

HIV AND AIDS IN PREGNANCY

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The problem of HIV infection in pregnancy should be considered through the prevention, detection, appropriate therapy and follow-up. Prevention and detection involve cooperation between the services of preventive medicine and counseling and gynecological services. The follow-up and the delivery of HIV-positive pregnant women is made according to strict protocols and requires the cooperation of gynecologist and infectious disease specialist, as well as the expectant mother. *Acta Medica Medianae* 2016;55(3):85-91.

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Introduction

Among women with human immunodeficiency virus (HIV) infection, pregnancy is the time when maintenance of maternal health and reduction of vertical HIV transmission are primary concerns. Few studies have examined adherence to antiretroviral treatment (ART) during pregnancy and in the postpartum period when the demands of childcare may significantly interfere with women's self-care behaviors (1).

Increasing rates of HIV infection in women worldwide, especially among those of childbearing age, reinforce the importance of understanding the management of HIV in pregnancy. Over the past decade, significant advances have been made in the prevention of vertical HIV transmission, including the use of single and combination antiretroviral therapy, elective caesarean section as

the preferred mode of delivery and the elimination of breast feeding (2).

Epidemiology

HIV incidence during pregnancy is four times higher than in non-pregnant population reported in a recent survey. Public health programs need to continue to reinforce prevention strategies and HIV retesting during pregnancy (3).

Epidemiological situation in Serbia

In spite of all measures undertaken, the number of pregnant women tested for HIV in Serbia remains unsatisfactory - less than 10% on an annual level. Some of the reasons given for this are: insufficient cooperation of gynaecological services with institutes for health protection; insufficient education of medical personnel; insufficient supply of institutions with test kits; insufficient education and low motivation of pregnant women; insufficient media promotion. Annually in Serbia, aside from all the undertaken measures, on average one HIV positive child is born to women not covered by testing as part of the comprehensive preventive programme. The chief goals of the National HIV-AIDS Strategy in Serbia is lowering to zero the transmission of HIV infection from mother to child so that by 2015 a maximum of 5% positive children should be born to HIV positive mothers, as well as increasing the number of advised and tested pregnant women (4).

Epidemiological situation in the world

The reduction in mother-to-child transmission of HIV is regarded as one of the most effective public health initiatives in the United States. In the absence of treatment, the risk of

vertical transmission of HIV is as high as 25-30%. With the implementation of HIV testing, counseling, antiretroviral medication, delivery by cesarean section prior to onset of labor, and discouraging breastfeeding, the mother-to-infant transmission has decreased to less than 2% in the United States (5).

The exact mechanism of mother-to-child transmission of HIV remains unknown. Transmission may occur during intrauterine life, delivery, or breastfeeding. The greatest risk factor for vertical transmission is thought to be advanced maternal disease, likely due to a high maternal HIV viral load (6).

More than 500,000 babies worldwide contract HIV from their mothers; 90% of these cases occur in developing countries. In 2005, AIDS claimed an estimated 2.4-3.3 million lives; more than 500,000 of which were children. One third of these deaths were in sub-Saharan Africa (7).

Pregnancy planning in women infected with HIV

The risk of sexual transmission must be considered even in the presence of an undetectable viral load. Conducting testing and considering reproductive techniques in women infected with HIV may be worthwhile in an effort to reduce the risk of infection to a healthy partner. In couples planning a pregnancy where only the male partner is infected, natural conception carries a risk of sexual transmission to the uninfected female. While antiretroviral therapy can reduce viral load in the blood to undetectable levels, some reports have shown that men can still have a substantial viral concentration in semen in the presence of an undetectable plasma viral load. When possible, confirmation of undetectable seminal plasma viral load may be considered. If HIV viral load cannot be suppressed, semen washing has been proposed and may decrease the HIV RNA and DNA to undetectable levels. After processing and rechecking for residual contamination, the spermatozoa can be used for intrauterine insemination or in vitro fertilization. Pregnancy does not appear to influence the progression of HIV disease and the survival of women infected with HIV (8-11).

For serodiscordant couples who want to conceive, the use of ART is recommended for the HIV-infected partner, with the strength of the recommendation differing based on the CD4-cell count of the infected partner. Additionally, NIH guidelines include discussion regarding pre-exposure prophylaxis (PrEP) studies in heterosexual couples (12-14).

Education of pregnant women infected with HIV

The Center for Disease Control and Prevention (CDC) recommends routine third-trimester screening in women with high-risk behaviors or

who exhibit signs or symptoms of the disease (15).

Stressing the importance of taking their medication regularly to decrease the possibility of the development of antiretroviral drug resistance may encourage women to comply with therapy. Cigarette smoking, concurrent use of drugs (cocaine, heroin), and unprotected intercourse have been associated with increased risk of perinatal transmission (16).

Even in the absence of antepartum treatment, intrapartum and early neonatal prophylaxis can reduce the mother-to-child transmission risk. Women should be extensively counseled regarding the ability to decrease the risk of perinatal transmission with highly active antiretroviral therapy (HAART) prophylaxis or treatment. In women who are being treated with HAART and planning pregnancy, the teratogenic potential of certain antiretroviral medications must be reviewed and effective contraception discussed. These medications should be stopped prior to planning a pregnancy (16).

Medical analyses in pregnant women infected with HIV

In pregnancy, the initial history should assess the status of the patient's HIV disease (eg, CD4+ T-cell count, viral load), the need for the beginning or altering antiretroviral medication, and ways to reduce perinatal transmission. A careful review of the medical and surgical history, gynecologic history, high-risk habits, and previous obstetric history should be done at the first prenatal visit (17).

The American Congress of Obstetrics and Gynecology (ACOG) recommends routine HIV screening for women aged 19-64 years and targeted screening for at-risk women outside of this age reference. All pregnant women should have their HIV serostatus evaluated when they first present for prenatal care (17).

For pregnant women infected with HIV, in addition to the standard prenatal assessment, continued assessment of HIV status is important. A complete blood count to assess anemia and white blood cell count as well as renal and liver function tests should be included. Initial evaluation includes CD4+ counts, which help determine the degree of immunodeficiency (6, 8).

Viral load, determined by plasma HIV RNA copy number (copies/mL) assesses the risk of disease progression. The viral load is important in decisions regarding maternal treatment and delivery management; however, because perinatal HIV transmission can occur even at low or undetectable HIV RNA copy numbers, the viral load is not used in pregnancy to decide whether to start antiretroviral medications. If viral load is detected, antiretroviral drug resistance studies (HIV genotype) should be performed before starting therapy unless the diagnosis is made late in pregnancy, in which case starting medications

while awaiting results is recommended. In general, pregnancy is not been associated with a risk of rapid progression of HIV (11). With appropriate therapy, the viral load should drop by 1 log within the first month and become non-detectable within 6 months after initiating treatment. The higher the viral load, the longer the decrease may take; however, if the viral load persists or increases at 6 months, treatment failure must be considered (6, 8).

Other laboratory studies should include a lipid profile, which is not usually obtained in pregnancy. Although cholesterol normally increases in pregnancy, the baseline values are required, as certain medications have been associated with increased triglyceride and cholesterol levels. Evaluation of other infectious disease states and possible opportunistic infections, such as syphilis, cytomegalovirus, and toxoplasmosis, also needs to be done (6, 8).

Initial obstetric ultrasonography for viability and dating is important for determining treatment and planning delivery. Potential teratogenicity is highest during the first trimester, and some patients may consider delaying treatment until after the first 12 weeks of pregnancy. A targeted ultrasonography may be warranted depending on medication exposure (6, 8).

Further analyses include opportunistic infection assessment, testing for other sexually transmitted diseases, testing for hepatitis B and hepatitis C (18, 19).

Antiretroviral therapy

Treatment during pregnancy

Mother-to-child transmission is linked to viral load. As such, antiretroviral therapy should be offered to all pregnant women infected with HIV to reduce the risk of perinatal transmission to below 2% (20). A combination antiretroviral therapy should be offered in all cases. As zidovudine (ZDV) is the only agent specifically shown to reduce perinatal transmission, it should be used whenever possible as part of the HAART regimen (21).

If a patient who is on a HAART regimen presents for prenatal care, continuing her treatment during the first trimester is reasonable, provided that care is taken to avoid medications that are contraindicated in early pregnancy. HIV antiretroviral drug resistance testing is recommended if a viral load is detectable. Considerations of drugs not usually used early in pregnancy may be necessary if drug resistance is confirmed and the patient receives extensive counseling regarding risk and benefits (15).

In an HIV-infected pregnant woman who has never been exposed to antiretroviral medication, HAART should be started as soon as possible, including the period of the first trimester. Again, recommendations are for drug-resistance testing and care to avoid medications that may

potentially cause adverse maternal and fetal effects (15).

If prenatal HIV testing was not performed and a rapid HIV test returns preliminarily positive, the patient should be treated like any other woman infected with HIV. Certainly, the gestational age and obstetrical scenario may dictate the treatment options available, but as the exposure risk to antiretroviral medication is minimal to both mother and fetus, antiretroviral therapy should be initiated (15).

The patient with a positive rapid test must be counseled regarding the possibility of a false-positive screen, and the results should be documented as preliminary in the medical chart. If this test was performed on arrival in labor, treatment with the ZDV protocol through labor is recommended, followed by administration to the neonate until confirmatory testing on the mother becomes available (15).

The mechanism of action with which these drugs reduce perinatal transmission includes lowering maternal viral load; however, as these drugs cross the placenta, there appears to be prenatal prophylaxis as well. The third component, prophylaxis of the newborn, further decreases the risk of perinatal transmission (12).

The antiretroviral drugs used in pregnancy fall broadly into three categories: the nucleoside and nucleotide analogue reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), and protease inhibitors (PIs). There are insufficient data to allow recommendations regarding the use of entry inhibitors or integrase inhibitors in pregnancy (12).

Combination regimens, usually including 2 NRTIs with either an NNRTI or 1 or more protease inhibitors (PIs) are recommended. NRTIs shown to be preferred for use during pregnancy are: ZDV and lamivudine (3TC). Alternate drugs are abacavir, emtricitabine and tenofovir. Nevirapine is a NNRTI preferably used during pregnancy. Atazanavir, a combination of lopinavir and ritonavir, and ritonavir are PIs preferred for use during pregnancy. Alternate PIs are darunavir and saquinavir. ZDV plus 3TC is a recommended dual-NRTI backbone regimen plus an NNRTI and 1 or more PIs for pregnant women with HIV (5, 8, 12).

Concern was raised that antiretroviral therapy may increase the incidence of adverse pregnancy outcomes. Several studies have shown that zidovudine monotherapy had no negative effect on pregnancy (22). The overall rate of adverse pregnancy outcome, including prematurity, low birth weight, stillbirth, and abnormal Apgar scores, was similar in women who received antiretroviral therapy during pregnancy and those who did not (23, 24).

Peripartum treatment

In any pregnant woman infected with HIV who presents in labor, whether her HIV-positive status was previously known or was determined by rapid test result, more than one treatment option is available during labor and delivery. All HIV-infected women with HIV RNA ≥ 400 copies/mL (or unknown HIV RNA) near delivery should be administered ZDV during labor, regardless of antepartum regimen or mode of delivery. IV ZDV is no longer required for HIV-infected women receiving combination ART regimens who have HIV RNA < 400 copies/mL near delivery (12).

If the patient is having a planned cesarean delivery, the IV infusion should begin three hours before the procedure (8, 20, 25). Another option is ZDV infusion followed by a single dose of 200 mg of nevirapine. This regimen should be followed by 3TC 150 mg every 12 hours. If the latter regimen is used in pregnancy, the patient must continue ZDV/3TC (Combivir) for at least 7 days postpartum to avoid nevirapine resistance (8). Women with documented drug resistance to ZDV or whose antepartum regimen did not include ZDV should still be given the intravenous ZDV protocol during labor and delivery or before cesarean delivery (8, 25). Furthermore, the other antiretroviral agents must be continued on schedule throughout the intrapartum or preoperative period. Stavudine is the only agent that can antagonize ZDV and should be stopped prior to the IV infusion of ZDV (20).

In patients attempting a vaginal delivery, all invasive procedures such as amniotomy, internal fetal scalp electrode, or scalp sampling should be avoided, as these may increase the risk of transmission (8).

When HAART is given solely for prevention of perinatal HIV transmission, it may be stopped in the postpartum period. The risk of promoting the development of resistant viral strains by using short courses of HAART can be decreased by using a maximally suppressive regimen and discontinuing all agents at the same time. The exception remains if the regimen includes a NRTI. The NRTI should be continued for an additional 7 days to decrease the risk of resistance (8).

Cesarean delivery before the onset of labor may prevent microtransfusion that occurs with uterine contractions, and avoiding vaginal delivery eliminates exposure to virus in the cervicovaginal secretions and blood at time of delivery (26, 27). The transmission risk was decreased by about 80% for women who had both an elective cesarean delivery and were taking antiretroviral medication (28). These studies did not adjust for viral load and were performed before HAART came into use. In patients on HAART with an undetectable viral load ($< 1,000$ copies), the risk of transmission is very low, and whether cesarean delivery offers any further benefit remains unknown. This led to an updated ACOG statement in 2000, stating that women infected with HIV whose viral loads are greater than 1,000 copies/mL

should be counseled regarding the potential benefit of scheduled cesarean delivery to further reduce the risk of vertical transmission of HIV beyond that achieved with antiretroviral therapy alone. However, data are insufficient to demonstrate a benefit for neonates of women with viral loads less than 1,000 copies/mL (25).

Longer duration of ruptured membranes may be associated with a higher rate of mother-to-child transmission. The International Perinatal HIV group meta-analysis found that the risk of vertical transmission increased by 2% for every increase of 1 hour in the duration of ruptured membranes. If cesarean delivery is performed after the onset of labor or rupture of membranes, the benefit of surgery may be lost. In this scenario, a decision regarding the route of delivery should be individualized (25, 28).

Operative risk may outweigh the potential benefit of further reducing HIV transmission. In a study by Louis *et al.* that compared the outcome of cesarean section in 378 women infected with HIV and in more than 54,000 uninfected women, HIV-infected women had a higher rate of intraoperative need for blood transfusion as well as increased incidence of postpartum endometritis, sepsis, pneumonia, admission to the intensive care unit, and maternal death (29).

In the HIV-infected group, morbidity and mortality were associated with infection and related to immune function, with the greatest risk being for women with a CD4 count less than 200 cells/mL (29).

Because morbidity is increased in women infected with HIV who undergo cesarean delivery, prophylactic antibiotics should be administered. Scheduled cesarean delivery should be discussed and recommended for women with viral loads greater than 1000 copies/mL, whether or not they are taking antiretroviral therapy (28).

Discussion of the option of scheduled cesarean delivery should begin as early as possible in pregnancy with every pregnant woman infected with HIV, to give her an adequate opportunity to consider the choice and plan for the procedure. The risks, which appear to be greater for the mother, must be balanced with the benefits expected for the neonate. The patient's autonomy must be respected when making the decision to perform a cesarean delivery, because the potential for maternal morbidity is significant (28).

Prophylaxis of HIV-exposed infants

All HIV-exposed infants should receive ZDV as prophylaxis as soon after delivery as possible and continue through age of six weeks. Additional prophylaxis with nevirapine is needed for HIV-exposed infants of women who did not receive antepartum ART (3 doses in the first week of life) (12).

Breastfeeding

In areas of the world where safe alternatives are available, breastfeeding is not recommended. This also applies to women on antiretroviral therapy. Passage of antiretrovirals into breast milk has been shown for several agents, including zidovudine and lamivudine (12).

Conclusion

Testing for HIV infection should become a routine analysis in prenatal diagnostics, since some countries of the developed world even require that all pregnant women or their newborns

should be tested. Treatment begun during pregnancy can prevent the disease in the child and improve the mother's health as well.

Counseling services are an important component of National AIDS Control Program which aims at creating awareness and promoting changes in reducing high risk behavior against HIV/AIDS. There should be cooperation between the HIV&AIDS counseling services and pregnancy counseling services of community health centers in our country in order to spread information about the importance of antenatal HIV screening.

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HIV I AIDS U TRUDNOĆI

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Problem HIV infekcije u trudnoći treba sagledati kroz prevenciju, otkrivanje i adekvatnu terapiju i praćenje stanja. Prevencija i otkrivanje podrazumevaju saradnju ginekoloških službi i službi preventivne medicine i savetovališta za trudnice. Praćenje statusa i porođaj HIV pozitivne trudnice vrši se po strogo određenim protokolima i zahteva saradnju ginekologa i infektologa, kao i trudnice. Pomenuti protokoli smanjuju, rizik vertikalne transmisije HIV infekcije smanjen je sa 25-30% na manje od 2%. *Acta Medica Medianae 2016;55(3):85-91.*

Ključne reči: HIV infekcija, trudnoća, vertikalna transmisija

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