section extraction, while at children born vaginally the infection rate was 16.5%. The risk was reduced by administering Zidovudine to HIV-positive patients in an advanced stage of infection [41,42].

If an HIV-positive patient presents to the emergency room with spontaneously ruptured membranes or advanced labor, we must consider the duration of time since the rupture of the membranes occurred, the stage of labor, the ART treatment received by the patient, as well as viremia. Depending on all these factors, the delivery route will be decided upon. If the patient has had spontaneously ruptured membranes for more than 4 hours or has advanced labor, the benefit of cesarean delivery no longer exists [43-45].

Patients who received ART therapy during pregnancy should continue medication during both labor and delivery. In addition to classical patient therapy, Zidovudine intrapartum can also be administered. The decision depends on the patient's viremia at 4 weeks antepartum. The loading dose is 2 mg/ kilo, followed by the maintenance dose of 1mg/ kilo/ hour until birth. Zidovudine is administered to HIV-positive patients with undetectable viremia (<50 copies/ ml) at 4 weeks

antepartum. In this situation, the risk of transmission is low, and the delivery route is chosen according to the obstetrical indications; the patient will follow the recommended ART therapy, and the newborn will receive post-exposure prophylactic treatment with Zidovudine for 4 weeks [39,46,47].

If the mother's viremia varies between 50 and 1,000 copies/ ml, there is an increased risk of transmitting the infection to the fetus, the delivery route being chosen by the obstetrician according to the obstetrical indications. The mother will continue the ART therapy prescribed by her infectious disease physician, to which Zidovudine may be added and good care should be taken in order to avoid the artificial rupture of the membranes and instrumentally assisted vaginal birth (by forceps). The newborn receives treatment for HIV, according to the treatment plan for chronic HIV infection. If the mother has a viremia greater than 1,000 copies/ ml, the risk of neonatal transmission is very high, and the birth is performed by scheduled cesarean section at 38 weeks of amenorrhea. The ART therapy is continued, to which the therapy with Zidovudine is added, and the newborn receives the classical treatment plan for HIV infection [19,20].

For patients who are not receiving the ART treatment, who have poor adherence to the treatment, increased viremia or are diagnosed during labor or are in the period of acute retroviral syndrome, the risk of vertical transmission of the infection to the fetus is very high. The delivery route depends on presentation and viremia. They should continue the ART therapy if it is already started and Zidovudine is given additionally. There should be no artificial rupture of the membranes or instrumental vaginal birth [48]. The children of these patients will receive post-exposure prophylactic treatment containing a combination of 3 antiretroviral: Zidovudine, Lamivudine, Nevirapine or Raltegravir for 6 weeks [39].

Zidovudine crosses the fetal-placental barrier rapidly and provides pre-exposure to HIV prophylaxis to the newborn, and postpartum administration for 6 weeks reduces the risk of infection by 66% [49,50]. Routine administration is not recommended in patients with viremia lower than 400 copies/ ml as it has been shown not to influence the risk of maternal-fetal transmission [46].

If the mother goes to the hospital with spontaneously ruptured membranes earlier than 37 weeks of amenorrhea, the birth route is chosen according to the obstetrical indications. Corticosteroids are recommended for fetal lung maturation, thus reducing the risk of respiratory distress syndrome in the newborn [45-47].

Neonatal prophylaxis is recommended for all newborns of HIV-positive mothers. The right moment for its initiation is in the first 6-12 hours of life, depending on the maternal viremia [46]. In case of neonatal toxicity with Zidovudine, Abacavir may be administered as an alternative after negative testing of HLA B5701 [39].

If the fetus is diagnosed with HIV, treatment is given throughout pregnancy. Viremia is tested after birth, and if it is undetectable, Lamivudine and Nevirapine can be stopped in case of a three-dose therapy. An alternative is to stop Lamivudine and Raltegravir, followed by two weeks of Zidovudine for a period of 6 weeks [38-40].

A study by Wong VV et al. analyzed the rate of vertical intrapartum transmission in newborns from mothers with acute retroviral syndrome. The study group includes patients who did not receive treatment or did not adhere to the treatment. This cohort was subdivided into three categories. The first group received treatment with Zidovudine alone for six weeks, and the transmission rate was 4.8%. The second subgroup consists of patients receiving triple antiretroviral therapy for 8 days with Lamivudine, Raltegravir and Zidovudine for six weeks, with a consecutive transmission rate of 2.2%. The latter group received triple antiretroviral therapy for two weeks with Nelfinavir, Lamivudine and Zidovudine. The first two medicines were given for two weeks and Zidovudine for six weeks, with a vertical transmission rate of 2.4% [47]. The most common side effect is neutropenia, which is common in case of triple therapy. Raltegravir is available in a neonatal form (syrup) and it has doses suitable for newborns. It is associated with a longer duration of viral suppression and has a lower toxicity than non-nucleoside reverse transcriptase inhibitors, Efavirenz [48].

In the postpartum period, patients will continue the antiretroviral therapy according to the plan, regardless of the clinical status and the CD4 count, with the goal of reducing the risk of disease progression and preventing sexual transmission [51-53].

The meta-analysis conducted by Nachega JB et al. studied the adherence to the postpartum treatment and showed that adherence decreased from 80% to 53% during breastfeeding [54].

Breastfeeding is not recommended because virions are released in breast milk, and this also applies to patients receiving antiretroviral therapy [55].

Conclusions

Viremia dosing in HIV-positive patients is required four weeks antepartum in order to determine the route of delivery.

In HIV-positive pregnant women with viremia lower than 50 copies/ ml, the route of delivery is determined by the obstetrical indications. Patients with viremia between 50-1,000 copies/ ml may give birth vaginally if Zidovudine is given during labor and if there is no other maternal or fetal cause to counteract this. If patients have a viremia higher than 1,000 copies/ ml, poor adherence to the treatment, they do not receive the ART treatment or are in acute retroviral syndrome, birth is performed by scheduled cesarean section at 38 weeks of amenorrhea.

Protease inhibitor therapy is more effective compared to nucleoside or non-nucleoside reverse transcriptase inhibitors. The risk of vertical transmission is lower if the newborn is given triple antiretroviral therapy.

Breast-feeding is contraindicated for HIV-positive patients, whether they are receiving antiretroviral therapy or not.

Conflict of interest disclosure

There are no known conflicts of interest in the publication of this article. The manuscript was read and approved by all authors.

Compliance with ethical standards

Any aspect of the work covered in this manuscript has been conducted with the ethical approval of all relevant bodies and that such approvals are acknowledged within the manuscript.

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