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Perinatal outcomes of 14 HIV-positive pregnant women followed up in a tertiary center in Turkey

Türkiye'de üçüncü basamak bir merkezde takip edilen 14 HIV pozitif gebe kadının perinatal sonuçları

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ABSTRACT

Aim: To evaluate theperinatal outcomes of 14 HIV (humanimmunodeficiency virus) positive pregnant women followed up in a tertiary center.

Materials and Methods: This is a retrospective cohort study conducted in Ankara Bilkent City Hospital perinatology clinic. All pregnant women who were followed up with a diagnosis of HIV positive between 2020 and 2023 were included in the study. Demographic characteristics of pregnant women, time of diagnosis, antiretroviral treatment received in the prenatal and intrapartum period, antiretroviral treatment received by infants and duration, and vertical transmission rate were evaluated.

Results: A total of 14 HIV-positive pregnant women were included in the study. Two cases (14.28%) were in the first trimester, one case (7.14%) was in the second trimester, 10 cases (71.42%) were in the third trimester, and one case (7.14%) was in the 10th postpartum day at first admission to hospital. Nine (64.3%) of the patients had regular hospital follow-ups with regular tests and treatment. While 5 (35.7%) did not attend regular follow-ups and did not receive regular treatment. The mean CD4+ count was 611±243 cell/mm^3 and the CD8+ count was 852±366 cell/mm^3. The mean CD4/CD8 ratio was 0.94±0.74. The maternal HIV plasma RNA copy numberwas not checked in one patient, the result was negative in 5 patients and was positive in the remaining 8 patients. The median HIV RNA was 471 (range 0-106559) copy/mL. Since the infants were born at different times, they were divided into 2 groups: 0-18 months and 18-40 months. All babies were regularly followed up by a pediatrician and an infectious disease specialist. All infants were given standard treatment with lamivudine/zidovudine and raltegravir. IV positivity was not detected in any of the babies in the controls performed after 18 months.

Conclusion: In conclusion, maternal HIV infection is associated with favorable outcomes if managed appropriately by a multidisciplinary team.

Keywords: HIV, humanimmunodeficiency virus, perinatal outcome, vertical transmission

ÖZ

Amaç: Üçüncü basamak bir merkezde takip edilen 14 HIV (insan immün yetmezlik virüsü) pozitif gebe kadının perinatal sonuçlarını değerlendirmek.

Gereç ve Yöntemler:: Bu, Ankara Bilkent Şehir Hastanesi perinatoloji kliniğinde yürütülen retrospektif bir kohort çalışması olupçalışmaya 2020-2023 yılları arasında HIV pozitif tanısıyla takip edilen tüm gebeler dahil edildi. Çalışmaya 2020-2023 yılları arasında HIV pozitif tanısıyla takip edilen tüm gebeler dahil edildi. Gebelerin demografik özellikleri, tanı zamanı, prenatal ve intrapartum dönemde aldıkları antiretroviral tedavi, bebeklere aldıkları antiretroviral tedavi ve süreleri, vertikal bulaşma oranları değerlendirildi.

Bulgular: Çalışmaya toplam 14 HIV pozitif gebe dahil edildi. Olguların 2'si (%14,28) birinci trimesterde, bir olgu (%7,14) ikinci trimesterde, 10 olgu (%71,42) üçüncü trimesterde ve bir olgu (%7,14) postpartum 10. günde idi. Hastalardan dokuzunun (%64,3) düzenli hastane takipleri ve düzenli tetkik ve tedavileri vardı. 5'i (%35,7) düzenli kontrollere gelmemiş ve düzenli tedavi görmemişti. Ortalama CD4+ sayısı 611±243 hücre/mm^3, CD8+ sayısı ise 852±366 hücre/mm^3 idi. Ortalama CD4/CD8 oranı 0,94±0,74 idi. Bir hastada annenin HIV plazma RNA kopya numarasına bakılmadı, 5 hastada sonuç negatif, 8 hastada ise pozitif çıktı. Medyan HIV RNA'sı 471 (aralık 0-106559) kopya/mL idi. Bebekler farklı zamanlarda doğdukları için 0-18 ay ve 18-40 ay olmak üzere 2 gruba ayrıldılar. Bebeklerin tamamı çocuk doktoru ve enfeksiyon hastalıkları uzmanı tarafından düzenli olarak takip edildi. Tüm bebeklere lamivudin/zidovudin ve raltegravir ile standart tedavi verildi. 18 ay sonra yapılan kontrollerde bebeklerin hiçbirinde HIV pozitifliğine rastlanmadı.

Sonuç: Sonuç olarak, annede HIV enfeksiyonu multidisipliner bir ekip tarafından uygun şekilde yönetildiğinde olumlu sonuçlarla ilişkili olduğu gözlenmiştir.

Anahtar Kelimeler: HIV, insan immün yetmezlik virüsü, perinatal sonuçlar, vertikal bulaşma

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INTRODUCTION

HIV is an RNA virus that could cause Acquired immunodeficiency syndrome (AIDS) in humans and is an important cause of mortality in some parts of the world in the last decades. The prevalence of HIV infection is 0,7 percent worldwide, but incidence varies and increasing in some countries (1).

The majority of adults who are infected with HIV are at reproductive ages and that makes this topic an important issue in the pregnant population. The pregnant population is special because of the changed immunity in that period, the role of perinatal transmission, and unique treatment regimens in pregnancy.

Perinatal HIV transmission can occur in utero, intrapartum, or during breastfeeding. In utero transmission accounts for 5%-10% of all perinatal transmissions (2). In utero transmission occurs by tranplacental or by ascending infection through the vagina. The main route of perinatal HIV transmission is intrapartum(3). Intrapartum transmission occurs through contact of infant mucous membranes with maternal blood or infected cervicovaginal secretions. There is increasing evidence in studies that maternal-fetal microtransfusions, which develop after disruption of the placental barrier, which can be seen from the early weeks of pregnancy, are frequent and recurrent conditions in pregnancy (4). The probability of HIV infection in breastfeeding women not receiving HAART (highly active antiretroviral therapy) is between 10-15% (5). With the use of retroviral drugs, the risk of transmission has decreased to 2%. Amniocentesis, chorionic villus sampling, use of vacuum or forceps, and use of fetal scalp electrodes in pregnant women not taking retroviral drugs are associated with an increased risk of perinatal transmission.

Maternal HIVRNA load is very important in maternal transmission, especially for values below 100 copies, the risk of transmission is low (6).

The management of HIV-positive pregnant women has improved in the last 3 decades with advances in drug development and prevention of vertical transmission. With the administration of antiretroviral drugs in developed societies such as the United States and Europe, mother-to-child transmission has fallen to its lowest level in history (7). The goal of using antiretroviral therapy (ART) during pregnancy is to reduce vertical transmission and treat maternal HIV disease (8). All HIV-positive pregnant women, regardless of CD4 cell count or plasma HIV viral load, should receive ART therapy to treat maternal infection and to prevent mother-to-child transmission. Antiretroviral therapy during the three phases (antepartum, intrapartum, and postpartum) is superior to intrapartum therapy alone and combination therapy is more effective than a single-drug regimen in reducing HIV transmission (9, 10). ART should be started before pregnancy or in the first trimester to prevent vertical transmission(11). Some mothers may want to postpone ART until after the first trimester is completed due to concerns about teratogenic effects, but delaying treatment, especially after the 28th week, leads to increased vertical transmission (12).

Treatment of infants should begin immediately after birth, ideally between 6 and 12 hours. The treatment regimen should be decided based on the treatment the mother received before birth, maternal viral load, and the baby's nutrition.

In our study, we aimed to evaluate the perinatal outcomes of HIV-positive Turkish pregnant women and HIV-positive immigrants who may have difficulty in reaching health institutions and treatment, to determine the current situation and to contribute to developing methods that will try to minimize vertical transmission by making projections for the future.

MATERIALS AND METHODS

This retrospective cohort study was conducted on all HIV consecutive cases who were followed up and delivered in the perinatology clinic of Ankara Bilkent City Hospital between January 2020 and December 2023. The study protocol was approved by the ethics committee with the reference number E2-23-5901 and all participants gave written consent.

Maternal age, gravida, parity, gestational age at first admission to hospital, duration of HIV positivity, antiretroviral treatment use, treatment regimen, treatment compliance, and continuity, smoking or drug use, complete blood count, renal function tests, liver function tests: presence and type of hepatitis, latent tuberculosis, history of amniocentesis or CVS, HIV RNA viral load, CD4 countduring pregnancy, OGTT result, HIV genotype resistance studies (If RNA copy count is above 500-1000), HLA-B5701 testing, the time between membrane rupture and birth, gestational age at birth, birth weight, route of delivery, 1 and 5 minute Apgar scores, admission to neonatal intensive care unit (NICU), intrapartum maternal viral load, intrapartum maternal retroviral therapy, accompanying disease, retroviral treatment received by the neonate,follow-up period of babies, mother's continuity of treatment were reported.

The patients were followed and treated by a multidisciplinary team consisting of a perinatologist, neonatologist, infectious disease specialist, pediatric infection specialist, and anesthesiologist.

The statistical analysis was performed by SPSS 22 (IBM Corp., NY). Kolmogrov-Smirnov test was used to assess whether the data is normally distributed. Mean and standard deviation values were used for normally distributed continuous variables. Whereas, median and range values were used to present continuous variables without normal distribution. Categorical variables were presented as numbers and percentages.

RESULTS

A total of 14HIV-positive pregnant women were included in the study. Prenatal demographic characteristics of HIV-positive pregnant women are summarized in Table 1. Sevenof the patients were Turkish citizens and the remaining 7 were immigrants. Fiveof the immigrants were from the break-up of the former Union of Soviet Socialist Republics and 2 were from Africa. Four of the immigrants were under regular medical check-ups, and three of them were not being followed up. The mean maternal age was 29.4±5.5 years. The median gravidity was 2 (range 1-4) and the median parity was 2 (range 0-3). The median time from the time of first diagnosis to the present was 4 (range 2-6) years. Four of the patients were smokers, and one of them had also used drugs in the past. Fivepatients were not given any hepatitis markers, the tests performed in the remaining 9 patients, results were negative in 8 patients, while 1 patient was found to be a Hepatitis B carrier. Twelveof the patients did not have an HPV DNA test, one of the 2 patients who had the test was negative, and the positive patient had multiple condylomas in the vulva and vagina.Latent tuberculosis was present in one patient. None of the patients underwent invasive diagnostic tests (amniocentesis, chorionic villus sampling).

Two cases (14.28%) were in the first trimester, one case (7.14%) was in the second trimester, 10 cases(71.42%) were in the third trimester, and one case (7.14%) was in the 10th postpartum day at first admission to hospital. Nine (64.3%) of the patients had regular hospital follow-ups and regular tests and treatment, while 5 (35.7%) did not attend regular follow-ups and did not receive

Table 1. Prenatal demographic characteristics of HIV-positive pregnant women (n=14)

Ethnicity	**Turkish**	**7(50%)**
	İmmigrants	**7(50%)**
First diagnosis time (years ago)		4 (range 2-6)
Maternal age		29.4±5.5
Gravidity		2 (range 1-4)
Parity		2 (range 0-3)
Smoking/drug abuse		4/1
Tuberculosis status		1
HPV DNA status	Not Tested	12
	Positive	1
	Negative	1
Hepatitis status	Not Tested	5
	Negative	8
	Positive	1
First admission	First trimester	2
	Second trimester	1
	Third trimester	10
	Postoperative	1
Regular follow-up visits and regular treatment intake	Yes	9 (64.3%)
	No	5 (35.7%)
CD4+ count		611±243
CD8+ count		852±366
CD4/CD8		0.94±0.74
Maternal HIV plasma RNA copies	Negative	5
	Positive	8
	Not Tested	1
WBC		8950±1030
AST / ALT		15.7±5.6 / 21.4±10.3
Urea / Creatinine		21.7±6.6 / 0..52±0.007

HIV: human immunodeficiency virus, HPV: Human papillomavirus, DNA: deoxyribonucleic acıd, RNA: Ribonucleic acid, WBC: white blood cell, AST: aspartate aminotransferase, ALT: alanine aminotransferase CD: cluster of differentiation

Table 2. Comparison of demographic and clinical characteristics of Turks and immigrants

Variables	Turkish (n=7)	Immigrants (n=7)	p
Age	28.71±2.19	29.0±1.09	0.74
Gravidity	2 (range 1-4)	2 (range 1-3)	0.63
Parity	2 (range 0-3)	1 (range 0-2)	0.37
ALT	20.14±2.52	31.5±8.77	0.31
AST	15±1.23	29.83±14	0.77
WBC	8.67±0.47	8.67±1.07	0.66
First diagnosis time (years ago)	4 (range 2-6)	3 (range 1-9)	0.93
First admission (weeks)	25.4±5.2	28.8±5.8	0.93
Urea	19.7±1.7	21±3.9	0.82
Creatinine	0.53±0.02	0.55±0.036	0.66
HIV RNA	12774±8231	21591±21242	0.9
CD8	845.4±180.5	738.5±165.2	0.8
CD4	718.4±85.2	420±86.7	0.1
APGAR 1st Minute	8 (range 7-8)	8 (range 7-8)	0.09
APGAR 5th Minute	9 (range 9-10)	9 (range 8-10)	0.66
Birth week	37.7±0.4	36.8±0.5	0.24
Birth weight (grams)	3095±104	2946±87	0.22

HIV: Human immunodeficiency virus, HPV: Human papillomavirus, DNA: deoxyribonucleic acıd, RNA: Ribonucleic acid, WBC: white blood cell, AST: aspartate aminotransferase, ALT: alanine aminotransferase CD: cluster of differentiation

regular treatment. The mean white blood cellcount (WBC) value at initial hospital admission was 8950±1030. The mean value of liver function tests at initial presentation was 15.7±5.6 IU/L for AspartateAminotransferase (AST) and 21.4±10.3 IU/L for Alanine Aminotransferase (ALT). The mean CD4+ count was 611±243 and the CD8+ count was 852±366. The mean CD4/CD8 ratio was 0.94±0.74.The maternal HIV plasma RNA copy numberwas not checked in one patient, the result was negative in 5 patients and was positive in the remaining 8 patients. The median HIV RNA was 471 copies/ml (range 0-106559).

Demographic and clinical characteristics of Turks and immigrant citizens were compared and summarized in Table 2. There were no significant differences in age, gravidity, parity, first diagnosis time and time since first diagnosis between the two groups. There were no significant differences between the two groups in terms of hemogram, liver function tests and kidney function test results. No significant difference was found when viral load, CD4 and CD8 counts were compared between the two groups. When the birth week, birth weight and Apgar scores were compared, no significant difference was found between the two groups.

Table 3. Intrapartum and short-term postnatal findings (0-7 days)

Gestational age at birth (weeks)		37.1±1.3
Ruptures of membranes	Yes	3
	No	11
Delivery type	Vaginal birth	1
	Cesarean birth	13
Cesarean section indications	HIV posivitiy, primigravid	6
	HIV positivity, previous cesarean section	7
Birth weight (grams)		2982±301
APGAR 1st minute (mean)		7 (range 7-8)
APGAR 5th minute (mean)		9 (range 8-10)
NICU admission	Yes	6
	No	8
Intrapartum treatment	Retroviral therapy	6
	Effective combined retroviral therapy	8

HIV: human immunodeficiency virus, NICU: neonatal intensive care unit

Table 4. Long-term outcomes of babies born to HIV-positive mothers

0-18 months	5
18-40 months	9
Treatment given	lamivudine/zidovudine and raltegravir
HIV positivity after 18 months	0

Intrapartum and short-term postnatal findings (0-7 days) are summarized in Table 3. At the time of delivery, eight of the pregnant women were already receiving effective combined antiretroviral therapy (ART), while 6 were untreated and antiretroviral therapy was started at that time.The mean gestational age at birth was 37.1±1.3 weeks. Three patients had membrane rupture, membranes were intact in 11 patients. 13 of the patients gave birth by cesarean section, and one by spontaneous vaginal birth.Of the patients who had a cesarean section, 7 of them were performed because they had a previous cesarean section, and 6 of them were performed because it was their first HIV-positive pregnancy. The mean birth weight of the infants was 2982±301 grams.The first-minute median APGAR score was 7 (range 7-8) and the fifth-minute median APGAR score was 9 (range 8-10). Six infants were followed up in the neonatal intensive care unit and 8 infants did not need the neonatal intensive care unit.The reason for follow-up in the intensive care unit was temporary tachypnea of the newborn.

Long-term outcomes of babies born to HIV-positive mothers are summarized in Table 4. Since the infants were born at different times, they were divided into 2 groups: 0-18 months and 18-40 months. All babies were regularly followed up by a pediatrician and an infectious disease specialist. All infants were given standard treatment with lamivudine/zidovudine and raltegravir.HIV positivity was not detected in any of the babies in the controls performed after 18 months.

DISCUSSION

Perinatal outcomes are generally favorable according to the results of the present study, although one-third of the cases had irregular antenatal follow-up. Due to the advances in the field of antiretroviral therapy and increasing knowledge among physicians, the management of pregnant women with HIV is not a nightmare anymore.

In a retrospective study including 258 HIV-positive and 258 HIV-negative pregnant women, maternal and fetal outcomes were compared. Adverse pregnancy outcomes such as anemia, puerperal sepsis, and low birth weight were significantly higher in the HIV-positive group. Cesarean delivery was found to be higher in the HIV-positive group compared to the control group. Preterm delivery rates were found to be higher in the HIV group who did not receive anti-retroviral treatment.The study concluded that HIV-positive status increased adverse outcomes and antiretroviral therapy decreased the risk of preterm labor (13).

In a cohort study involving 249 HIV-positive pregnant women, adverse outcomes were evaluated. The study compared two groups of patients who received HAART treatment from early weeks and patients who did not receive HAART during pregnancy but received nevirapineintrapartum.The rate of preterm delivery, fetal growth restriction, and cesarean delivery was significantly higher in the group not receiving treatment compared to the group receiving treatment.In the untreated group, the frequency of low birth weight (less than 2500 grams), 5th-minuteAPGAR score less than 7, and admission to the neonatal unit were higher. Education level was significantly lower in the group that did not receive treatment. In the study, it was concluded that adverse outcomes may be higher in the group that did not receive treatment, they benefited less from the health system due to low education level and could not benefit from early HAART treatment (14).

In a retrospective case-control study including 62 HIV-positive and 100 HIV-negative pregnant womenpregnancy outcomes were compared.HIV-positive women were found to be younger in age and had lower mean parity than the control group. In addition, the HIV-positive group had higher positive syphilis serology, longer mean duration of labor, perineal tear, puerperal sepsis, and higher mean length of hospital stay, rates of low birth weight, birth asphyxia, neonatal intensive care unit hospitalization were higher in the HIV positive group.However, no significant difference was found between the two groups in terms of recurrent vulvovaginitis, hepatitis B surface antigenemia, stillbirth, congenital anomaly, miscarriage, preterm delivery, mode of delivery, rupture of membranes, and mean time between delivery.In the study, it was concluded that adverse pregnancy outcomes were high in HIV-positive patients who did not receive treatment (15).

In a single-center retrospective study including 105 patients, perinatal outcomeswere evaluated in adolescent HIV-positive pregnancies.In the HIV-positive adolescent group, higher rates of perinatal acquired HIV infection, higher duration of HIV infection, and longer duration of antiretroviral therapy were found. Preterm delivery and low birth weight were higher in adolescent HIV-positive pregnant women compared to healthy pregnant womenthan in adolescent HIV-negative healthy controls. The rates of preeclampsia and preterm labor were similar between HIV-positive and HIV-negative adolescent groups. The study concluded that adolescent

HIV-positive pregnant women were at higher risk of adverse perinatal outcomes compared with HIV-negative adolescent women, but were comparable to adult HIV-positive pregnant women (16).

A retrospective single-center study evaluated the uptake of preventive interventions to prevent transmission from HIV-positivemothers to infants. The study evaluated 542 HIV-positive living mothers and 551 infants born to these mothers. The majority of mothers (95.5%) were receiving antiretroviral therapy before delivery, had a viral copy number less than 1000, and 65% were receiving intrapartum zidovudine. The majority of HIV-exposed infants were in the low-risk group (82.6%) and received postnatal antiretroviral treatment (98.9%). Among low-risk infants, 53.2% were born by cesareans. Among high-risk infants, 84.4% were delivered by cesarean section, 78.1% received intrapartum zidovudine and 62.5% received antiretroviral combination therapy. A section and received intrapartum (62.9%) and postpartum (96.5%) zidovudine treatment. Nineinfants from the high-risk group were infected with HIV (17).

A retrospective single-center study included 138 patients and described the steps to prevent vertical transmission. HIV diagnosis was mostly (73.5%) made during pregnancy and 50.7% of patients had been receiving retroviral therapy for at least 6 months. Seven percent were diagnosed at the time of delivery. Opportunistic infection developed in 10 patients. Five patients had pulmonary tuberculosis, and 3 patients hadoral candidiasis.One patient had CMV infection and one patient had molloscum contagiosum. Unfortunately, data on maternal CD4+ count and viral load were mostly (78% and 84%) unavailable. Thirty patients were examined for CD4+ count; 8 were found to be less than 200, 22 patients were examined for viral load and 6 were found to be more than 400. Seventy-two percent of babies were born with a normal birth weight (2500-3500 grams).Almost all infants received antiretroviral prophylaxis (97.9%) and formula feeding. PCR HIV was analyzed in 16 infants at 6 weeks of age and 13 infants at 6 months of age. There was 1 infant with viral load results >400 copies/ml. Maternal CD4 levelswere not significantly correlated with neonatal virology status. This study concluded that HIV diagnosis is important because starting antiretroviral therapy in the first weeks of pregnancy is important in preventing vertical transmission(18).

Meticulous follow-up, strict compliance with antiretroviral therapy, providing emotional support for the mother, a multidisciplinary approach, and appropriate management of labor are the key steps in achieving favorable outcomes in pregnancies complicated with HIV. Thus, pregnant women with HIV should be followed up in tertiary reference centers with a high level of experience. Although formerly regarded as a deadly disease in the past decades, promising advances in pharmacy therapy have increased life expectancy and quality of life in patients living with HIV. Moreover, antiretroviral therapy and proper management of labor have substantially decreased vertical transmission of HIV in pregnant individuals. For this reason, obstetricians may encourage pregnancy in women with HIV positivity. However, physicians should be cautious about the higher risk of obstetric complications. Additionally, HIV positivity is reported to be higher in handicapped populations like immigrants, sex workers, drug users, and minorities. This situation brings together other risk factors like sexually transmitted diseases, poor nutrition, partner violence, social isolation, opportunistic infections, and low compliance with antiretroviral therapy. Thus, management of pregnant women with HIV is a challenging issue and a comprehensive clinical protocol should be formed by health authorities.

The main strength of the present study is the relatively high number of parameters. Single-center experience and a low number of participants are the main limitations.

In conclusion, maternal HIV infection is associated with favorable outcomes if managed appropriately by a multidisciplinary team.

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