Characteristics of HIV-infected women on antiretroviral therapy who develop preeclampsia in South Africa: a case series

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Hypertensive disorders such as preeclampsia/eclampsia and HIV are important diseases contributing to the incidence of maternal deaths and illness in South Africa. Antiretroviral therapy (ART) is an instrumental medical treatment that specifically targets the HIV virus. ART involves multiple drugs that act on the HIV virus at various points in its biologic life cycle. This treatment during pregnancy has significantly decreased mother-to-child transmission (MTCT) of HIV. Additionally, hypertensive disorders in pregnancy are characterized by increased blood pressure during the gestational period. This spectrum of disorders includes gestational hypertension, mild preeclampsia, severe preeclampsia, superimposed preeclampsia on chronic hypertension, eclampsia and HELLP syndrome, which is characterized by hemolysis, elevated liver enzymes and low platelet count. Among patients who are HIV-positive in South Africa, hypertensive disorders in pregnancy remain one of the most common complications. Therefore, the relationship between hypertensive disorders, HIV, and ART during pregnancy requires further investigation.

As access to ART has increased among women of reproductive age, there is a concern about the safety of these medications in pregnancy. Five cases of HIV-infected patients on ART who developed preeclampsia were identified in a specialized antenatal clinic offering antiretroviral services within the Department of Obstetrics and Gynecology at Charlotte Maxeke Johannesburg Academic Hospital (CMJAH). The maternal and neonatal characteristics and management of labor and delivery in these cases are described. The purpose of this paper is to present a case series of HIV-positive pregnant women on ART who developed preeclampsia and to perform a literature review of the relationship between ART, HIV and preeclampsia. There is a need for early identification and close follow-up of HIV-infected patients on ART who develop preeclampsia to facilitate better obstetric outcomes in these high-risk pregnancies.

Introduction

Hypertensive disorders and HIV infection are important diseases that contribute to maternal deaths and morbidity in South Africa. Hypertensive disorders in pregnancy currently account for up to 19% of maternal deaths in South Africa,[1] while HIV-related complications is the leading cause of maternal death in South Africa.[2] In October 2004, to combat HIV, three-drug combination antiretroviral therapy (ART) became available to all pregnant women in South Africa with a CD4 cell count below 200 cells/mm^3 or with WHO clinical stage 4 disease. CD4 T-cells, the main targets of the HIV virus, are responsible for regulating immune responses, and patients suffering from a WHO Clinical stage 4 disease are defined as HIV-positive individuals with an AIDS-defining illness of stage 4 in the WHO classification system.[4] A CD4 cell count below 200 cells/ mm^3 was the international standard for initiating the three-drug combination ART regimens at the time the chart review was undertaken.[5] The CD4 count and HIV viral load, the level of virus in blood in copies/ml, are used as clinical markers of immune status and disease activity in HIV-positive patients.

Pregnant women comprise one of the largest populations receiving ART in South Africa.[6] ART during pregnancy reduces maternal mortality and morbidity and is the most effective intervention to prevent mother-to-child transmission (MTCT) of HIV. ART decreases viral load in the pregnant patient which thereby decreases the risk of HIV transmission to the fetus with longer duration of therapy during pregnancy emerging as the important factor in determining the effectiveness of preventing MTCT.[6,7]

The effectiveness of ART during pregnancy triggered the expansion of the MTCT program in South Africa to provide ART for all pregnant women with a CD4 count less than 350 cells/mm^3 or WHO clinical stage 3 or 4 disease in April 2010 with further expansions in 2013-2014 to include either a CD4 count of 500 cells/mm^3 or universal access (treating all pregnant and breastfeeding women regardless of CD4 and clinical stage).[8] Policies regarding the initiation of ART are determined by local and national governments with policy guidance from the World Health Organization.

A specialized antenatal clinic offering antiretroviral services was established in July 2004 within the Department of Obstetrics and Gynecology at Charlotte Maxeke Johannesburg Academic Hospital (CMJAH). Within this clinic, ART is rapidly initiated in HIV-infected pregnant women who qualify for treatment, and patients are subsequently closely monitored during the remainder of their pregnancy. After delivery, patients are followed up in a specialized postnatal clinic. Among this cohort of women, hypertensive disorders, such as preeclampsia, are one of the most common complications of pregnancy.[7] With the expansion of ART usage during pregnancy, it has become increasingly important to understand ART's effects, not only in regard to MTCT of HIV, but also in regard to other maternal health issues such as hypertensive disorders in pregnancy. Understanding the relationship between ART and its potential role in hypertensive disorders in pregnancy will allow for optimal obstetric care in this high-risk population.

This report aims to retrospectively examine five cases of preeclampsia among HIV-positive women on ART and to review the current literature on the relationship between preeclampsia, HIV and ART.

Existing literature on preeclampsia, HIV and ART

There is little information on the relationship between HIV, ART and the risk of preeclampsia, with several previous studies yielding inconsistent information on the association of these factors.[9,10] A study from the United Kingdom demonstrated that HIV-infected women who had not received any ART had lower rates of preeclampsia than those on ART.[11] The rates of preeclampsia were similar for HIV-positive and HIV-negative women in their cohort. A study performed in Spain reported that women who were started on ART prior to pregnancy had higher rates of preeclampsia and subsequent fetal death compared to HIV-negative women, but no comparison was made to women who started ART during pregnancy.[12] Similarly, a study performed in Latin America and the Caribbean showed results that HIV-infected women with ART initiation prior to pregnancy had a higher rate of preeclampsia; however, there were no comparison groups in this study.[13]

These results differ from those of a study from Brazil in which women on ART had lower rates of preeclampsia compared to HIV-negative pregnant women.[14] Another study conducted in the U.S. showed no difference in preeclampsia rates between HIV-positive women on ART and HIV-negative women.[15] Another study performed in Canada showed that HIV-positive women on ART did not have a higher risk of preeclampsia compared to HIV-negative women, but they did have risk of having lower birth weight infants.[16] However, these studies did not assess the risk factors for developing preeclampsia in HIV-positive patients and did not evaluate the risk of preeclampsia on HIV-patients who were not undergoing ART. In South Africa, a study performed at Chris Hani Baragwanath Hospital in Soweto showed that HIV infection was not protective against the development of preeclampsia. However, the CD4 cell counts of all the patients enrolled in the study were not recorded, limiting the ability to draw conclusions from the study about the role of disease stage and ART in contributing to preeclampsia.[17]

The above studies fail to show conclusive evidence on the relationship between HIV, ART and the risk of developing preeclampsia. These studies also have several limitations including relatively small sample sizes and the lack of adjustment for confounding variables that could influence outcomes within the patient population studied. As the number of pregnant women on ART in South Africa rises, so does the need to explore the relationship between HIV, ART and complications such as preeclampsia.

Methods

We report a case study of five patients at CMJAH treated from January until December 2009 who developed preeclampsia on ART during pregnancy (Table 1). Forty-eight cases of preeclampsia were identified after reviewing both maternal and birth records at CMJAH. Among these cases of preeclampsia, we were able to identify a subset of six cases of HIV-infected women on ART during pregnancy. One patient was excluded from this case series because the diagnosis of preeclampsia was made at an outside institution. The gravidity (the sum of all pregnancies including terminations less than 6 months), parity (the sum of all births greater than 6 months) denoted as GxPx and Apgar scores (score recorded at 1 and 5 minute intervals post delivery to assess how the baby tolerated the delivery) were recorded.

Hypertensive disorders encompass a spectrum of disorders. The following criteria were used to define the various hypertensive disorders in our case series. Preeclampsia is defined as systolic blood pressure 140 mm Hg or greater or diastolic blood pressure 90 mm or greater after 20 weeks gestation and proteinuria (300 mg or greater over 24 hours, 1+ on urine dipstick or protein-to-creatinine ratio of 0.3 or greater). Severe preeclampsia is defined as systolic blood pressure 160 mm Hg or greater or diastolic blood pressure of 110 mmHg or greater after 20 weeks gestation, proteinuria (5 grams of greater over 24 hours or 3+ on urine dipstick), oliguria, visual disturbances, right upper quadrant or epigastric pain and impaired liver function. HELLP syndrome is defined as preeclampsia with hemolysis, elevated liver enzymes and low platelet count . Superimposed preeclampsia is the development of preeclampsia in a patient with existing hypertension prior to 20 weeks gestation. Eclampsia is defined as the development of seizures in a patient with preeclampsia who has no known seizure history.[3]

At the time of labor and delivery, all patients were managed according to a standard protocol for hypertensive disorders in pregnancy at CMJAH, as defined by the Obstetrics and Gynecology department for managing parturient patients with preeclampsia.[18] The management protocol was as follows: patients with preeclampsia were all admitted for observation prior to delivery; patients were treated with Methyldopa 500 mg orally twice daily and Nifedipine 10mg orally three times daily; magnesium sulfate was given to all patients for seizure prophylaxis. Methyldopa and Nifedipine are the most common medications used for blood pressure control during pregnancy because they do not cause developmental malformations. Blood pressure was recorded every 30 minutes until stable and then recorded hourly. Indications for delivery included pregnancy >38 weeks for patients with mild preeclampsia and pregnancy >32 weeks for patients with severe preeclampsia, eclampsia or HELLP syndrome. Conservative management was recommended for patients with severe preeclampsia who had a gestational age of 26-32 weeks and an approximate expected fetal weight of 900-1500 grams.

All patients were started on a standard first-line ART regimen in pregnancy, which included stavudine, lamivudine and nevirapine. During the time under review, CD4 cell counts were measured at baseline and every six months after treatment initiation. Viral load monitoring was not routinely performed in this population due to financial constraints of the public hospital in this resource-limited setting.

The research was approved by the University of Witwatersrand Human Ethics Committee and exemption was granted by the Institutional Review Board at the University of California, Los Angeles.

Cases

Case 1

A 28-year-old G_4P_3 female presented at gestational week 35 with a blood pressure of 155/94 mmHg. Her past medical history was significant for HIV infection diagnosed during a previous pregnancy in 2008 with a baseline CD4 count of 18 cells/mm^3. She was started on the standard ART regimen at this time and her pregnancy was complicated by gestational hypertension. Her previous pregnancy was a normal vaginal delivery, which resulted in the birth of a live healthy infant. Approximately one year later she returned to the clinic for a subsequent pregnancy with a CD4 count of 275 cells/mm^3. At the gestational age of 37 weeks, she developed a headache and blurry vision and presented to the obstetric ward. At this time she was managed per the standard hospital protocol for hypertensive patients during delivery. She had a vaginal delivery at 37 weeks gestation age, which was complicated by a footling breech presentation of the fetus. There were no other maternal complications and the infant was born alive and healthy. Maternal symptoms resolved after delivery and her blood pressure normalized.

Case 2

A 40-year-old G_7P_4 female presented with preeclampsia superimposed on chronic hypertension at 36 weeks gestational age. Her chronic hypertension was untreated prior to pregnancy. She had a past history of spontaneous abortions. She was diagnosed with HIV in the current pregnancy with a baseline CD4 count of 54 cells/mm^3 and viral load of 1100 copies/ml. She was initiated on the standard ART regimen at gestational week 15. Her blood pressure was well-controlled during pregnancy until 36 weeks, at which time she presented with preeclampsia with a blood pressure of 150/90 mm Hg and was managed per the standard protocol for delivery of hypertensive patients. She ultimately required medical induction of labor for imminent eclampsia at 38.5 weeks gestation. Maternal and neonatal outcomes after delivery were uneventful and her symptoms resolved. She was managed for chronic hypertension.

Case 3

A 24-year-old G_1P_0 female presenting with past medical his-

Table 1 Summary of Cases

Characteristics	Case 1	Case 2	Case 3	Case 4	Case 5
Maternal Age (years)	28	40	24	28	25
Gravidity/Parity[1]	G4P3	G7P3	G1P0	G3P2	G2P1
Gestational Age at time of Pre-eclampsia Diagnosis (weeks)	35	38	37	34	38
Classification of Preeclampsia	Preeclampsia	Superimposed Pre-eclampsia	Eclampsia	Preeclampsia complicated by partial HELLP syndrome[4]	Preeclampsia
Pertinent Medical History	History of Gestational Hypertension in previous pregnancy	History of chronic hypertension	Asthma	History of chronic thrombocytopenia	None
CD4 count closest to delivery (cells/mm^3)	275	54	239	232	112
VL closest to delivery (copies/ml)	NA[2]	1100	3300	NA[2]	680
Gestational Age at ART initiation (weeks)	Previous Pregnancy	15w	32	NA[2]	22
ART Regimen	stavudine, lamivudine, nevirapine	stavudine, lamivudine, nevirapine	stavudine, lamivudine, nevirapine	stavudine, lamivudine, nevirapine	stavudine, lamivudine, nevirapine
Number of weeks prior to delivery on ART (weeks)	68.5	23.5	7.0	NA[2]	16.4
Number of weeks on ART prior to onset of preeclampsia (weeks)	66.5	23.5	5.0	NA[2]	16.4
Mode of Delivery	NVD[3] (complicated by footling breech presentation)	NVD[3] (Induction of Labor)	NVD[3]	Emergency cesarean section for partial HELLP syndrome	Emergency cesarean section for imminent eclampsia + sterilization (bilateral tubal ligation)
Gestational Age at delivery (weeks)	37	38	39	34	38
Birthweight (grams)	NA[2]	3100	2650	1840	2900
Apgars	4/10,7/10	9/10, 10/10	0/10,0/10	6/10, 9/10	6/10, 9/10
Fetal Outcome (at delivery)	Alive/Healthy	Alive Healthy	Intrauterine Fetal Death	Alive/ Healthy	Alive/ Healthy

[1]G, Gravidity- Sum of all pregnancies, including terminations <6 months; P, Parity-Sum of all births > 6 months; [2]NA, not available; [3]NVD, normal vaginal delivery; [4]HELLP, Hemolysis, Elevated Liver Enzymes, Low Platelets.

tory significant for mild asthma was diagnosed with HIV during her current pregnancy and started on the standard ART regimen at 32 weeks gestational age. She presented with preeclampsia at gestational week 37 with a blood pressure of 160/90 mmHg. She developed headaches and seizures at gestational week 39. She received diazepam for treatment of her seizures, but her pregnancy ended in intrauterine fetal demise. She underwent a spontaneous vaginal delivery of the nonviable fetus. Her blood pressure at the time of delivery was 192/106 mmHg. Her CD4 count and viral load near delivery were 239 cells/mm^3 and 3300 copies/ml, respectively. The patient did well after delivery with normalization of blood pressure and no recurrence of seizures.

Case 4

A 28-year-old G_3P_2 female was initially diagnosed with pre-eclampsia at gestational week 34. Her past medical history was significant for HIV infection and chronic thrombocytopenia (low platelet count) of unknown etiology, possibly related to HIV. She had two previous uncomplicated pregnancies with cesarean deliveries. At 34 weeks she developed partial HELLP syndrome (two of three features of HELLP syndrome). She underwent an emergency cesarean section, which was complicated by severe bladder injury. Her CD4 count near delivery was 232 cells/mm^3. Maternal symptoms of HELLP resolved after delivery except for the chronic thrombocytopenia. The neonate had a low birth weight of 1840 grams and was given oxygen at the time of delivery; however, the baby survived without any known complications.

Case 5

A 25-year-old G_2P_1 female with a history of a previous cesarean section for fetal distress was diagnosed with HIV in the current pregnancy. She was started on the standard ART regimen at gestational week 22. Her CD4 count and viral load were not known at baseline but were reported near delivery as 112 cells/mm^3 and 680 copies/ml, respectively. At 38 weeks she presented with a BP of 153/111mmHg and a headache. A diagnosis of preeclampsia was made. She was managed according to the standard preeclampsia protocol but required cesarean section for possible imminent eclampsia and a bilateral tubal ligation. Her pregnancy outcome was successful without any neonatal complications and her blood pressure normalized after delivery.

Discussion

This case series describes five HIV-infected patients who de-

veloped preeclampsia on ART at a public tertiary academic medical center in Johannesburg, South Africa. These cases highlight the importance of exploring the relationship between HIV and ART and its effect on hypertensive disorders during pregnancy. The cases in our study encompass a broad range of hypertensive disorders in pregnancy. Among the hypertensive disorders, there were two cases of preeclampsia, one case of eclampsia, one case of superimposed preeclampsia and one case of preeclampsia complicated by partial HELLP syndrome. The patient with the superimposed preeclampsia had a history of chronic hypertension, which was diagnosed prior to pregnancy. This patient was our only patient in this cohort with a history of a hypertensive disorder prior to pregnancy. There is little information on the effects of ART on pregnancy in patients with known hypertension. Additionally, most of our patients were diagnosed with HIV in the current pregnancy in which they experienced hypertensive disorders. There was one case where the patient was diagnosed in the previous pregnancy and subsequently started on ART during a previous pregnancy at which time she developed gestational hypertension. It is unclear whether the gestational hypertension in her previous pregnancy had a relationship with the initiation of ART and whether this proves to be a risk factor for developing gestational hypertension in future pregnancies.

Hypertensive disorders are associated with preterm delivery, which is defined as delivery at less than 37 weeks gestation. However, in our case series, only one patient had a delivery prior to 37 weeks. Additionally, out of the recorded birth weights, only one was considered low birth weight (less than 2500 grams), which occurred in the patient who had a gestational age of 34 weeks at the time of delivery. Although this patient had low birth weight baby, this neonate had good Apgar scores and remained healthy during the immediate postpartum period. Four out of five of the neonates were alive and healthy at the time of delivery and in the immediate postpartum period. However, one neonate presented as an intrauterine fetal demise (IUFD). In this case, the patient's pregnancy was complicated by eclampsia, which is one of the most severe hypertensive disorders in pregnancy since the patient developed seizures.

There may be a possible relationship between the number of weeks on ART and the development of hypertensive disorders in pregnancy; however, this has not been previously explored. The number of weeks on ART in our population ranged from 5.0-66.5 weeks. The patient with gestational hypertension in the previous pregnancy was started on ART during her previous pregnancy and had the longest duration of treatment in our study, although the duration of treatment before the onset of gestational of hypertension in her previous pregnancy is not known. Given the widespread increased use of ART, the duration of ART and development of hypertensive disorders in pregnancy might be an important area for future research.

Although these cases are variable in outcomes, they highlight the importance of early identification and proper obstetric management of HIV-positive patients who undergo ART during pregnancy and develop hypertensive disorders such as preeclampsia/eclampsia.

Risk Factors for Preeclampsia and a possible role of HIV and ART

The risk factors for developing preeclampsia include first pregnancy, multiple gestation (twins, triplets, etc.), obesity, family history of preeclampsia/eclampsia, preeclampsia in a previous pregnancy, pre-gestational diabetes mellitus, collagen vascular disease (systemic lupus erythematosus), chronic hypertension, chronic renal disease and maternal age less than 20 or greater than 35.[19] Among the risk factors within our population, there was a case of gestational hypertension in a previous pregnancy as well as a case of chronic hypertension. Patients with preeclampsia during pregnancy are at increased risk for developing preeclampsia in a future pregnancy.[19] We are unaware if counseling was provided for early follow-up during recurrent pregnancies in the two patients in our population with hypertensive disorders in a previous pregnancy. Given the known risk factors for preeclampsia, it is important to appropriately counsel women regarding this risk. The integration of family planning counseling with HIV services can be instrumental in improving outcomes in future pregnancies.

No cases of diabetes mellitus or systemic erythematous lupus were reported. Diabetes mellitus is a metabolic disease characterized by increased blood sugar levels and systemic erythematous lupus is an autoimmune disorder where the immune system attacks normal, healthy cells. All patients had a maternal age of greater than 20 and only one patient had a maternal age greater than 35. In those patients with no traditional risk factors, HIV and/or ART may play a role in the development of hypertension and the cascade leading to preeclampsia, eclampsia and HELLP; however, the relative contributions of HIV and ART to preeclampsia remain unclear.

Several hypotheses have been suggested about the mechanism by which ART predisposes patients to preeclampsia. Researchers have proposed that the immune restoration by ART increases a women's response to fetal antigens subsequently increasing the risk of preeclampsia.[9] Additional theories include liver toxicity induced by ART, which could contribute to the development of preeclampsia.[20] These hypotheses have never been tested and require further investigation.

Preeclampsia and Maternal and Infant Outcomes in HIV-infected Women

Preeclampsia can lead to poor maternal and neonatal outcomes. In our sample, one intrauterine fetal demise and no maternal deaths were reported. Of note, the one patient who developed intrauterine fetal demise progressed from preeclampsia to eclampsia at gestational week 39. In a retrospective study of 59 patients with eclampsia at a tertiary academic center in Nigeria, the rate of intrauterine fetal demise in this population was high at 13.5 %.[21] This data raises concern in regards to eclampsia as a cause of adverse neonatal outcomes. Additionally, the rates of emergency cesarean section increase in patients with preeclampsia can lead to further complications in the setting of immune compromise from HIV-infection, such as poor wound healing and postpartum infection.[22] In our population, we had two cases of emergency cesarean sections, and one of these deliveries was complicated by severe bladder injury. Earlier identification with optimal obstetric management of patients with preeclampsia can prevent the need for emergency cesarean section and associated complications, and improve overall pregnancy outcomes for both mother and infant.

Patients with preeclampsia in the South African population often present late in pregnancy[24], as do patients with HIV-infection. Many women are diagnosed with HIV infection during pregnancy because this is often their first interface with the health system as adults due to cultural and socioeconomic barriers that make access to healthcare challenging.[24] Among the five patients started on ART who developed preeclampsia in our study, only one patient was known to be HIV-infected and conceived on ART, suggesting that women are either belatedly diagnosed with HIV or are HIV-positive without proper access to the health system. Therefore, there is a critical need to identify HIV infection in women of reproductive age prior to pregnancy to prevent transmission to partners, to counsel and plan for healthy pregnancies and to improve overall pregnancy outcomes for the mother and infant. An integrated antenatal ART clinic can play an essential role in managing high-risk pregnancies by facilitating early ART and appropriate management of preeclampsia; however, there is a need for strategies within the broader HIV healthcare system to improve early identification for HIV-infected women, as well as improved retention of these women in care who are likely to have additional pregnancies in the future.

Limitations

Our study has several limitations, which reflect the challenges of providing HIV care for pregnant women in resource-limited populations. We were unable to report HIV viral load for every patient and CD4 cell data were limited since, at the time of data collection, these tests were performed infrequently due to lack of available funding. Additionally, we do not have data on body mass index, additional medical co-morbidities and detailed past obstetric history for patients in our study. This important information would be valuable in future studies as they can be important markers of overall health and these factors may be associated risk factors for poor outcomes in pregnancy.[25] There were several women who were lost to follow-up immediately after delivery. It is difficult to assess whether HIV and/or ART are associated with the development of

preeclampsia due to the small sample size of the case study. We do not have a denominator of the total number of HIV-infected women on ART who did not develop hypertensive disorders and therefore cannot report on incidence given the absence of controls in this study.

Conclusions

Preeclampsia and HIV are both major causes of maternal morbidity and mortality in South Africa. As the number of women of reproductive age with HIV continues to increase, it is important to assess the relationship of HIV and ART to obstetric complications such as preeclampsia. This case series explores the limitations in early detection of HIV and hypertensive disorders in pregnancy followed by timely interventions in preventing maternal and perinatal complications in resource-limited settings. Well-designed clinical studies are needed to explore specific contributions of HIV and ART to preeclampsia in HIV-infected women and to understand the optimal clinical management for women in these settings.

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