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Original Article

Pre-eclampsia and gestational hypertension are less common in HIV infected women

David Hall [a,*], Stefan Gebhardt [a,b], Gerhard Theron [a], Debbie Grové [a]

[a] Department of Obstetrics and Gynecology, Stellenbosch University and Tygerberg Hospital, South Africa
[b] Department of Obstetrics and Gynecology, Paarl Hospital, South Africa

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ABSTRACT

Objective: To determine whether pre-eclampsia and gestational hypertension are less common in HIV infected women.
Methods: This prospective cohort study was performed in the Western Cape province of South Africa. HIV negative and positive pregnant women without chronic renal or chronic hypertensive disease were continuously recruited. During the study period HIV positive patients received either mono- or triple (HAART) antiretroviral therapy for prevention of vertical transmission or maternal care. Only routine clinical management was performed. The development of hypertensive disease during pregnancy was recorded.
Results: 1093 HIV positive and 1173 HIV negative cases were identified during pregnancy and evaluated again after delivery. Significantly fewer cases of pre-eclampsia $n = 35$ (3.2%) were recorded in the HIV positive group than in the HIV negative group, $n = 57$ (4.9%) ($p = 0.045$; OR 0.65 95% CI 0.42–0.99). There were also significantly fewer cases of gestational hypertension recorded in the HIV positive group compared to the HIV negative group ($p = 0.026$; OR 0.53 95% CI 0.30–0.94). Multiple logistic regression analysis confirmed the reductive effect of HIV on pre-eclampsia and gestational hypertension.
Conclusion: Pre-eclampsia and gestational hypertension are less common in HIV infected women being managed with mono- or triple anti-retroviral therapy.

Introduction

Human immune deficiency virus (HIV) infection and hypertensive diseases of pregnancy, especially pre-eclampsia, are very important conditions in developing countries. For obstetricians in South Africa, HIV is a common, non-pregnancy related infection that has been associated with a large number of documented maternal deaths [1]. Pre-eclampsia is a pregnancy related condition that affects multiple organ systems, with an incidence of 3–5% [2]. It too has had a persistent and strong association with maternal mortality in South Africa, as well as in developed countries of the world [2,3]. Complications of pre-eclampsia also constitute important causes of severe acute maternal morbidity in South Africa [4,5]. Pre-eclampsia exacts a toll on the fetus and neonate as well. Hypertensive diseases of pregnancy have been shown to be important causes for delivery of very low-birth weight babies and perinatally related losses in South Africa [6].

The etiology of pre-eclampsia is known to be multifactorial with certain authors proposing that the immune system plays a key role [7]. Immune tolerance is induced by contact between paternal antigens in the semen and the female genital tract through sexual intercourse. However in the case of a new partner (primipaternity), particularly if there is an insufficient duration of exposure to sperm antigens, the risk of pre-eclampsia increases [8,9].

* Corresponding author. Address: Department of Obstetrics and Gynecology, Stellenbosch University and Tygerberg Hospital, PO Box 19063, Tygerberg 7505, South Africa. Tel.: +27 21 938 9059.
E-mail address: drh@sun.ac.za (D. Hall).

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During pregnancy there is up-regulation of the immune response, with pre-eclampsia representing an excessive generalized maternal inflammatory response. Thus when conditions of acquired or induced immune deficiency are present, as in the state induced by HIV, immune hyper reactivity may be inhibited thus lowering the incidence of pre-eclampsia. In 2002 Wimalasundera et al., found that women with HIV-1 infection who received no antiretroviral therapy had a significantly lower rate of pre-eclampsia than HIV infected women receiving triple antiretroviral therapy [10]. By 2007 more studies had been published but the results were conflicting probably because the studies were all small or retrospective [9]. Due to the uncertainty of whether HIV lowers the rate of pre-eclampsia and gestational hypertension it was necessary to clarify the interaction of these two important diseases. This objective informed this large, cohort study.

Materials and methods

The study was conducted at the Paarl Provincial Hospital, a primary and secondary level institution in the Western Cape province of South Africa. The community served by this hospital comes largely from low socio-economic circumstances. At the time of the study, standard practice required that all patients booking for maternity care be offered counseling and voluntary testing for HIV. CD4 counts were performed on those who tested positive. Determination of the viral load was not performed routinely. Most women booking within this defined system deliver at the Paarl Hospital. During the study period the provincial policy of antiretroviral therapy for maternal care or prevention of mother to child transmission (MTCT) was as follows: HIV positive patients with a CD4 count of $\geqslant$200 cells/mm^3 received monotherapy to prevent MTCT. This comprised of AZT (zidovudine) (300 mg b.d. from 34 weeks' gestation and 300 mg 3-hourly in labor) as well as nevirapine (200 mg once in labor). HIV positive patients with a CD4 count of <200 cells/mm^3 received triple therapy (HAART = stavudine [D4T], lamivudine [3TC] and nevirapine [NVP]) once they had demonstrated that they were able to comply with such therapy. In 2010 the provincial protocol was revised and the CD4 count threshold for triple therapy was changed to 350 cells/mm^3.

The study population consisted of a continuous cohort. At the booking clinic, or as soon as possible thereafter, all eligible HIV positive and negative women were approached for consented recruitment by the clinic personnel. Pregnant women were recruited continuously without matching until the target numbers were achieved. This meant that the HIV negative cohort was completed before the HIV positive cohort. Women booking between 20 and 36 weeks were included if there was no hypertension and no proteinuria. Exclusion criteria were limited to:

- Chronic hypertension (hypertension before pregnancy or present before 20 weeks' gestation).
- Women known with chronic renal disease (hypertension and proteinuria before pregnancy or present before 20 weeks' gestation).
- Women with hypertension and proteinuria at first visit (after 20 weeks' gestation).
- Women booking after 36 weeks' gestation.

Gestation was determined by means of the last normal menstrual period and clinical palpation (at first antenatal visit), or by ultrasound measurements done before 24 weeks gestation. After delivery, files of the study patients were drawn and the data were captured. The primary outcome of the study was to determine the incidence of hypertensive disease in the HIV positive and negative groups, respectively. Hypertensive diseases of pregnancy were classified and diagnosed according to the criteria of the International Society for the Study of Hypertension in Pregnancy [11]. Hypertension was defined as a systolic blood pressure of at least 140 mmHg and/or a diastolic blood pressure of at least 90 mmHg on $\geqslant$2 separate occasions. Significant proteinuria was defined as $\geqslant$300 mg of total protein in a 24-h urine collection or persistent values $\geqslant$1+ on diagnostic strips when a 24-h urine collection was not performed.

To attain statistical significance ($p = 0.05$ at a power of 80%) the study required 2250 (1125×2) women to demonstrate a decrease in the rate of pre-eclampsia from 8% to 5%. Chi-squared and Fisher's exact tests were used for the comparison of frequencies, with the Student t and Mann–Whitney test for comparison of means and medians, respectively. Multiple logistic regression analysis was performed using variables which are known to increase the risk of pre-eclampsia. A p value of <0.05 was regarded as significant. Epistat version 9® and SAS version 9.3® programmes were used for statistical analysis. The protocol was approved by the Committee for Human Research at Stellenbosch University (N05/07/107) that requires researchers to abide by the Declaration of Helsinki for experiments involving humans.

Results

The study ran from March 2007 until February 2011. During this time 3531 pregnancies were recruited at booking or a subsequent visit. From this group the details of 2266 (64.2%) deliveries were obtained from the files after delivery. The discrepancy between enrollment into the study and availability of data at delivery (1265 files) is explained by the fact that many enrolled women did not deliver at the study hospital due to re-location in a mobile population and referral to other hospitals. In addition, the study hospital was rebuilt and the main clinic relocated leading to the loss of some original patient records. In this study 1093 HIV positive pregnancies and 1173 HIV negative pregnancies were available for file review after delivery. The number of HIV positive cases was therefore 32 short of the power calculation. The baseline characteristics of the pregnancies are shown in Table 1.

During the pregnancies only two cases in each group showed symphysis-fundus growth below the 10th centile on the antenatal chart. Doppler flow velocimetry of the umbilical artery was performed in 53 HIV positive and 63 HIV negative cases. Four of these tests were abnormal