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HIV AND PRE-ECLAMPSIA: IS THERE A CONNECTION?

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A research report submitted to the Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, in partial fulfillment of the requirements for the degree of Master of Medicine in the branch of Obstetrics and Gynaecology

Johannesburg, 2006

DECLARATION

I, Karlyn Annesa Frank, declare that this research report is my own work. It is being submitted for the degree of Master of Medicine in the branch of Obstetrics and Gynaecology in the Universtity of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other University.

---------- day of ----------, 2006.

In memory of my father
Kristy Louis Frank
1945-1993

Publications and Presentations:

Frank KA, Buchmann EJ, Schackis RC. Does human immunodeficiency virus infection protect against preeclampsia/eclampsia? Obster Gynecol 2004;104:238-242.
(A copy of the published article is submitted as appendix A)

Frank KA. How does HIV seropositivity affect the incidence of pre-eclampsia. Proceedings of the Twenty Second Conference On Priorities in Perinatal Care In Southern Africa

ABSTRACT

Objective

In view of recent suggestions that HIV infection may protect against pre-eclampsia, this study was done to estimate whether untreated HIV positive pregnant women have a lower rate of preeclampsia-eclampsia than HIV negative women.

Methods

Subjects for this study were pregnant women from Soweto, South Africa, who gave birth from March to December 2002 at midwife-run clinics or at the Chris Hani Baragwanath Hospital, and in whom the HIV status was known. A sample size calculation indicated that 2588 subjects would be required to show statistical significance at $P<0.05$ with a power of 80% for a reduction in the rate of preeclampsia from 8% to 5% with HIV seropositivity, assuming an HIV seroprevalence rate of 30%. Data collection was by record review from randomly selected patient files and birth registers.

Results

In the total sample of 2600 women, 1797 gave birth at the hospital and 803 at the midwife-run clinics. The HIV seroprevalence rate was 27.1%. Hypertension was found in 17.3% of women, with 5.3% having preeclampsia-eclampsia. The rates of preeclampsia-eclampsia were 5.2% in HIV negative and 5.7% in HIV positive women ($P=0.61$). CD4 count results were available for only 13 women (0.5%).

Conclusion

HIV seropositivity was not associated with any reduction in the risk of developing preeclampsia-eclampsia.

Acknowledgements

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Table of Contents **Page**

Declaration 2

Dedication 3

Table of contents 4

Publications and presentations 5

Acknowledgements 6

Abstract 7

Introduction 8

Methods 11

Results 16

Conclusion 22

References 23

Appendices 24

List of Tables

Table 1. Basic clinical and laboratory data in HIV negative and HIV positive women, showing means with standard deviations where applicable.

Table 2. Frequencies of hypertensive disorders of pregnancy in HIV negative and HIV positive women.

Table 3. The influence of gestational age at delivery on the frequency of proteinuric hypertension in HIV negative and HIV positive women.

Introduction

Background and literature review

It has recently been suggested that infection with HIV in pregnant women might reduce the risk of developing preeclampsia.[1] One of the pathogenetic explanations for preeclampsia is maladaptation of the immune system to paternal antigens.[2] Local immune hyperreactivity may cause incomplete trophoblastic invasion of the uterine spiral arteries, thus exposing the placental site to vasoconstriction and the eventual development of preeclampsia. Another theory suggests that pre-eclampsia may be the result of an exaggerated maternal inflammatory response to trophoblastic tissue.[3] Both explanations for the development of pre-eclampsia implicate an active immune system. Immune deficiency, induced by HIV or any other cause, could therefore inhibit a tendency to immune hyperreactivity and thus theoretically prevent the development of preeclampsia.

A study by Wimalasundera *et al* described the rarity of preeclampsia in untreated HIV positive women as compared to HIV negative women and HIV positive patients on antiretroviral drugs, and raised intriguing questions about the roles of HIV infection, impaired immunity and antiretroviral drugs in the pathogenesis of preeclampsia.[1] The authors contend that effective antiretroviral therapy might restore the immune response to fetal antigens, and hence reinstate the pathological process that results in preeclampsia. These findings can be questioned on the basis of a small sample size, high risk referral hospital population, and possibly the influence of preterm delivery.

In their article, Wimalaundra *et al* cited an American study that described an unusually low rate of preeclampsia (0.7%) in a population of pregnant HIV positive women.[4] However, on closer reading of that article, it was apparent that hypertensive women requiring elective delivery were specifically excluded, thus removing the bulk of these patients from their study population, and invalidating any inferences about HIV and preeclampsia.

An extensive search of the scientific literature using the Pubmed search engine, found very few additional articles that discussed the possible relationship between preeclampsia and infection with HIV.

A Brazilian case-control study, by Mattar *et al*[5], which undertook a retrospective analysis of the incidence of pre-eclampsia in HIV seropositive women on antiretroviral therapy showed a low incidence of this condition in the study population as compared to healthy controls. The study failed to show an increase in the incidence of preeclampsia in response to well controlled antiretroviral therapy and therefore, immune reconstitution. The authors state that antiretroviral therapy possibly restores different immunological parameters than those associated with the development of preeclampsia. However, the method of selection of the study sample and HIV status of the controls were not clearly defined limiting the interpretation of their data. A controversial issue raised in a letter to the Lancet by Mawson[6] hypothesizes that highly active antiretroviral therapy (HAART), in fact, *causes* preeclampsia by a direct toxic effect on the liver affecting retinoid-related processes which are thought to underlie the development of preeclampsia in non-HIV-

related pregnancies. It is clear that the current understanding of the relationship between HIV and preeclampsia is based on patchy scientific evidence and is at best speculative.

Objective of this study

In view of the high rates of both HIV seroprevalence (29.3%)[7] and preeclampsia (7.8%)[8] in the region served by Chris Hani Baragwanath Hospital (greater Soweto), without the confounding variable of antiretroviral therapy, the author felt well placed to investigate the relationship between the two conditions. The objective of this study was to investigate whether untreated HIV positive pregnant women had a lower rate of preeclampsia than HIV negative women.

Methods

Setting

The study was set in Soweto, a large urban settlement to the south west of Johannesburg, South Africa, with a population of approximately two million residents. Chris Hani Baragwanath hospital (CHB), a 3200 bed institution, provides hospital care to the residents of this area, and also functions as a tertiary referral center for hospitals in neighboring regions. Several primary care clinics in Soweto refer patients to CHB when necessary. Five of these clinics, Zola, Dobsonville, Mofolo, Lillian Ngoyi and Chiawelo, operate midwife obstetric units where deliveries are performed. All complicated and high risk deliveries are transferred to CHB for further management. The referral criteria are set out in manuals distributed to each clinic.[9] Women with hypertension in pregnancy are referred to CHB for further management. HIV seropositivity is not considered a high-risk obstetric condition and HIV positive women are managed by midwives if they have no obstetric reason for referral to CHB. In Soweto, all antenatal HIV testing is conducted by the Perinatal HIV Research Unit at CHB. Testing is done on blood using Determine™ HIV-1/2 (Abbott Japan Co. Ltd.) rapid immunochromatographic test, with positive results submitted for confirmation using Capillus™ HIV-1/HIV-2 (Trinity Biotech plc, Ireland) rapid latex aggregation test. HIV positive women are given single dose intrapartum nevirapine to prevent mother to child transmission, and their newborns receive a single dose of nevirapine shortly after delivery, in line with the HIVNET 012 protocol.[10] At the time that this study was undertaken CD4 counting was not routinely performed because maternal antiretroviral therapy was not given to HIV positive patients in South African government hospitals.

Study population and sampling

The study population consisted of pregnant Soweto residents, who delivered in public health facilities (CHB and the Soweto clinics) from March to December 2002. Only women who attended antenatal clinics and underwent HIV testing, and who gave birth at a gestational age of 20 weeks or more, were included in the study. Non-Sowetan patients were excluded because many of these are high risk obstetric referrals from other hospitals. Referral may be related to both HIV infection and preeclampsia, and inclusion of these patients might have introduced confounding. The sample size was calculated using Epi-Info 6 statistical software. In order to attain statistical significance (P=0.05 at a power of 80%), a sample size of 2588 was required to show a decrease in the rate of preeclampsia from 8% in HIV negative women, to 5% in those who were HIV positive, assuming an HIV seroprevalence rate of 30%. This number was rounded up to 2600 and divided into representative proportions of hospital and clinic deliveries, based on the previous years' total confinements. This calculation gave a sample that required a sample of 1797 hospital and 803 clinic deliveries. For the hospital cohort, randomly selected clusters were used, based on the last three digits of the eight-digit provincial hospital number. Number allocation of files in the hospital bears no relationship to demographic or clinical characteristics, and the use of such clusters was not expected to result in any bias or design effect in analysis. Each cluster was selected from an electronically generated list of random three-digit numbers. All files ending with these numbers (clusters) were drawn from the hospital record room and files in each cluster were individually assessed for eligibility. For the clinic cohort, the sample was stratified to

include a representative number of women from each of the five clinics, based on the annual number of deliveries recorded in 2001. At each clinic, a simple random sample was used based on numbered deliveries in the birth register.

Data Collection

Data collection was done by record review. For the hospital confinements, patient files were used to obtain HIV results, which are usually recorded once a woman has agreed to be tested. For the clinic confinements, demographic and obstetric data was obtained from birth registers, and the HIV results were obtained from the results books in the Perinatal HIV Research Unit. CD4 count results were noted if they were available. Further data collected included maternal age, parity, gestation at delivery, weight and haemoglobin concentration. Weight and haemoglobin concentrations were not obtainable for the clinic cohort, as this information is not routinely recorded in the birth registers. A search was made in each case for hypertensive disease, its severity, the presence or absence of proteinuria, and whether the condition had its onset during the pregnancy and if so at what gestation. All data collection was undertaken by the author and two other clinicians, using a data sheet designed for the study. This is attached as appendix B.

Definitions

The definitions of hypertensive disorders used for this study are taken from those proposed by Davey and MacGillivray in 1988.[11] These definitions were used because they form the basis for clinical management of hypertensive disorders at Chris Hani Baragwanath Hospital, and because they are explicitly clear and easy to apply.[12]

Proteinuria was defined as 1+ on reagent strip on at least two occasions, or 300 mg in a 24 hour specimen of urine. *Hypertension* was defined as a diastolic blood pressure of ≥110 mmHg on any one occasion, or a diastolic blood-pressure of ≥90 mmHg on two or more occasions, ≥4 hours apart. *Chronic hypertension* was defined as hypertension detected before 20 weeks of gestation, or hypertension known to have been present before the pregnancy. *Pre-eclampsia* was defined as hypertension associated with proteinuria, which developed after 20 weeks of pregnancy.

Where the mother initiated antenatal care after 20 weeks of pregnancy, pre-eclampsia was defined if it was detected subsequent to a normal blood pressure reading at a previous antenatal visit (this is a modification of the Davey and MacGillivray definitions). *Severe preeclampsia* was defined as a diastolic blood pressure of ≥120mmHg on any one occasion or a diastolic blood pressure of ≥110 mmHg on two or more occasions, ≥ 4hours apart, associated with proteinuria. *Superimposed pre-eclampsia* was defined as pre-eclampsia developing in a woman known to have chronic hypertension. *Gestational hypertension* was defined as non-proteinuric hypertension developing after 20 weeks of gestation, or a recording of hypertension subsequent to a normal blood pressure reading in a woman who initiated antenatal care after 20 weeks. *Unclassified hypertension* was defined as hypertension detected at a first antenatal visit after 20 weeks of pregnancy, in a woman with no history of hypertension.

Statistical analysis

Data was analysed on Epi-Info 6 statistical software, using the chi-squared test and Fisher's exact test for comparison of frequencies, and Student's t-test and the Mann-

Whitney test for comparison of means and medians respectively. A P value of less than 0.05 was accepted as indicating statistical significance. To exclude confounding explanatory variables, stratified analysis using the Mantel-Haenszel test was performed. Permission to undertake the study was obtained from the University of the Witwatersrand's Human Research Ethics Committee (HREC), and from the hospital authorities. A copy of the HREC clearance form is attached as appendix C.

Results

To achieve the necessary sample size of 1797 hospital subjects, 3333 files were reviewed. Of these, 878 were excluded because they belonged to women who were not resident in Soweto; and 658 had no results, either because they were not tested (404), were tested, but results could not be found (160), or declined HIV testing (94). For the clinic cohort of 803 subjects, the number of exclusions was not recorded. The total sample was 2600. In the hospital cohort, 516 women were HIV positive (28.7%), and in the clinic cohort, 188 women (23.4%) were HIV positive (P=0.005). The HIV seroprevalence rate for the whole sample was 27.1% (95% confidence interval 25.4-28.8%). CD4 counts were available for 13 women (0.5%). Ten women had AIDS, six on the basis of CD4 counts of less than 200/mm^3, and four because they had AIDS-defining conditions. Two of these women died in the puerperium. Baseline obstetric information is shown in Table 1, which compares clinical data between HIV positive and HIV negative women. Primiparity was more frequent in HIV negative women (42.5% vs. 33.9%; P<0.0001). HIV positive women had lower mean haemoglobin values (11.5 vs. 10.9 g/dL; P<0.0001) and lower mean weights (69.1 vs. 71.5 kg; P=0.008) than HIV negative women, although this data was available only for hospital confinements.

Table 1.Basic clinical and laboratory data in HIV negative and HIV positive women, showing means with standard deviations where applicable

	HIV negative (n=1896)	HIV positive (n=704)	P value
Mean age (years)	26.1 ± 6.7	26.6 ± 5.5	0.009
Primiparous women	805 (42.5%)	238 (33.8%)	<0.001
Mean weight (kg))*	71.5 ± 15.7	69.1 ± 13.8	0.008
Mean haemoglobin concentration (g/dL)*	11.5 ± 1.5	10.9 ± 1.4	<0.001
Mean gestational age at delivery (weeks)	38.0 ± 3.0	37.7 ± 3.2	0.023

*Weights and haemoglobin concentrations were unknown in clinic confinements (n=803), as this information was not available in the birth registers.

Four hundred and fifty women (17.3%) were found to be hypertensive, with 150 (5.8%) having proteinuric hypertension. One hundred and eight HIV negative women had proteinuric hypertension (5.7%), compared to 42 HIV positive women (6.0%; P=0.75). The corresponding frequencies for preeclampsia (preeclampsia, eclampsia and superimposed preeclampsia) were 98 (5.2%) compared to 40 (5.7%; P=0.61) respectively. The frequencies of the different grades of hypertension are shown in Table 2.

Table 2. Frequencies of hypertensive disorders of pregnancy in HIV negative and HIV positive women.*

	HIV negative n=1896	HIV positive n=704
Proteinuric hypertension	108 (5.7%)	42 (6.0%)
Preeclampsia	58 (3.1%)	21 (3.0%)
Severe preeclampsia	29 (1.5%)	15 (2.1%)
Eclampsia	6 (0.3%)	2 (0.3%)
Superimposed preeclampsia	5 (0.3%)	2 (0.3%)
Unclassified proteinuric hypertension	9 (0.5%)	2 (0.3%)
Chronic proteinuric hypertension (renal disease)	1 (0.1%)	0 (0.0%)
Gestational hypertension	183 (9.7%)	65 (9.2%)
Unclassified nonproteinuric hypertension	32 (1.7%)	5 (0.7%)
Chronic hypertension without proteinuria	22 (1.2%)	5 (0.7%)
Total 'pregnancy induced hypertension' (excluding unclassified + chronic)	281 (14.8%)	105 (14.9%)

*None of the differences between HIV negative and HIV positive subjects reached statistical significance at $P<0.05$ (Chi-squared and Fisher's exact tests).

Mantel-Haenszel stratified analysis was performed to identify confounding explanatory variables, and examined the influence of age less than 30 years, primiparity, weight less than 60 kg, haemoglobin level less than 10 mg/dL, clinic delivery, and delivery at less than 37 weeks, on the development of proteinuric hypertension. Only gestational age at delivery proved to be confounding. Women who gave birth before 37 weeks had a 15.3% rate of proteinuric hypertension if they were HIV negative, compared to 8.4% if they were HIV positive (P=0.025). HIV negative and HIV positive women who delivered at term (≥37 weeks) did not differ significantly in rates of proteinuric hypertension (3.3% vs. 5.1% respectively). This is shown in Table 3.

Table 3.The influence of gestational age at delivery on the frequency of proteinuric hypertension in HIV negative and HIV positive women.*

Gestational age at delivery	Less than 37 weeks n=550		37 weeks and above n=2050	
	n	%	N	%
Proteinuric hypertension in HIV negative women	57/372	15.3	50/1524	3.3
Proteinuric hypertension in HIV positive women	15/178	8.4	27/526	5.1
P value	0.025		0.054	

*Excludes one patient with chronic proteinuric hypertension (renal disease)

Discussion

This study failed to show any association between HIV seropositivity and the risk of developing preeclampsia. This lack of association was observed for all grades of hypertension, whether mild or severe, non-proteinuric or proteinuric. The study sample was representative of an entire community of public health service users and was not restricted to high risk obstetric cases delivered in hospitals, unlike the study described by Wimalasundra *et al.*[1] This study showed HIV positive women were found to be slightly older than controls and were less likely to be primiparous. Amongst the hospital cases analysed, HIV positive women also weighed less and had lower haemoglobin levels than HIV negative women. However, these variables did not confound the results. The confounding influence of preterm delivery seen in this study is interesting but may be explained in the following discussion. HIV positive women are known to have higher risks of preterm delivery than HIV negative women perhaps as a result of systemic infection, chorioamnionitis or associated weight loss. [13,14,15] Those who are destined to become preeclamptic may not, by delivering prematurely, develop the condition. HIV seropositivity, or any condition causing preterm birth, can therefore 'protect' against preeclampsia by simply shortening the pregnancy. It should be noted that our study could not specifically investigate the relationship between immune deficiency and preeclampsia, due to the very low rate of CD4 count testing. This made it impossible to distinguish immune deficient women in the study population from those who were HIV positive but asymptomatic and healthy. Patients with CD4 counts of more than 200 have been shown to be at low risk for opportunistic infections, suggesting a fairly competent innate immunity.[16] Perhaps, the severely dampened immunity in patients with critically

low CD4 counts, may protect against the development of preeclampsia. Mandatory CD4 count testing should be performed on HIV positive patients enrolled in future studies in this field.

Some limitations are inherent in our research. All women who did not attend antenatal clinics were necessarily excluded from this study. This number is however, less than 5% in Soweto[17], and should not materially affect the results. Women who refused HIV testing and those whose results could not be retrieved were excluded from the study. In terms of its value as a local audit, this study exposes a deficiency in retrieving and recording HIV results. It is difficult to speculate on whether this shortfall is health-care provider or patient related, but the consequences of this are potentially serious to HIV positive women for whom the necessary precautions to prevent HIV transmission are not taken, especially considering our findings of the local HIV seroprevalence rate of 27.1%, the availability of nevirapine for the prevention of mother to child transmission of HIV, and more recently, the provision of HAART.

Conclusion

HIV infection may be protective by resulting in preterm delivery before the clinical onset of preeclampsia. This study could, however, find no direct association between HIV infection and a reduction in the risk of developing preeclampsia. Any further study should investigate the role of HIV related immune deficiency, by including indices of immunity, such as CD4 counts, and a large enough sample size.

Until such studies are completed, clinicians should not consider infection with HIV to be protective against preeclampsia.

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