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CLINICAL ARTICLE

Association of HIV and highly active antiretroviral therapy with clinical and biochemical indices among women with pre-eclampsia

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ABSTRACT

Objective: To determine whether clinical and biochemical features associated with pre-eclampsia are significantly altered among women with HIV infection taking highly active antiretroviral therapy (HAART). *Methods:* A prospective observational cohort study was conducted between July 2013 and September 2014 at Prince Mshiyeni Memorial Hospital, Durban, South Africa. Women with and without pre-eclampsia and HIV infection were enrolled at booking and followed up until delivery. Specific demographic data, clinical features, laboratory indices, and complications were analyzed. *Results:* Of 193 participants, 98 had pre-eclampsia (45 [45.9%] with HIV infection). There were no significant differences in clinical features and laboratory indices among the study groups except for γ-glutamyl transferase levels, which were significantly higher among women with pre-eclampsia and HIV infection (26.9 ±40.9 U/L) than among those with pre-eclampsia but no HIV infection (17.1 ± 14.0 U/L; $P=0.001$). Perinatal and maternal complications were similar, and there were no maternal deaths. *Conclusion:* Clinical features, laboratory indices, and complications among women with pre-eclampsia and HIV infection taking HAART were similar to those among women with pre-eclampsia without HIV infection. Current guidelines remain appropriate; however, frequent hepatic function tests should be conducted.

1. Introduction

Pre-eclampsia is a multi-organ disorder of pregnancy associated with significant maternal and neonatal morbidity and mortality [1]. It complicates 2%–10% of pregnancies, and is directly associated with 10%–15% of maternal deaths overall [2]. Maternal manifestations of pre-eclampsia include multisystem involvement, whereas adverse perinatal outcomes include small-for-gestational-age neonates, fetal growth impairment, and stillbirth.

Model-based estimates of the global proportions of maternal deaths among women with HIV infection range from 7% to 21%, and the effects of HIV on the risk of maternal death are uncertain [3]. Moreover, it is estimated that 25% of pregnancy related deaths in Sub-Saharan Africa are attributable to HIV [4]. Although the use of antiretroviral therapy has significantly reduced the rate of mother-to-child transmission of HIV, it is also associated with perinatal complications [5].

In South Africa, a middle-income country, pre-eclampsia (and other hypertensive disorders of pregnancy) and HIV/AIDS are implicated by the National Confidential Enquiries Committee on Maternal Deaths in South Africa as leading causes of maternal deaths [6]. However, the relationship between HIV infection and pre-eclampsia remains unclear despite recent research [7,8]. Currently, there is no consensus on whether pregnant women who are infected with HIV are at lower, equal, or higher risk of pre-eclampsia as compared with the general population, and the treatment of these conditions remains largely empirical. Furthermore, there is a paucity of data on the clinical and biochemical alterations that might occur when pre-eclampsia and HIV infection coexist, particularly among women taking highly active antiretroviral therapy (HAART). Because of its beneficial effects, HAART has been incorporated into the National Antiretroviral Treatment Guidelines [9]. However, the immune reconstitutive effects of HAART during pregnancy have not been investigated.

The aim of the present study was to determine whether clinical features, blood pressure measurements, biochemical indices, and pregnancy outcomes differ between women with pre-eclampsia and HIV infection taking HAART and those without HIV infection.

2. Materials and methods

The present prospective observational cohort study was conducted between July 1, 2013, and September 30, 2014, among pregnant women attending the Maternity Unit of Prince Mshiyeni Memorial Hospital. The study center is a large regional hospital in Durban, KwaZulu-Natal, South Africa, that serves a semi-urban population of

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2 million individuals with approximately 12 000 deliveries annually. The prevalence of prenatal HIV seropositivity in the area is approximately 37% [9], and the incidence of hypertensive disease in the region is 12%–18% [10].

Both pre-eclamptic and normotensive women with and without HIV infection were enrolled in the study. To ensure ethnographic and anthropometric consistency, all patients enrolled were of Black African origin and Zulu ethnic origin. Additionally, all eligible women were resident in the Umlazi Township area south of Durban. Women with gestational hypertension, renal disease, diabetes mellitus, chronic hypertension, or collagen vascular disease were excluded, as were those who smoked or consumed alcohol or recreational drugs.

All patients were referred from local clinics within the catchment area before booking at the hospital or were booked directly at the study institution's maternity unit. The study women were recruited by convenience sampling at booking and followed up until after delivery. Ethical approval for the study was obtained from Prince Mshiyeni Memorial Hospital and the University of KwaZulu Natal, and written informed consent was obtained from all patients.

The management of women attending the maternity unit included a full clinical assessment, relevant investigations, antihypertensive medications, monitoring, and timely delivery, as described in the Maternity Guidelines of South Africa [11]. Calcium supplementation was administered routinely to all patients attending the clinic. HIV was diagnosed via a rapid test kit, and blood pressure was recorded at initial booking and during the prenatal, intrapartum, and postpartum periods. All patients with HIV infection were given a daily fixed-dose combination of HAART (300 mg tenofovir, 200 mg emtricitabine, 600 mg efavirenz) per national guidelines [12]. Body mass index (BMI, calculated as weight in kilograms divided by the square of height in meters) was calculated for each woman and used to classify them as normal weight (BMI 18 to <25), overweight (BMI 25 to <30), and obese (BMI ≥30).

Pre-eclampsia was defined as a blood pressure greater than or equal to 140 mm Hg systolic or greater than or equal to 90 mm Hg diastolic on two occasions at least 4 hours apart after 20 weeks of pregnancy for a woman with previously normal blood pressure [13]. All patients with pre-eclampsia had a proteinuria level of 1 or higher on urine dipstick testing. Early onset pre-eclampsia was defined as pre-eclampsia occurring before 34 weeks of pregnancy. Severe pre-eclampsia was diagnosed when any of the following criteria was present: systolic blood pressure of 160 mm Hg or higher, diastolic blood pressure of 110 mm Hg or higher, impaired renal or liver function, thrombocytopenia, pulmonary edema, cerebral or visual disturbances, persistent right upper-quadrant or epigastric pain unresponsive to treatment, or fetal criteria including fetal growth impairment, oligohydramnios, and fetal death [13].

Blood samples were obtained during the prenatal period and analyzed for variables, such as hemoglobin levels, platelet counts, urea and creatinine levels, lactate dehydrogenase (LDH), and γ-glutamyl transferase (GGT), at the institutional laboratory.

Patient data were obtained from the institution's maternity case records and laboratory data were obtained from the National Health Laboratory Services computerized database at the study institution. For the present analysis, the women enrolled were divided into four groups: normotensive women without HIV infection, normotensive women with HIV infection, women with pre-eclampsia but no HIV infection, and women with pre-eclampsia and HIV infection. Specific demographic, clinical, and laboratory data were recorded and compared among the four groups.

Statistical analysis was done using SPSS version 22 (IBM, Armonk, NY, USA). Data were reported as descriptive statistics. Comparisons of mean across groups were done using the Kruskal–Wallis nonparametric test for variables that are not normally distributed. The Student *t* test was used to compare the difference in means between women with pre-eclampsia but no HIV infection and those with pre-eclampsia and HIV infection. The χ^2 test was used to test the association across groups. For all tests, an α value of 0.05 was accepted as the level of significance. The decision to reject the null hypothesis was based on the *P* value (probability of committing a type 1 error).

3. Results

In total, 193 women were recruited during the study period and were followed up until after delivery. Among the study population, 98 women had pre-eclampsia (45 [45.9%] with HIV infection and taking HAART and 53 [54.1%] without HIV infection), and 95 women were normotensive (45 [47.4%] with HIV and taking HAART and 50 [52.6%] without HIV infection) (Fig. 1).

The mean age of the entire study population was 26.5 ± 7.2 years. Women with pre-eclampsia and HIV infection were significantly older than women with pre-eclampsia and no HIV infection ($P=0.003$) (Table 1). Booking occurred at the local clinic for 179 (92.7%) women, and at an average of 22 ± 7.8 weeks of pregnancy; the mean number of prenatal visits before delivery was 4 ± 2. Mean BMI was high in all groups (Table 1). The mean CD4 cell count did not differ significantly between women with HIV infection with and without pre-eclampsia (Table 1).

Among the 98 women with pre-eclampsia, the prevalence of early-onset and severe disease did not differ between women with and without HIV infection (Table 2). In most cases, blood pressure was controlled using one therapeutic agent (usually methyldopa), with no significant difference in the number of antihypertensive drugs used among women with and without HIV infection (Table 2). There was no significant difference in the highest blood pressure recorded at booking or during the prenatal, intrapartum, and postpartum periods (Table 2).

Analysis of the biochemical indices investigated showed no significant differences between the two groups, apart from γ-glutamyl transferase (GGT), which was significantly higher among women with pre-eclampsia and HIV infection than among those without HIV infection ($P=0.001$) (Table 3). CD4 counts were compared only between women with HIV infection and pre-eclampsia, and those with HIV infection and no pre-eclampsia, because CD4 testing is not routinely performed for women without HIV infection in the study institution.

The mean birth weight among all 193 study patients was 2.8 ± 0.3 kg, and more female than male neonates were delivered (108 [56.0%] vs 85 [44.0%]). The mean birth weight of neonates delivered by women with pre-eclampsia was lower than that of neonates delivered by normotensive women (2.49 ± 0.4 vs 3.14 ± 0.3 kg). Birth weights were similar between women with pre-eclampsia with and without HIV infection (Table 4). Other outcomes were similar between women with pre-eclampsia with and without HIV infection (Table 4). There were no maternal deaths during the study.

4. Discussion

The present study found that the clinical measures, laboratory indices, and complications associated with pre-eclampsia were not significantly altered in the presence of HIV infection and treatment with HAART. However, significantly higher levels of γ-glutamyl transferase were observed among women with pre-eclampsia taking HAART. This

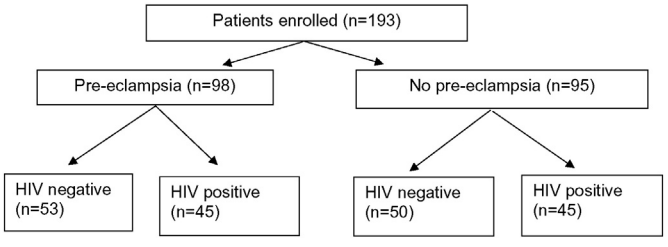

Fig. 1. Flow diagram of the study population.

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