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ORIGINAL ARTICLE

Pregnancy Outcomes in HIV-Infected Women: Experience from a Tertiary Care Center in India

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ABSTRACT

Background and Objectives: There is conflicting data on the effect of HIV infection as well as antiretroviral therapy (ART) on pregnancy outcome. The objectives of this study were to compare pregnancy outcomes in women with and without HIV infection, and to evaluate the effect of HAART on pregnancy in HIV-infected women.

Methods: This is a prospective case record analysis of 212 HIV-infected women delivering between 2002 and 2015, in a tertiary health care center in India. The pregnancy outcome in HIV-infected women was compared to 238 HIV-uninfected controls. Women received ART for prevention of mother to child transmission as per protocol which varied during the period of study. Effect of use of ART on preterm birth (PTB) and intrauterine growth restriction (IUGR) was analyzed.

Results: HIV-infected women were more likely to have PTB, IUGR, and anemia (9.4%, 9.9%, 5.2%) compared to uninfected women (7.6%, 5%, 3.8%), this did not reach statistical significance (P-value = >0.05). The incidence of PIH, diabetes mellitus and intrahepatic cholestasis of pregnancy was similar in both groups. Mean birth weight was significantly lower in neonates of HIV-infected women (2593.60±499g) than HIV-uninfected women (2919±459g) [P-value=0.001]. neonatal intensive care unit admissions were also significantly higher in infants born to HIV-infected women (P-value=0.002). HIV-infected women on ART had decreased incidence of PTB and IUGR.

Conclusion and Global Health Implications: Good antenatal care and multidisciplinary team approach can optimize pregnancy outcomes in HIV-infected women.

Key words: Human Immunodeficiency Virus • Preterm Birth • Intrauterine Growth Restriction • Antiretroviral Therapy

1. Introduction

Perinatal transmission of human immunodeficiency virus (HIV) infection occurs in the absence of any interventions. The benefits of antiretroviral treatment (ART) in decreasing mother to child transmission (MTCT) of HIV infection are largely undisputed.[1]

Current practice has adopted the use of highly active antiretroviral therapy (HAART) in an attempt to suppress viral load below detection, to minimize MTCT of HIV. In India, the program for Prevention of Mother to Child Transmission (PMTCT) of HIV was launched in the year 2002. With effect from 2014, India adopted the World Health Organization (WHO) instigated Option B+ for prevention of MTCT of HIV.[1] There are now two concerns in HIV-infected women becoming pregnant: The effect of HIV infection on pregnancy and the effect of HAART on pregnancy outcome. The published literature shows conflicting results on this.[2-6] The objective of this study was to compare pregnancy outcome in women with and without HIV infection. Since we are using HAART to prevent MTCT from 2010 onwards, also to evaluate the effect of HAART on pregnancy in HIV-infected women.

2. Methodology

The data used in this study was prospectively collected from a single unit in the department of Obstetrics & Gynecology at All India Institute of Medical Sciences, New Delhi, India. The PMTCT program was started in 2002. The HIV-infected women who delivered in this program included those diagnosed infected on routine antenatal screening as well as women referred after being diagnosed with HIV infection. Approval from Institute's Ethical committee was obtained to use this data for analysis and publication. Two hundred twelve HIV-infected women delivered between 2002 and 2015 were included in the study. Women undergoing medical termination of pregnancy/abortion were excluded. All women were linked to the ART center and were looked after in consultation with HIV physician. On registering in antenatal care, they underwent antenatal investigations as per routine practice, CD4 counts and screened for other sexually transmitted infections. Glucose tolerance test with 75 grams was done for all women at 24-26 weeks of gestation to screen for gestational diabetes. A CD4 count was repeated every 3 months. Women on ART were also monitored for drug toxicity.

The type of antiretroviral (ARV) prophylaxis women received for prevention of perinatal transmission depended on the time period of the study. From 2002-2006 women received either single dose nevirapine (sdNVP) intrapartum or sdNVP tailed with 7 days of zidovudine and lamivudine (ZDV± 3TC) and the newborn was given sdNVP 2 mg/kg. In years 2007-2010 women were advised ZDV 300 mg BD from 28 weeks gestation. Due to financial constraints, women opted for ZDV+3TC from 28 weeks onwards that they received free from ART clinic as ZDV alone was not available in ART clinic. Newborns received sdNVP or ZDV 2 mg/kg for 7 days. Following the new WHO guidelines, from 2010, women are receiving triple-drug ART (Tenofovir 300 mg+Lamivudine 300 mg +Efavirenz 600 mg) for MTCT. The Government of India rolled out WHO B+ from 2014.

Women were counseled about the benefits and risks of elective cesarean delivery and formula feeding, the majority opted for cesarean delivery and exclusive breastfeeding to prevent perinatal transmission. Since the implementation of WHO B+ option, we are encouraging women for vaginal delivery and exclusive breastfeeding.

Obstetric outcomes noted were preterm birth (PTB), pregnancy-induced hypertension (PIH)/preeclampsia, gestational diabetes, anemia and intrahepatic cholestasis of pregnancy. Neonatal outcomes studied were birthweight, intrauterine growth restriction (IUGR), Apgar scores, neonatal intensive care unit (NICU) admission and perinatal transmission. These outcomes were compared with 238 low-risk pregnant women who were not HIV-infected. As a second part of the analysis, the effect of HAART on PTB and IUGR was studied. For this, women receiving no ART or sdNVP were compared with those receiving HAART or ZDV/3TC. The outcome parameters were statistically analyzed, Odds ratio and confidence intervals were calculated. Chi-square test was used to compare the obstetric outcomes between two groups. Categorical variables were compared with Chi-square/Fisher's exact test. A P value of <0.05 was considered as statistically significant. All statistical analysis were carried out using STATA Software Version 12.0.

3. Results

The study includes data on 212 HIV-infected women who delivered within the study period.

3.1. Baseline maternal characteristics

Mean age of HIV positive women was 25.72±3.6 years. The majority of women belonged to low or middle socio-economic status. Of the total, 79% of women were referred to us after diagnosed with HIV infection. The couple was discordant for infection in 15% cases. Primiparity and multiparity were equally distributed. About 16% women had a previously infected child. Of the total women, 200 (94.35%) were diagnosed in index pregnancy, the remaining 12 were already on HAART at the time of conception (Table 1).

From history, we could elicit sexual contact as a prime mode of infection in these women (63.75%), followed by blood transfusion (5.2%), needle injury (1.4%) and in 29.7% we could not determine the mode of transmission. Out of 212 HIV-infected women, 26 (12.26%) were co-infected with another sexually transmitted disease (Genital herpes - 7, Pulmonary tuberculosis - 4, Warts - 1, HbsAg - 9, HCV - 3, Syphilis - 2). The CD4 count was more than 200 in 89% women.

Majority, 83.5% of the women booked with us before 28 weeks and they received more than 4 weeks of ARV drugs for prophylaxis, 8 women did not receive any ARV treatment. Single dose NVP with or without tail was given to 27 (12.7%), ZDV or ZDV+3TC to 97 (45.7%) and HAART (Tenofovir 300 mg+Lamivudine 300 mg+Efavirenz 600 mg) to 80 (38%) HIV-infected women.

3.2. Obstetric outcome

Out of 212 HIV-infected women, 90.6% (192) delivered after 37 completed weeks of gestation, 91.5% (194) had a cesarean delivery, 40.72% (79) women undergoing cesarean section opted for tubal sterilization, as the method of contraception. Table 2 shows the comparison of obstetric complications in HIV-infected women with controls (HIV-uninfected women). HIV-infected women were more likely to deliver preterm, have IUGR and anemia compared to HIV-uninfected women, this was not statistically significant. There were no maternal or neonatal

Table 1: Selected sociodemographic characteristics (n=212)

Variables	N (%)
Education	
Illiterate	30 (14.2)
Primary education (up to 5th grade)	9 (4.2)
Secondary	66 (31.1)
Higher education	107 (50.5)
Order of marriage	
1st order	207 (97.6)
Higher	5 (2.4)
Income per capita (Indian Rupees, INR)	
<5000 INR	111 (52.4)
5000-10000 INR	46 (21.7)
>10000 INR	55 (25.9)
Location of diagnosis	
AIIMS	44 (20.8)
Referred	168 (79.2)
Husband's occupation	
Professional	28 (13.2)
Government employee	22 (10.4)
Skilled laborer	115 (54.2)
Unskilled laborer	79 (21.3)
Family type	
Nuclear	98 (46.2)
Joint	114 (53.8)
Serodiscordancy	
Husband +ve	170 (80.2)
Husband -ve	32 (15.1)
Status unknown	10 (4.7)
Parity	
Primiparous	101 (47.6)
Multiparous	111 (52.4)
Prior child affected	18/111 (16.2)
Time of diagnosis	
Prepregnancy	12
During pregnancy	200
1st trimester	84
2nd trimester	81
3rd trimester	35

INR: Indian Rupees

deaths. One woman had postpartum hemorrhage but did not require blood transfusion. Two had wound infection managed with dressing and antibiotics and two had febrile morbidity. There were 3 instances of needle prick to health professionals all received post-exposure prophylaxis and are negative for HIV on follow-up. Majority of women opted to top feed their babies.

3.3. Neonatal outcome

Newborns of HIV-infected women had significantly lower mean birth weight and significantly greater number of NICU admission as shown in Table 3. Eighteen out of 212 newborns required NICU admission (indications were: low birth weight-4, transient tachypnea of newborn-4, respiratory distress-2, sepsis-3 and others -5). Though the NICU admissions were higher in women who were infected, the mean Apgar score of their babies was significantly higher than controls, we do not have a possible explanation for this. Of 99 babies for whom follow-up is available 7 tested HIV ELISA positive at 18 months. All seven HIV-infected babies were delivered by cesarean section. Out of seven, two mothers received HAART, two received AZT, two were on ZDV+3TC for prevention of perinatal transmission and one didn't receive any prophylaxis and all babies received formula feeds except one.

3.4. Effect of ART on PTB and IUGR

HIV-infected women who were on HAART or on the dual drug had a lower risk of PTB compared to women receiving sdNVP or no drugs, and this was statistically significant (P value= 0.039), There was no difference in incidence of IUGR in the three groups (P value= 0.739) as shown in Table 4.

4. Discussion

In this cohort, with regular antenatal care and multidisciplinary approach we demonstrated a similar obstetric and perinatal outcome in HIV-infected and uninfected women. The only significant finding was that the mean birth weight was lower in newborns of HIV-infected women. Early studies from developing countries reported adverse pregnancy outcomes in HIV-infected women. Kumar et al.[7] from India, matched 160 HIV-infected pregnant women with uninfected controls. None were on ART, and 47% women were in CDC class III & IV. They found HIV

Table 2: Comparison of obstetric complications among HIV positive and HIV negative women

Variable	HIV positive N=212	HIV negative N=238	OR	95% CI	p value
PIH	10 (4.7)	14 (5.9)	0.79	0.34-1.82	0.583
IUGR	21 (9.9)	12 (5.04)	2.07	0.99-4.32	0.48
PTB	20 (9.4)	18 (7.6)	1.27	0.65-2.48	0.476
Anemia	11 (5.2)	9 (3.8)	1.39	0.56-3.43	0.47
GDM	7 (3.3)	15 (6.3)	0.51	0.2-1.27	0.141
ICP	14 (6.6)	9 (6.52)	1.01	0.43-2.41	0.98

PIH: Pregnancy Induced Hypertension; IUGR: Intrauterine Growth Restriction; PTB: Preterm birth; GDM: Gestational Diabetes mellitus; ICP: Intrahepatic Cholestasis of Pregnancy; OR: Odds Ratio

Table 3: Comparison of neonatal outcome among HIV positive and negative women

Variables	HIV +ve (n=212)	HIV -ve (n=238)	p value
Mean parity	1.66±0.81	0.6±0.7	0.001
Mean birth weight	2593.60±499	2919±459	0.001
Mean apgar score at 5 min	9.01±0.35	8.8±0.7	0.001
Congenital malformations	1/212 (0.5)	0	0.600
NICU admissions	18/212 (8.5)	5/238 (2.1)	0.002
Breast feed	34/212 (16.03%)		
Top feed	178/212 (83.9%)		

Table 4: Effect of ART on PTB and IUGR

Variable	N (%)	p value	OR	95 CI
IUGR (n=21)				
NO Rx/sdNVP	4/31 (12.9%)		1(REF)	
HAART	7/80 (8.8%)	0.739	0.64	0.18-2.34
ZDV/Duovir	10/97 (10.1%)		0.76	0.22-2.61
Preterm births (n=20)				
NO Rx/SdNev	7/31 (22.6%)		1(REF)	
HAART	5/80 (6.3%)	0.039	0.23	0.07-0.79
ZDV/Duovir	8/97 (8.1%)		0.30	0.1-0.91

IUGR: Intrauterine growth restriction; PTB: Preterm birth; sdNVP: Single dose nevirapine; HAART: Highly active antiretroviral therapy; ZDV: Zidovudine; Duovir: Zidovudine+Lamivudine

infection had a detrimental effect on pregnancy in terms of abortion, prematurity, intrauterine fetal death and maternal and neonatal mortality. AIDS-related signs and symptoms were risk factors responsible for adverse outcomes. In a larger cohort of 1449 from South Africa, untreated HIV-infected women, adverse pregnancy outcome associated were low birth weight (LBW), abortions and stillbirths.[8] In another study from India, Lionel J et al[9] reported the obstetric outcome in 109 HIV-infected women, these women were significantly more likely to have PIH, anemia, and stillbirths. They did not comment on preterm births. Fetal deaths were more likely in women who did not receive MTCT prophylaxis. Also, data on prenatal care, medical history was not available.

Brocklehurst et al.[10] conducted systematic review and meta-analysis to study pregnancy outcome in HIV-infected women. Prospective cohort studies with control were included. They have not differentiated between symptomatic and asymptomatic women, women receiving or not receiving ART. There was an association, though not strong, between HIV infection and abortions, stillbirths, perinatal and neonatal mortality, LBW, IUGR, and PTB. This association was stronger in studies from developing countries. In a meta-analysis, which included 44 studies, Calvert C et al.[11] found that HIV-infected women have three times higher incidence of puerperal sepsis and endometritis. Parisaei et al.[12] from London and Patil S[13] et al from India reported similar antenatal and postnatal complications in HIV-infected women who received ART compared to the uninfected antenatal population.

The better outcome in this cohort is explained by regular antenatal care, majority of women diagnosed in pregnancy were asymptomatic and others were already on HAART. Pregnancy outcome is affected by many factors. The adverse outcome in women from developing countries could be because of the poor socio-economic status of these women, marginalized population because of stigmata of HIV and poor access to antenatal care. Women who were asymptomatic or on treatment are likely to have a better outcome.

Studies have also linked adverse obstetric and perinatal outcome with the use of HAART. It may be difficult to distinguish whether the adverse outcomes are because of HIV infection or antiretroviral drugs. In a systemic review of literature from developing countries (1993-2013), Fekadu M et al.[14] found that there is a relative association between ART and occurrence of adverse perinatal outcomes especially when protease inhibitor (PI) based regimens were used and ART was started prior to conception or during first trimester. Frequently observed adverse birth outcomes were LBW, PTB and small for gestational age (SGA). In a study from Spain,[15] obstetric and perinatal outcome in 167 HIV-infected women was noted. There was increased preterm births in women without ART and those on combined HAART, especially protease inhibitors. There was a higher incidence of gestational diabetes in women receiving PI. Higher low birth weight rates in infected women were linked to risk behavior and HIV stage. Ikpim et al.[16] from Nigeria assessed that HIV-positive status increased adverse pregnancy outcomes such as anemia, puerperal sepsis, LBW and cesarean section. ART appeared to reduce the risk of PTB in HIV-infected women. Another study from Brazil[17] concluded that patients who were on ART prior to conception had significantly higher chances of LBW (33.3%) and PTD (26.3%) in comparison to women who started ART during pregnancy (LBW=16.5% & PTD= 17.7%). Haeri et al.[2] compared 151 HIV-infected women on HAART and 302 HIV- uninfected women. They reported that smoking, drug abuse, and spontaneous PTB were more common among HIV-infected women. HIV-infected women were more likely to deliver an SGA infant, but this was due to higher tobacco and cocaine use. Neonatal outcomes were otherwise similar, HAART did not increase maternal complications. In another study by Olagbuji,[18] increased incidence of IUGR, PTB, and LBW was reported in HIV-infected pregnant women on HAART. Ekouevi et al.[3] compared 151 HIV-infected women who received HAART and 175 who received ZDV or ZDV+3TC or sdNVP from Africa and concluded that HAART reduced MTCT but was associated with LBW and this association was statistically significant. Darak et al.[5] also reported

that women receiving HAART had higher chances of adverse pregnancy outcomes (48%), PTB (25%), and LBW (34%) compared to women on ZDV (32%, 13%, and 22% respectively). Preconception HAART was significantly related to LBW children.

Taha et al.[19] analyzed birth outcomes among infants of treatment-naïve, HIV-infected women from a series of studies on MTCT of HIV in Blantyre, Malawi. Six MTCT studies contributed data from 8753 HIV-infected mothers and 8874 HIV-exposed infants to this analysis. The overall proportions of LBW, PTB, and LBW among full-term infants which were 12.9%, 7.6%, and 5.2%, respectively. Young et al.[6] examined the relationship between maternal BMI at study enrollment, gestational weight gain, and hemoglobin concentration among 166 women initiating ART in rural Uganda and concluded that women with poor nutritional status are at increased risk for LBW, preterm delivery, and composite adverse birth outcomes. The conflicting results from various studies can be partly explained by the effect of ART, other contributing factors could be maternal disease status, nutritional status, and geographical location. Type and duration of treatment with HAART may affect pregnancy outcome. When we analyzed the rate of preterm birth in our cohort, women on HAART were less likely to deliver preterm and this was significant. Our women did not receive protease inhibitors as one of the drugs. Majority of women had exposure to ART after the first trimester of pregnancy. There was no increase in small for gestational age babies in women on HAART. With advances in the medical field, use of HAART in reducing MTCT is one of biggest success stories. It gives hope of having an uninfected, healthy baby for these women.

5. Conclusion and Global Health Implications

With good antenatal care and multidisciplinary approach HIV-infected women can have good pregnancy outcome. Keeping in view the data from published literature and the present study, we have to counsel that they may be at increased risk of an adverse outcome like PTB, IUGR, and anemia, which may be due to disease or ART. Medical service providers need to understand this while taking care of a pregnant HIV-infected woman. A multidisciplinary team approach to management involving an HIV physician, experienced obstetrician, and neonatologist are essential to optimize maternal and fetal outcome.

Compliance with Ethical Standards

Conflict of Interest: *The authors declare no conflicts of interest.* ***Ethical Approval:*** *The study was approved by an Institutional Review Board. Consent: This study was based on the analysis of existing data.* ***Funding Support:*** *None.*

Key Messages

- Antenatal care and close monitoring in pregnancy can optimize the outcome for HIV-infected women and baby.
- HIV infection or ART in pregnancy may predispose to adverse pregnancy and perinatal outcome, the evidence for this is still conflicting.

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