Evaluation of Perinatal and Postnatal Outcomes of Delivery Type, Delivery Period and Follow-up Labor in HIV Positive Pregnancies from the Perspective of Fetal Infection

HIV Positive Pregnancies: An Epidemiological and Clinical Perspective

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Results: Fifteen infants’ (60% male, 40% female) mothers were diagnosed in 2 (13.3%) before pregnancy, 7 (46.7%) of the mothers during pregnancy, and 6 (40%) of the mothers during delivery. It was ascertained that eight mothers (53.3%) received antiretroviral treatment during pregnancy and 2 (13.3%) mothers delivered by normal spontaneous vaginal route. Zidovudine prophylaxis was started in one of the babies born with a normal spontaneous vaginal route, and the HIV virus load was still negative after eight weeks of prophylaxis and the prophylaxis was discontinued, the other baby was taken by the mother without permission. Premature membrane rupture was detected in three (20%) pregnant women, and the longest labor time was 16 hours. Eleven (73.3%) pregnant women received intravenous zidovudine therapy and 13 (86.6%) babies received antiretroviral prophylaxis. The viral load of the others was negative except one of the 11 babies whose HIV viral load was examined. The patient with a positive HIV viral load (300,000 copies/mL) was born by cesarean at 38 weeks of gestation and her mother was diagnosed during delivery and triple antiretroviral prophylaxis (zidovudine, lamivudine, nevirapine) was started on to baby.

Conclusion: Although HIV prevalence is not high in Turkey, the number of cases has been increasing over the years. Perinatal transmission of the HIV virus from mother to baby can be reduced by measures to be taken before, during and after birth. In particular, it should be ensured that HIV infection is not diagnosed late or missed during pregnancy, and HIV-infected pregnant women should be followed up by centers which specialize in HIV.

Keywords: Human immunodeficiency virus, perinatal transmission, HIV-contacted baby

Introduction

Although human immunodeficiency virus (HIV) infection emerged in the 1970s for the first time in Central Africa, its clinical picture could be identified in the 1980s. Perinatal transmission from the infected pregnant woman to the baby was recognized in 1982 (1). As of the end of 2018, there are over 37.9 million individuals in the world infected with HIV (2). The number of children aged under 15 years infected with HIV is 1.7 million (4.4%). Along with reducing perinatal HIV transmission with increasing treatment options for HIV transmission from the mother to the baby, HIV prevalence is increasing in adolescents older than 15 years and young adults (2).

In our country, there are 20,202 HIV (+) individuals reported by detecting HIV confirmation test positive, and there are also 1786 cases of acquired immunodeficiency syndrome (AIDS) from 1985 until June 30th, 2019 (3). Considering the number of individuals infected by HIV on yearly basis, there is a progressive increase in the number of individuals infected with HIV (3). Women in the reproductive age group comprise 14.8% and children under the age of 19 comprise 3.3% of the individuals infected with HIV. Twenty-five point eight percent of the children aged under 19 years infected with HIV have been infected due to perinatal transmission from mother to baby (3). In line with these data, it can be said that HIV infection is a serious health problem in our country and should not be assessed as a rarely seen condition.

HIV remains a global health problem with an estimated 32 million deaths until today (4). HIV has turned into a chronic disease with the increase in rates of prevention, diagnosis and care, and many HIV positive women wish for pregnancies (5).
Health Institution of Turkey. Mothers whose confirmation tests and/or HIV RNA values were determined positive were included into the study. Time of HIV diagnosis of the mothers, antiretroviral treatment during pregnancy and the drugs given, delivery type, gestation week, history of early membrane rupture (EMR), labor period, and intravenous zidovudine administration during delivery were recorded. The sex of the baby, antiretroviral prophylaxis and duration and HIV viral load during delivery were examined. Presence of neural tube defect had been evaluated by ultrasonography prenatally or antenatally.

Data analyses were performed on SPSS 24.0 (IBM Corporation, Armonk, NY, USA). Continuous data were expressed as mean ± standard deviation for normal distributions and as median (minimum-maximum) for conditions that did not fit normal distribution. For categorical data, number (n) and percentages (%) were used.

**Limitations of the Study**

Limitations of our study are as follows: its retrospective nature, small number of patients, HIV viral load could not be evaluated in all babies born from a HIV positive mother, and pregnant women received different treatment during their pregnancies or were left untreated.

**Results**

It was determined that a total of 15 deliveries took place from 13 HIV positive women during the course of ten years in our hospital. Mean age of the pregnant women was 27 ± 7.5 years. HIV diagnosis was made before pregnancy in 2 (13.3%), during pregnancy in 7 (46.7%) and during delivery in 6 (40%) cases. Four (57%) of the cases were diagnosed during pregnancy. It was seen that 2 (15.4%) of the pregnant women diagnosed during delivery had negative Anti-HIV values in the second trimester. Eleven (84.6%) pregnant women who did not have any Anti-HIV result were tested prior to the time of diagnosis. Antiretroviral treatment was used in 8 pregnancies (57.1%), and 11 pregnant women (73.3%) received intravenous zidovudine prophylaxis during delivery. Pregnant women who were administered with intrapartum zidovudine prophylaxis had C/S, and zidovudine prophylaxis was given through i.v infusion at a loading dosage of 2 mg/kg during delivery and at a 1 mg/kg/h dosage until the umbilical cord was clamped. Two pregnant women (13.3%) were determined to have given birth through normal spontaneous vaginal route (NSVG). While history of EMR was detected in three (20%) pregnancies, the longest labor period was determined as 16 hours (Table 1). EMR duration was 12 hours in 2 out of 3 pregnant women and 6 hours in the other.

**Table 1. Clinical and laboratory characteristics of the mothers infected with HIV**

| Age of pregnancy (year) | n (%) |
|-------------------------|-------|
| 20-35                   | 12 (80) |
| > 35                    | 3 (20) |

| Time of HIV diagnosis | n (%) |
|-----------------------|-------|
| Before pregnancy      | 2 (13.3) |
| During pregnancy      | 7 (46.7) |
| During delivery       | 6 (40) |

| Type of delivery | n (%) |
|-----------------|-------|
| NSVR            | 2 (13.3) |
| C-section       | 13 (86.7) |

| Early membrane rupture | n (%) |
|------------------------|-------|
| Yes                    | 3 (20) |
| No                     | 12 (80) |

| Antiretroviral treatment (ART) during pregnancy | n (%) |
|------------------------------------------------|-------|
| Yes                                             | 8 (57.1) |
| No                                              | 7 (42.9) |

| ART inception | n (%) |
|---------------|-------|
| Before conception | 2 (25) |
| First or second trimester (< 28 weeks) | 6 (75) |

| Intrapartum prophylaxis | n (%) |
|-------------------------|-------|
| None                    | 4 (26.7) |
| Intravenous zidovudine  | 11 (73.3) |

| HIV-1 RNA at the period closest to delivery | n (%) |
|--------------------------------------------|-------|
| <1000 copies/mL                            | 6 (75) |
| ≥ 1000 copies/mL                           | 2 (25) |

| CD4 lymphocyte count at the period closest to delivery | n (%) |
|-------------------------------------------------------|-------|
| < 500 cell/mm³                                        | 4 (50) |
| ≥ 500 cell/mm³                                        | 4 (50) |

NSVR: Normal spontaneous vaginal route.
Nine (60%) of the babies born from HIV infected mothers were males and 6 (40%) were females. Two (13.3%) babies were born prematurely. Median birth gestation week of the babies was 38 weeks and 2 days (min: 34 weeks 4/7 days, max: 40 weeks). Thirteen babies (86.6%) received antiretroviral prophylaxis (Table 2). Prophylaxis started in the first 6 hours of 53.9% of the babies receiving antiretroviral prophylaxis.

Mother of one of the babies born with normal spontaneous vaginal route had received diagnosis during delivery, and EMR ongoing for 12 hours had been detected during presentation to hospital but could not be administered with intranatal zidovudine treatment since delivery occurred shortly after presentation. Postnatally, the baby was started on zidovudine prophylaxis, and prophylaxis was terminated during follow-up upon determining that HIV viral load was still negative after 8-week prophylaxis, and the other baby was taken by the mother without permission. Therefore, viral load could not be tested in the babies of the mothers who delivered with normal spontaneous vaginal route.

One of the three patients with early membrane rupture delivered with normal spontaneous vaginal route. HIV viral load was confirmed negative in two of the babies whose mothers had EMR. The other pregnant woman was a foreign national, diagnosed during delivery, had a C-section but HIV load could not be tested for the baby postnatally.

When evaluated for labor durations, two pregnant women had a 12-hour long labor and one had a 16-hour long labor. HIV viral load was negative in the babies of three patients with prolonged labor.

Out of the 11 babies (73.3%) who were tested for HIV viral load, all but one had negative viral load. While first HIV RNA levels of the babies with negative HIV viral load were tested within 72 hours postpartum in 7 (63.6%) of the babies, the viral load was tested on postpartum day 9 in 2 (18.1%) and when the baby was 3-month-old in 1 (0.9%). The case with a positive HIV viral load (300.000 copies/mL) on postnatal day 2 was born with a C-section in the 38th gestation week, and while the mother’s Anti-HIV was found negative in the 6th month, it was found positive during delivery. While the mother received intravenous zidovudine prophylaxis during delivery, the baby was started on a triple (zidovudine, lamivudine, nevirapine) antiretroviral prophylaxis. During follow-up, the patient whose viral load decreased under prophylaxis was accepted as pediatric HIV and was followed with triple treatment according to guideline recommendations (8) in the first month.

### Discussion

Perinatal transmission of HIV from the mother to the baby can be reduced by taking precautions prenatally, intranatally and postnatally. While vertical HIV infection transmission is 12-40% in mothers who has never received treatment, it is possible to lower this rate below 1% if necessary precautions are taken (9-11). There are international and national monitoring and treatment programs. Strategies to stop HIV epidemic in 2030 have been set up by the United Nations HIV/AIDS (UNAIDS) program (12). An HIV/AIDS control program covering the years 2019-2024 is available from the General Directorate of Public Health, Ministry of Health, Turkey to fight with HIV/AIDS (13). One of the most important steps of this program is the continuity of surveillance studies. Considering the literature from our country, there are no other studies on perinatal HIV except for the studies and case reports by Sütçü M. et al. and İnkaya A. et al. (14,15). As a center for pediatric HIV, we wished to publish our data of 10 years and emphasize the necessity of surveillance studies consisting multicenter pediatric HIV centers on the matter.

Today, thanks to increasing treatment options on HIV infection and prolonged survival, HIV positive women who are in their reproductive age show an increasing wish to have babies (5,15). In a systemic review on pregnancy wishes and related factors of HIV positive women, pregnancy wish has been detected as 23%-58% in high income societies, whereas, in low-income societies, the rate been diagnosed before pregnancy in our study were diagnosed during their first pregnancy and had their second children form their planned second pregnancies.

In our study, HIV diagnosis was made in 6 (40%) of the pregnant women during delivery. Four (66.6%) of these pregnant women were not followed regularly for their pregnancies. One of the two pregnant women diagnosed during delivery was followed regularly. Anti-HIV test of the regularly followed pregnant woman was negative in the sixth month of her pregnancy, but her Anti-HIV test done prior to delivery

| Table 2. Clinical and laboratory characteristics of the babies in contact with HIV |
|---------------------------------|-------------|----------|
| Sex                             | n (%)       |
| Female                          | 6 (40)      |
| Male                            | 9 (60)      |
| Gestational age                 |             |
| Preterm (<37 weeks)             | 2 (13.3)    |
| Term (≥37 weeks)                | 13 (86.7)   |
| ARV prophylaxis                 |             |
| Yes                             | 13 (86.6)   |
| No                              | 2 (13.4)    |
| ARV prophylaxis starting time   |             |
| < 6 h                           | 7 (53.9)    |
| ≥ 6 h                           | 6 (46.1)    |
| HIV recent status               |             |
| Infected                        | 1 (6.7)     |
| Not infected                    | 10 (66.7)   |
| Unknown                         | 4 (26.6)    |
| ARV: Antiretroviral             |             |
was positive and confirmed as positive. HIV viral load of the pregnant woman detected at birth was 20,000,000 copies/ml, she had a C-section, did not have a history of EMR, and received intrapartum zidovudine treatment. Since it is known that combination treatment is effective in preventing intrapartum HIV infection in babies with HIV positive mothers who did not receive antiretroviral treatment during pregnancy (17,18), the baby was started on triple antiretroviral prophylaxis. Triple prophylaxis was continued in the baby whose HIV RNA was 300,000 copies/ml postnatally. The case whose control HIV viral load was detected positive is still followed by our clinic with the diagnosis of pediatric HIV. It was seen in our study that the rate of pregnant women diagnosed at delivery was 40%, and the rate of those who could not receive antiretroviral treatment during their pregnancies was 46.7%. In the literature, this rate has been reported as 23.2% in the study by Indarti J. et al. conducted in Endonesia, one of the countries where HIV is endemic (18). Our rates were found rather high when compared to the study by Sütçü M. et al. in our country. We believe that this situation is caused by the high rate of pregnant women who were not regularly followed (57.1%).

Decreasing the number of pregnant women who are diagnosed during delivery and therefore go into labor with high HIV viral load for not having received antiretroviral treatment during the early phase of pregnancy is vital in the prevention of perinatal HIV transmission (19). Center for Disease Control and Prevention (CDC) and the American Obstetrics and Gynecology (ACOG) recommend HIV scanning in the early phase of pregnancy and to be repeated in the last trimester if the woman is in the risky group (20,21). We are of the opinion that ensuring that HIV serology is tested at the beginning of the first and last trimester by all centers following pregnancies and using rapid diagnostic tests for unfoled pregnant women who arrive with being in labor will significantly decrease HIV transmission from the mother to the baby (22). Despite detecting Anti-HIV negative in the second trimester of the mother of our case diagnosed with pediatric HIV, confirming a positive result prior to delivery underlines the importance of repeating Anti-HIV test in high-risk pregnant women.

History of EMR was present in three pregnant women in our study. One of these pregnant women was diagnosed with HIV at the 36th gestation week, developed 12-hour long EMR four days after diagnosis and premature delivery occurred with emergency C-section. The desired viral suppression could not be achieved since there was a short period of time between diagnosis and delivery, and the pregnant woman went into delivery with a high viral load (726,000 copies/mL). Another pregnant woman with a 12-hour long EMR was diagnosed during delivery, presented to the hospital with being in labor and gave birth through normal spontaneous vaginal route. Both babies were started on antiretroviral prophylaxis within the first 2 hours postnatally, and HIV RNA of the babies tested at birth and follow-up was found negative. A 3-hour EMR history was present in the last pregnant woman with EMR, she was diagnosed during delivery, and an emergency C-section had to be performed. The woman left the hospital without permission after delivery, and HIV RNA could not be tested for the baby. In a meta-analysis investigating the effect of EMR presence and duration on HIV transmission from mother to the baby, it has been reported that there is a 2% hourly increase in the rate of HIV transmission with EMR duration in women who do not receive antiretroviral treatment during pregnancy or in those who just receive oral zidovudine.(23)

In our study, vertical transmission of HIV in 2 (66.6%) of the pregnant women with EMR did not occur; however, since we are unaware of the other baby’s HIV status, a comment could not be made in relation to EMR duration and HIV.

When evaluated in terms of delivery type, 2 (13.3%, 2/15) of the 13 HIV positive pregnant women who gave birth in our hospital delivered their babies through normal spontaneous vaginal route. Both of these patients were diagnosed during delivery. Postnatally, HIV RNA was detected negative in one baby, but since the pregnant woman left the hospital after delivery, HIV RNA could not be tested in her baby. Therefore, we do not know the rate of HIV in women giving birth with normal spontaneous vaginal route. C/S rate was 86% in our study and was found high when compared to literature data (24,25). Eight (61.5%) of the mothers of 13 babies (86.7%) born with C/S had received antiretroviral treatment during their pregnancies, postnatal HIV RNA was tested in 10 (76.9%) and HIV RNA was tested positive in 1 baby (10%). It is known that planned C-section delivery reduces the vertical transmission of HIV at a rate of 50% compared to the normal spontaneous vaginal route in pregnant women who have not received antiretroviral treatment during pregnancy (26,27). There are studies reporting that normal spontaneous vaginal route does not constitute an increase in the risk of HIV transmission as regards planned C-section in pregnant women who have received effective antiretrovirals during their pregnancy and ensured viral suppression (28,29). Moreover, in the Cochrane evaluation of six studies carried out on women with HIV in the literature, it has been concluded that emergency C-section, planned C-section and normal delivery are related to high, moderate and low risk for postnatal morbidity, respectively (30). Therefore, ACOG does not routinely recommend planned C-section performed to only prevent perinatal HIV transmission when considering the low perinatal transmission rate in this group where women have received antiretroviral treatment during pregnancy and have HIV RNA below 1.000 copies/mL (31). Again, in this group, it has been reported that EMR duration is not associated with the increase in perinatal transmission risk and that it does not the necessity of absolute C-section to prevent HIV transmission (31).
In the babies of HIV infected mothers giving birth in our hospital, the rate of being infected with HIV was 9% (1/11). Again, in two studies conducted in our country, HIV transmission rate from mother to baby has been found at varying rates of 6.2% and 8.3% (14,15). In surveillance studies conducted in high income countries like the UK and Spain, transmission rates have gradually decreased and fell to the level of 0.4% (11,32). However, this rate is 9% in countries with limited sources and particularly HIV endemic countries of Eastern and Southern Africa (33). According to June 2019 data of the Ministry of Health of Turkey, the rate in our country is 0.8% (3). Compared to this rate, that the rate in our hospital was detected quite high could be due to the fact that the number of pregnant women unfollowed was high and there were 4 babies whose HIV statuses were unknown. In a research conducted by UNAIDS in 2013, HIV test which is routine in pregnancy is not performed in 54% of pregnant woman in low- and moderate-income countries (34). We are of the opinion that perinatal HIV transmission will be significantly reduced in our country with at least two Ante-HIV tests performed during pregnancy, early detection of cases, antiretroviral treatment given to HIV positive mother during pregnancy, going into labor with low or negative viral load, and starting antiretroviral prophylaxis in the early period.

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