Association between preeclampsia and HIV: a case-control study in urban South Africa

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BACKGROUND: Preeclampsia is a considerable cause of maternal and infant morbidity and mortality. Although its etiology is unknown, preeclampsia has been described as a state of exaggerated maternal inflammatory response. Therefore, it has been hypothesized that preeclampsia would occur less commonly in states of immune deficiency.

OBJECTIVE: This study aimed to compare the prevalence of treated and untreated HIV infections among preeclamptic cases and controls, determine infant outcomes, and evaluate the association between HIV and preeclampsia after adjusting for known predictor variables, including maternal age, gravidity, body mass index, and smoking.

STUDY DESIGN: This case-control study investigated the association between preeclampsia and HIV infection using secondary data from an unrelated study. We defined preeclamptic cases as pregnant women who were normotensive until 20 weeks of gestation and thereafter had at least 1 high blood pressure measurement either before or at delivery and proteinuria, defined as protein excretion of ≥300 mg within 24 hours or >2 protein on dipstick urinalysis. The prevalence of HIV infection was compared between cases and controls. Multivariate logistic regression analysis was used to assess the association between preeclampsia and potential confounding variables and reported using odds ratios and 95% confidence intervals.

RESULTS: There were 571 cases with preeclampsia and 596 normotensive controls included in this study. The median age was 27 years for cases and 26 years for controls (P=.008). Most participants (69%) had ≥2 previous pregnancies with no difference between the cases and controls (P=.176). Overall, 43% of the participants were obese, with a mean body mass index of 29 (interquartile range, 24.5−34.2), with higher proportions of women who were overweight and obese in the group with preeclampsia (P=.031). The prevalence of HIV was significantly lower in cases than in controls (24% vs 30%, respectively; P=.014). Compared with 16% of infants born preterm to normotensive controls, 48% of infants were born preterm born to women with preeclampsia (P<.001). Compared with 14% of infants born with low birthweight to normotensive controls, 53% of infants were born with low birthweight to women with preeclampsia (P<.0001). Untreated HIV infection was negatively associated with preeclampsia (unadjusted odds ratio, 0.330; 95% confidence interval, 0.197−0.552; P<.0001), whereas factors associated with preeclampsia were

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advanced maternal age (odds ratio, 1.673; 95% confidence interval, 1.209−2.316; *P*=.002) and obesity (odds ratio, 1.611; 95% confidence interval, 1.023−2.537; *P*=.040). After adjusting for maternal age, gravidity, smoking, and body mass index in the multivariate regression, only obesity remained significantly associated with preeclampsia (adjusted odds ratio, 1.624; 95% confidence interval, 1.024−2.575; *P*=.039).

CONCLUSION: Before the large-scale rollout of antiretroviral therapy in a setting with a high burden of HIV and preeclampsia, untreated HIV infection was found to have a protective effect against preeclampsia. The protective effect against preeclampsia was not apparent for HIV infection treated with antiretroviral therapy.

Key words: antiretroviral therapy, HIV, immune reconstitution, infant outcomes, preeclampsia

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Why was this study conducted?

This study aimed to investigate the association between preeclampsia and HIV infection.

Key findings

There was a significant negative association between untreated HIV infection and preeclampsia.

What does this add to what is known?

Untreated HIV infection had a protective effect against preeclampsia, suggesting the requirement for further scrutiny of the effect of antiretroviral regimens on preeclampsia incidence.

Introduction

Preeclampsia, a multisystem condition of unknown etiology defined as new onset of hypertension >140/90 mm Hg occurring at or after 20 weeks of gestation with proteinuria, complicates 2% to 17% of pregnancies worldwide.[1−9] Furthermore, it has been associated with significant maternal and infant morbidity and mortality, particularly in low- and middle-income countries.[2,4,6−9] Delivery of the fetus and placental products is the only treatment of preeclampsia; thus, preeclampsia is associated with poor neonatal outcomes, such as intrauterine growth restriction, preterm birth, and neonatal death.[1]

The risk factors for preeclampsia include the extremes of maternal age (<20 and >35 years), obesity, primigravidity, genetics (family history or history in previous pregnancies), race (African ancestry), and underlying medical conditions, such as chronic hypertension, diabetes mellitus, and cardiac and renal diseases.[5,7,10]

Preeclampsia may represent a state of an exaggerated inflammatory maternal response, with a shift from the more anti-inflammatory T helper 2 (Th2) response associated with pregnancy in normotensive women to a proinflammatory T helper 1 (Th1) response.[4,11,12] Dysregulation of the complement system has also been shown to occur in preeclampsia.[13] Thus, it has been proposed that in states of immune suppression, such as HIV infection, preeclampsia would be less likely to develop, particularly if the women living with HIV are treatment naïve.[6,14−17] During untreated HIV infection, there is a shift from a Th1 to a Th2 response.[18−20] This shift has been found to be reversed with the use of antiretroviral therapy (ART). Moreover, HIV and preeclampsia may interact via the body's mechanisms of immune tolerance. A key tolerogenic enzyme indoleamine 2,3-dioxygenase (IDO) is reduced in the placenta of women with preeclampsia, suggesting a loss of immune tolerance to the foreign antigens of the fetus.[21] In contrast, during HIV, elevated levels of enzyme activity have been reported.[22] IDO is an enzyme that synthesizes nicotinamide, a key component of the cellular cofactor nicotinamide adenine dinucleotide (NAD or NAD + hydrogen in oxidized and reduced form), which is decreased with advanced age and obesity.[23] IDO catalyzed nicotinamide synthesis may be a point of intersection between HIV and preeclampsia.[24]

An increased risk of preeclampsia has been described in pregnant women with HIV, with this risk being associated with the use of ART before pregnancy and thought to possibly be owing to the toxic effects of ART.[11,25] However, the heterogeneity and small sizes of the studies investigating the association between HIV and hypertensive disorders in pregnancy have resulted in differing conclusions.[17]

This study aimed to investigate the association between HIV infection and preeclampsia by stratifying women with HIV infection into treatment-naïve and treatment-experienced groups. The main objective was to compare the prevalence of HIV infection, either treated or untreated, in pregnant women with preeclampsia compared with normotensive pregnant women. The second objective was to describe outcomes of the infants born to women with preeclampsia in terms of preterm birth, birthweight, and Apgar scores to highlight the substantial public health burden caused by preeclampsia. Moreover, we described the effect of known associations with preeclampsia, that is, age, body mass index, gravidity, and smoking.

Materials and Methods

This was a case-control study using secondary data from the database of the group B *Streptococcus* (GBS) serocorrelates study (protocol number V98_28OBTP), a multicentered case-control study conducted to determine a serocorrelate of protection against invasive GBS disease in infants <90 days. Data collected during the GBS study included demographic information and obstetrical,

medical, and behavioral history. Data on weight were collected at GBS study enrolment and therefore represented the participant's weight gained during pregnancy. Of note is that the GBS serocorrelates study period was during the transition phase to triple ART.

Here, the definition of a case with preeclampsia was a pregnant woman who participated in the GBS serocorrelates study between July 2014 and December 2016, was initially normotensive until 20 weeks of gestation, and thereafter had at least 1 high blood pressure measurement (systolic blood pressure of >140 mm Hg and/or diastolic blood pressure of >90 mm Hg), either before or at delivery, with proteinuria (defined as protein excretion of ≥300 mg within 24 hours or >2 protein on dipstick urinalysis). A control was defined as a pregnant woman who participated in the GBS serocorrelates study but in whom preeclampsia was not diagnosed and who did not meet the criteria for a case. The case-control status was verified by manual inspection of the participants' recruitment records, which were kept by the GBS study team. The exclusion criteria were an unknown or unrecorded HIV status and a history of chronic hypertension. The exclusion criteria were applicable to both cases and controls.

Assuming a power of 80%, a 1:1 case-to-control ratio, an HIV prevalence of 30% among controls, and an odds ratio (OR) of 0.62, a sample size of 1169 (572 cases and 597 controls) was determined. Eligible cases were drawn sequentially from the GBS study secondary database according to the provisional diagnosis of "pregnancy-induced hypertension or preeclampsia" until the required sample size was obtained. Blood pressure and urine protein results from the participants' files were used to confirm the final diagnosis. Concerning controls, every fifth GBS participant that met the case-control definition was included until the required number of controls was obtained. If the fifth GBS participant did not meet the criteria, the next fifth GBS participant's file was assessed for eligibility until the required number of participants was obtained.

In 2014, women were either placed on lifelong triple ART with first-line agents tenofovir, lamivudine or emtricitabine, and nevirapine or treated with single-agent zidovudine from 14 weeks of gestation, depending on the clinical criteria. In 2015, any woman with HIV was offered lifelong triple therapy irrespective of CD4 count. In this study, we defined ART as triple ART. Single-dose nevirapine administered to the mother in labor only was not included as ART use. A primigravid woman was defined as one with no history of previous pregnancies at the time of study recruitment, whereas a multigravid woman was one with a history of 1 or more previous pregnancies.

Stata statistical software (version 15, StataCorp, College Station, TX) was used for data analysis. Categorical data were summarized as frequencies and percentages and presented in tables, whereas numeric data were described as medians and ranges. All P values of <.05 were considered statistically significant. The association between preeclampsia and potential confounding variables was examined using multivariate logistic regression analysis and presented as unadjusted ORs and adjusted ORs (aORs). A cutoff P value of.2 was used to choose predictor variables that were included in the multivariate analysis, and variables with a P value of ≤.05 were kept in the final model. Model fit was assessed using the Hosmer-Lemeshow statistic.

Ethical approval was obtained from the Faculty of Health Sciences Research Ethics Committee of the University of Pretoria (ethics reference: 76/2018). Furthermore, institutional clearance was obtained from the GBS study group. Written informed consent for data and sample collection and utilization for future studies was obtained from women for participation in the parent study (Wits Human Research Ethics Committee ethics reference: 140203).

Results

The GBS study database included data of 38,233 participants, all of whom were Black Africans. Of the participants, 4042 (10%) had a history of hypertensive disease in pregnancy recorded during the current pregnancy. Based on the completeness of data of the required variables, we included 571 cases with preeclampsia and 596 controls in this study. The characteristics of the cases and controls are summarized in Table 1. Most participants were between the ages of 20 and 34 years (893 [77%]), with a median age of 27 years among cases and 26 years among controls (P=.008). There was no significant difference between the proportions of cases and controls that were pregnant for the first time (P=.176).

The overall HIV prevalence among study participants was 27% at the time of recruitment into the GBS study. The prevalence of HIV was significantly lower in women with preeclampsia than in women in the control group (24% vs 31%, respectively; P=.014). Among participants who were HIV positive, there was no difference between cases and controls in median CD4+ count (435 cells/μL among cases and 390 cells/μL among controls; P=.563). Of note, 82% of women with HIV and known treatment status were on triple ART in the group with preeclampsia, whereas only 56% of women were on triple ART in the normotensive control group (P<.0001).

The rate of obesity at study enrolment was higher in the group with preeclampsia than in the control group (50% vs 38%, respectively; P=.031). Of the 932 participants whose smoking history during pregnancy was available, 911 (98%) were nonsmokers; 1.3% of smokers were in the group with preeclampsia, and 3.1% of smokers were in the control group (P=.069).

The proportion of infants born preterm was higher in the group with preeclampsia than in the control group (48% vs 16%, respectively; P<.0001). Among mothers of preterm infants, there was no difference in the proportion of mothers with HIV in the group with preeclampsia vs the control group (29% vs 33%, respectively; P=.461). The proportion of infants with low birthweight was higher in the group with preeclampsia than in the control group (298 [53%] vs 82 [13.9%], respectively;

TABLE 1
Characteristics of pregnant women with preeclampsia (cases) vs normotensive pregnant women (controls)

Variable	Overall, n (%)	Preeclampsia, n (%)	Control, n (%)	*P* value
Mom's age (y)				
<20	94 (8.1)	47 (8.2)	47 (7.9)	.008
20–34	893 (76.5)	417 (73.0)	476 (79.9)	
≥35	180 (15.4)	107 (18.7)	73 (12.2)	
Gravidity				
Primigravid	367 (31.3)	190 (33.2)	177 (29.5)	.176
Multigravid	804 (68.7)	382 (66.8)	422 (70.5)	
Mom's HIV status				
Positive	321 (27.4)	138 (24.1)	183 (30.6)	.014
Negative	850 (72.6)	434 (75.9)	416 (69.4)	
HIV status and treatment				
HIV negative	850 (72.6)	434 (75.9)	416 (69.4)	<.0001
HIV positive, treatment experienced	216 (18.4)	113 (19.8)	103 (17.2)	
HIV positive, treatment naïve	82 (7.0)	21 (3.7)	61 (10.2)	
HIV positive, unknown treatment status	23 (2.0)	4 (0.7)	19 (3.2)	
Mom's median CD4 (IQR)	n=126; 393.5 (217.0–559.0)	n=49; 435.0 (229.0–559.0)	n=77; 390.0 (215.0–558.0)	.563
HIV treatment status in HIV-infected women				
HIV positive, treatment experienced	216 (67.3)	113 (81.9)	103 (56.3)	<.0001[a]
HIV positive, treatment naïve	82 (25.5)	21 (15.2)	61 (33.3)	
HIV positive, unknown treatment status	23 (7.2)	4 (2.9)	19 (10.4)	
Mom's BMI status				
Underweight	4 (1.3)	1 (0.7)	3 (1.9)	.031[a]
Normal	85 (27.7)	30 (20.7)	55 (34.0)	
Overweight	85 (27.7)	42 (29.0)	43 (26.5)	
Obese	133 (43.3)	72 (49.7)	61 (37.7)	
Mom's median body mass index (IQR)	n=310; 28.8 (24.5–34.2)	n=146; 29.8 (25.6–35.4)	n=164; 27.3 (23.3–32.8)	.002[a]
Mom's smoking status				
Yes	21 (2.3)	6 (1.3)	15 (3.1)	.069
No	911 (97.7)	443 (98.7)	468 (96.9)	
Gestation known				
Term birth	796 (68.4)	295 (51.9)	501 (84.2)	<.0001[a]
Preterm	367 (31.6)	273 (48.1)	94 (15.8)	
HIV status among mothers with preterm births				
Positive	110 (30.0)	79 (28.9)	31 (33.0)	.461
Negative	257 (70.0)	194 (71.1)	63 (67.0)	
Infant birthweight				
Low birthweight (<2500 g)	380 (32.9)	298 (52.8)	82 (13.9)	<.0001[a]
Normal birthweight	774 (67.1)	266 (47.2)	508 (86.1)	
HIV status among mothers with low birthweight infants				
Positive	111 (29.2)	85 (28.5)	26 (31.7)	.575

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(continued)

TABLE 1
Characteristics of pregnant women with preeclampsia (cases) vs normotensive pregnant women (controls)Please check if changes made to Table 1 are okay. *(continued)*

Variable	Overall, n (%)	Preeclampsia, n (%)	Control, n (%)	*P* value
Negative	269 (70.8)	213 (71.5)	56 (68.3)	
Infant Apgar score (5 min)				
Low (0−3)	8 (0.7)	6 (1.1)	2 (0.4)	.017[a]
Moderately abnormal (4−6)	18 (1.6)	14 (2.5)	4 (0.7)	
Reassuring (7−10)	1095 (97.7)	532 (96.4)	563 (98.9)	

BMI, body mass index; *IQR*, interquartile range.

[a] Statistically significant.

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P<.0001). Among infants whose Apgar scores were available, 1095 (97%) had a score of >7.

Untreated HIV infection was a protective factor against preeclampsia (unadjusted OR, 0.330; 95% confidence interval [CI], 0.197−0.552; *P*<.001), whereas advanced maternal age of >35 years and obesity were significantly associated with preeclampsia (Table 2). After adjusting for maternal age, smoking, and gravidity, only obesity remained a significant predictor for preeclampsia (aOR, 1.624; 95% CI, 1.024−2.575; *P*=.039).

Discussion

Principal findings

The overall HIV prevalence of 27% in our study was consistent with the national antenatal sentinel survey estimates of 28% in 2014 and 30% in 2015 in Gauteng Province, South Africa.[26] The prevalence of HIV was significantly lower in women with preeclampsia than in normotensive women, a finding that has been described in the literature.[6,11] Furthermore, untreated HIV infection was found to be a protective factor against preeclampsia, similar to what

TABLE 2
Univariate and multivariate logistic regression of the association between preeclampsia and known predictor variables

Variable	Univariate OR (95% CI)	*P* value	Multivariate Adjusted OR (95% CI)	*P* value
HIV and ART[a]				
HIV positive (treatment experienced) vs HIV negative	1.052 (0.780−1.418)	.742	1.203 (0.677−2.137)	.529
HIV positive(treatment naïve) vs HIV negative	0.330 (0.197−0.552)	<.0001[b]	0.324 (0.103−1.021)	.054
HIV status				
Positive vs negative	0.723 (0.558−0.936)	.014[b]		
Maternal age (y)				
<20 vs 20−34	1.141 (0.746−1.746)	.543		
≥35 vs 20−34	1.673 (1.209−2.316)	.002[b]		
BMI group				
Obese vs not obese	1.611 (1.023−2.537)	.040[b]	1.624 (1.024−2.575)	.039[b]
Gravidity				
Primigravid vs multigravid	1.186 (0.926−1.518)	.177		
Smoking				
Yes vs no	0.423 (0.163−1.099)	.078		
Hosmer-Lemeshow fit statistics	0.975			

ART, antiretroviral therapy; *BMI*, body mass index; *CI*, confidence interval; *OR*, odds ratio.

[a] Note: The proportion of HIV-infected women whose HIV treatment status was unknown was excluded from the logistic regression analysis; [b] Statistically significant.

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has been described in other studies.[14,25] It has been postulated that among treatment-experienced pregnant women who are HIV positive, the immune reconstitution associated with ART use and the toxic mechanism involving endothelial inflammation and liver damage result in the loss of the protective effect from untreated HIV, resulting in an increased risk of preeclampsia.[11,14,16,18,27] There are conflicting data regarding the type of ART regimens associated with preeclampsia, particularly concerning the use of protease inhibitors.[28–30] Although our study did not include details of the regimen of the treatment-experienced women who are HIV positive, it is likely that most of the women were on an efavirenz-based regimen rather than a protease-based regimen. Although other studies have examined the association between HIV and preeclampsia, the differences in the study design and inclusion of preeclampsia-associated comorbidities in other studies make the comparison of the study results challenging.[12,28,30–32] Moreover, our data showed that advanced maternal age and obesity were risk factors for preeclampsia.

The association between advanced maternal age (>35 years) and preeclampsia has been proposed to be because of the age-related damage of vessels,[5,33–35] whereas obesity has also been found to be a risk factor for preeclampsia, particularly in the setting of HIV infection.[5,11,36] These associations lend strength to our study as we have replicated the findings of others.

Preterm birth and low birthweight have been described to occur more commonly among infants born to women who are HIV positive.[1,2,32,37] Moreover, preeclampsia has been described as associated with up to 15% of preterm births.[1] However, the public health burden of preeclampsia in terms of neonatal outcomes in low- or middle-income countries is often not fully appreciated. Here, of all infants born to women with preeclampsia, 48% were preterm, whereas 53% were of low birthweight, irrespective of the HIV status of the mother. Of the 367 preterm infants in this study, 273 (74%) were born to mothers with preeclampsia. Of the 380 infants with low birthweight, 53% were born to mothers with preeclampsia, irrespective of the HIV status of the mother. Prospective studies are required to document the magnitude of the contribution of preeclampsia to adverse birth outcomes in the country.

Future interventions addressing preeclampsia would make a huge effect on infant health in South Africa.

Clinical implications

The effect of different antiretroviral regimens on the incidence of preeclampsia in women with HIV should be prospectively studied.

Research implications

We recommend prospective studies of preeclampsia rates in women with and without HIV in South Africa, including the analysis of the effect of different antiretroviral regimens. The contribution of preeclampsia to the burden of adverse infant birth outcomes and neonatal admissions should be quantitatively described in African countries. A negative association between preeclampsia and HIV may yield testable hypotheses of potentially protective factors against preeclampsia, including investigation of the enzyme activity of IDO, known to be elevated in HIV and protective in maternal-fetal tolerance at the placenta.

Strengths and limitations

Our study had several limitations. The participants' original hospital records were not reviewed; thus, the missing data in the secondary database could not be accounted for. All participants were African American; thus, the association between preeclampsia and race could not be assessed. As such, the findings of this study cannot be generalized to women of other races. Moreover, our sampling approach had some bias because participants were not matched; thus, limiting the ability to account for the differences in results observed. The CD4+ count results of the participants were not all recent at the time of recruitment to the GBS study, and therefore, did not reflect the current immunologic status of the participants at the beginning of our study.

In addition, our study had strengths, such as a large dataset that allowed us to make robust statistical comparisons and systematic selections of cases and controls. Our sample incorporated a large proportion of women with HIV who were both treatment naïve and treatment experienced. Our findings of significant univariate associations with well-established risk factors, such as advanced maternal age and obesity, suggested that our study design was robust for the detection of factors positively and negatively associated with preeclampsia.

Conclusions

Our study showed that untreated HIV infection in Black women was negatively associated with preeclampsia. Although these results suggested that untreated HIV infection is protective against preeclampsia, considering the risk of mother-to-child transmission of HIV, initiating treatment on the day that pregnancy is confirmed as per current South African national HIV management guidelines is still the best practice. Thus, the optimal management of preeclampsia in the context of HIV would involve close monitoring of women with treated HIV infection and preeclampsia. The high burden of preeclampsia on infant birth outcomes makes it imperative to confirm whether the choice of ART regimen influences the risk of preeclampsia. ■

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