East African Medical Journal Vol. 97 No. 11 November 2020
RISK FACTORS FOR ADVERSE PREGNANCY EVENTS WITH HIV IMMUNE RECONSTITUTION SYNDROME AMONG ART NAÏVE PREGNANT WOMEN OF REPRODUCTIVE AGE IN SELECTED HOSPITALS, NAIROBI, KENYA

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RISK FACTORS FOR ADVERSE PREGNANCY EVENTS AND CORRELATION WITH HIV IMMUNE RECONSTITUTION INFLAMMATORY RESPONSE AMONG WOMEN OF REPRODUCTIVE AGE IN SELECTED HOSPITALS, NAIROBI, KENYA

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ABSTRACT

Introduction: **More than 10% of the global disease burden is due to pregnancy complications and related birth outcomes and despite recent advances in obstetric medicine, it remains a public health concern.**

Objective**: This study sought to determine the incidence and risk factors for adverse pregnancy outcomes and association with maternal-HIV-immune reconstitution inflammatory Syndrome (IRIS).**

Design**: A prospective cohort was used. Subjects were followed from the end of first trimester for six and half months. Chi-square test was used to establish the association between the variables at p-value < 0.05. Regression analysis was performed to identify independent predictors of APFOs. Adjusted odds ratio at 95% confidence interval was determined.**

Setting**: Kenyatta National and *Mbagathi* Hospitals, Nairobi County, Kenya.**

Results**: Cumulative incidence of APFOs were 27(26.5%) compared to 11(10.8%) in IRIS cases versus non-IRIS cases respectively. Women with IRIS had 2.46 relative risk of experiencing an adverse pregnancy outcome compared to those without IRIS.**

Conclusion**: Maternal HIV-IRIS was significantly associated with adverse pregnancy outcome in *bivariate* analysis. Multiple regression dropped maternal HIV-IRIS revealing the following as independent predictors: HIV-RNA viral load at baseline of above 50 copies/ml [AOR=2.7; 95%CI: 1.2-6.3; P=.017], Maternal placental syndrome hypertensive event [AOR=0.1; 95%CI: 0.0-1.0; P = .052] and mother's general health during delivery [AOR= 4; 95%CI: 4.0:1.8-9.1; P=.001].**

INTRODUCTION

Anti-retro-viral therapy (ART) during pregnancy should focus on reducing prenatal transmission and treat maternal human immunodeficiency virus (HIV) disease. ART can cut perinatal transmission by several mechanisms, including lowering maternal ante-partum viral load and pre-exposure and post exposure prophylaxis of the infant. Therefore, for prevention of perinatal transmission of HIV, joined ante-partum, intra-partum, and infant anti-retro-viral prophylaxis is important (1). Initiating combination anti-retro-viral therapy (ART) can meet suppression of viral replication and an increase in CD4+ T-cell counts in most patients (2), resulting in dramatic decrease in morbidity and AIDS-related mortality(3). However, ART initiation is not without risk of complications, particularly in the first 6 months(4). Mortality related with IRIS is uncommon; however, associated high morbidity contributes to burden on the health-care system(5). This has become a public health concern, as ART use has been associated with increased IRIS inform of opportunistic conditions and other non-infectious conditions.

In HIV-infected pregnant women, the administration of ART during pregnancy and/or intra-partum significantly reduces the risk of mother-to-child transmission (MTCT) of HIV (6). ART also has directly and indirectly been found to be of significant contribution to poor pregnancy outcomes (7). Also, subgroup of patients experiences a clinical deterioration as a consequence of rapid and dis-regulated restoration of antigen specific immune responses during the treatment(8,9).

Given that the evidence for the incidence of up to 30 percent of ART res-ponders developing one or more inflammatory syndromes consistent with IRIS (10), the conditions associated with it will have their greatest impact in resource-poor countries, where patients are often very immune-deficient, including pregnancy associated immune-depression and opportunistic pathogens when therapy is commenced(11).

MATERIALS & METHODS

The present study was conducted at Kenyatta National and Mbagathi Hospitals both located in Nairobi County. The study design was a prospective cohort, and the subjects were recruited and followed from the end of first trimester for six and half months after they were confirmed to be HIV positive and put-on ARV with a defined case of HIV-IRIS as exposed and non-exposed cohort, immediately after the first trimester. A pretested questionnaire was used and matching by age and parity was performed. There were three visits post IRIS identification stage: at sixth month, at delivery and within two weeks post-delivery. The data collected was analyzed using SPSS version 25.0. Chi-square test was used to establish the association between the dependent and independent variables and the level of statistical significance was set at p-value < 0.05. Multiple logistic regression analyses were performed to adjust for confounding. AOR with corresponding 95% confidence interval was estimated. The approval to carry on with the research was sought from KNH/UON- ERC and permission for the selected facilities' entry and data collection was sought accordingly.

RESULTS

Social-demographic and economic characteristics: Table 1 shows selected social-demographic characteristics. The common maternal age was 30-39 years, larger proportion of this age category being in women who did not experience APFOs though not significant 19 (18.4) ; 84 (81.6) [OR = 0.9; 95% CI: 0.7-2.4; P=

.728]. Adverse pregnancy outcomes were more likely among separated mothers [OR=4.2; 95%CI: 1.0-16.9; P=0.044]. There was a difference in the proportion of woman's level of education among women experiencing adverse pregnancy outcomes and those not experiencing but this observation was not significant (P>0.95). There was no statistically significant observation at (P>0.05) between the other social-demographic characteristics.

Table 1

Comparison of Social-demographic characteristics between women experienced adverse pregnancy outcomes and those who did not

Variable	APO		OR (95% CI)	P value
	Yes n (%)	No n (%)		
Maternal age in years				
20-29	15 (20.5)	58 (79.5)	1.0	
30-39	19 (18.4)	84 (81.6)	0.9 (0.4-1.7)	0.728
40-49	4 (14.3)	24 (85.7)	0.6 (0.2-2.1)	0.473
Location/address				
Nairobi	29 (17.8)	134 (82.2)	0.8 (0.3-1.8)	0.541
Outside Nairobi	9 (22.0)	32 (78.0)	1.0	
Education level				
No formal education	1 (4.8)	20 (95.2)	1.0	
Primary	4 (16.7)	20 (83.3)	4.0 (0.4-39.0)	0.233
Secondary	22 (20.2)	87 (79.8)	5.1 (0.6-39.8)	0.123
Higher/university	11 (22.4)	38 (77.6)	5.8 (0.7-48.1)	0.104
Occupation				
Unemployed	15 (17.4)	71 (82.6)	1.0	
Civil servant	4 (25.0)	12 (75.0)	1.6 (0.4-5.6)	0.479
Self-employed	18 (17.8)	83 (82.2)	1.0 (0.5-2.2)	0.946
Religion				
Christian	36 (19.0)	153 (81.0)	1.5 (0.3-7.1)	0.742
Muslim	2 (13.3)	13 (86.7)	1.0	
Marital status				
Single	11 (18.3)	49 (81.7)	1.2 (0.5-2.6)	0.693
Married	21 (16.0)	110 (84.0)	1.0	
Separated	4 (44.4)	5 (55.6)	4.2 (1.0-16.9)	**0.044**
Windowed	0	1 (100)	0	1.000
Income source				
Employed	3 (25.0)	9 (75.0)	1.4 (0.3-6.1)	0.680
Self employed	25 (19.2)	105 (80.8)	1.0 (0.4-2.3)	0.961
House wife	9 (19.6)	37 (80.4)	1.0	

Incidence of APOs over the entire follow-up period: Table 2 below shows 26.47% in IRIS APOs compared to 10.78 % in non-IRIS. IRIS cases had higher risk of APO [OR=3; 95%CI: 1.4-6.4; P=.004].

Table 2

Cumulative incidence and OR of APO

Variable	**APO**		**OR (95% CI)**	**P value**
	Yes n (%)	**No n (%)**		
IRIS				
Yes	27 (26.5)	75 (73.5)	3.0 (1.4-6.4)	0.004
No	11 (10.8)	91 (89.2)	1.0	

APOs and enrollment baseline characteristics: Table 3, APO incidence was significantly more among women with opportunistic [OR= 2.3; 95%CI: 1.1-4.8; P=.013], slightly significant with the CD4 Count of <350 cells per cubic millimeter [OR=2.1; 95%CI: 1.0-4.4; P=.051]. HIV ribonucleic acid viral loads level of <50 copies/ml was protective [OR=0.4; 95%CI: 0.2-0.7; P=.004]. There was no significant difference with respect to woman's HIV, previous medical history, neurological extensive physical examination, full blood count and basic blood chemistry (P>.05).

Table 3

Comparison of women with and without APOs in relation to baseline characteristics

Variable	APO		OR (95% CI)	P value
	Yes n (%)	No n (%)		
WHO-HIV Staging-2016				
Primary stage	12 (18.5)	53 (81.5)	1.0	-
Clinical stage 1	17 (15.2)	95 (84.8)	0.8 (0.4-1.8)	0.570
Clinical stage 2	8 (33.3)	16 (66.7)	2.2 (0.8-6.3)	0.141
Clinical stage 3	1 (33.3)	2 (66.7)	2.2 (0.2-26.4)	0.531
Medical History				
Previous illnesses				
Yes	8 (32.0)	17 (68.0)	2.3 (0.9-5.9)	0.096
No	30 (16.8)	149 (83.2)	1.0	
Opportunistic infections				
Yes	20 (27.8)	52 (72.2)	2.3 (1.1-4.8)	**0.013**
No	18 (13.6)	114 (86.4)	1.0	
Extensive Physical exam				
Neurological				
Yes	6 (26.1)	17 (73.9)	1.6(0.6-4.5)	0.392
No	32 (17.7)	149 (82.3)	1.0	
Skin				
Yes	9 (25.0)	27 (75.0)	1.6 (0.7-3.7)	0.287
No	29 (17.4)	138 (82.6)	1.0	
CD4 counts				
<350	26 (23.6)	84 (76.4)	2.1 (1.0-4.4)	**0.051**
>350	12 (12.9)	81 (87.1)	1.0	
HIV viral loads				
> 50 copies/ml	20 (13.7)	126 (86.3)	0.4 (0.2-0.7)	**0.004**
< 50 copies/ml	18 (31.0)	40 (69.0)	1.0	
Full Blood Count				
Abnormal	7 (31.8)	15 (68.2)	2.3 (0.9-6.0)	0.141
Normal	31 (17.0)	151 (83.0)	1.0	
Basic blood Chemistry				
Abnormal	1 (16.7)	5 (83.3)	0.8 (0.1-7.7)	1.000
Normal	37 (18.7)	161 (81.3)	1.0	

APOs by maternal health (during pregnancy) and/or at birth and Type of ARV Combination: Table 4: Maternal hypertensive disorder was protective for APO [O. R=0.2; 95% CI: 0.1-1; P=0.031]. Type of ART combination was insignificant (P> 0.05).

Table 4

APOs by maternal health (during pregnancy) and/or at birth and Type of ARV Combination

Variable	APO		OR (95% CI)	P value
	Yes n (%)	No n (%)		
Prophylaxis during Pregnancy				
Yes	22 (21.6)	80 (78.4)	1.5 (0.7-3.0)	0.281
No	16 (15.7)	86 (84.3)	1.0	
Maternal Substance Abuse				
Yes	1 (7.1)	13 (92.9)	0.3 (0.04-2.5)	0.475
No	37 (19.5)	153 (80.5)	1.0	
MPS				
Yes	2 (5.7)	33 (94.3)	0.2 (0.1-1.0)	**0.031**
No	36 (21.3)	133 (78.7)	1.0	
Maternal anemia				
Yes	3 (27.3)	8 (72.7)	1.7 (0.43-6.7)	0.433
No	35 (18.1)	158 (819)	1.0	
Caesarean section delivery				
Yes	5 (21.7)	18 (78.3)	1.2 (0.4-3.6)	0.776
No	33 (18.2)	148 (81.8)	1.0	
Maternal Body Mass index (BMI)				
< 18.5 kg/m² (Underweight)	5 (15.6)	27 (84.4)	1.1 (0.4-3.2)	0.899
18.5 – 25.0 kg/m²(normal)	15 (14.7)	87 (85.3)	1.0	
25.0 - 29.9 kg/m² (overweight)	14 (26.4)	39 (73.6)	2.1 (0.9-4.7)	0.080
> 30 kg/m² (obese)	4 (23.5)	13 (76.5)	1.8 (0.5-6.2)	0.363
Any other maternal infections/conditions/co-morbidities				
Yes	4 (23.5)	13 (76.5)	1.4 (0.4-4.5)	0.531
No	34 (18.3)	152 (81.7)	1.0	
Obstetrical Interventions				
Stress test	2 (33.3)	4 (66.7)	1.0	-
Amniocentesis	27 (18.8)	117 (81.3)	0.5 (0.08-2.7)	0.386
Tocolysis	1 (9.1)	10 (90.9)	0.2 (0.01-2.9)	0.237
Rhesus factor				
Positive	35 (19.3)	146 (80.7)	1.6 (0.5-5.7)	0.580
Negative	3 (13.0)	20 (87.0)	1.0	
Parity				
1	12 (13.6)	76 (86.4)	1.0	-
2-3	21 (21.9)	75 (78.1)	1.8 (0.8-3.9)	0.149
4-5	5 (27.8)	13 (72.2)	2.4 (0.7-8.1)	0.145
6-7	0	2 (100)		
Any previous adverse infant outcome				
Yes	6 (25.0)	18 (75.0)	1.5 (0.6-4.2)	0.406
No	32 (17.8)	148 (82.2)	1.0	

Multivariate level analysis of risk factors for adverse pregnancy outcomes: Multivariate analysis was performed to evaluate the independent risk factors associated with adverse pregnancy outcomes. Seven (7) variables that were associated with adverse pregnancy outcomes at P<0.05 during bivariate analysis were considered in a multiple regression analysis. These included: (1) woman's IRIS status, (2) Separated marital status, (3) opportunistic infections, (4) HIV-RNA viral loads at baseline, (5) Cluster of differentiation at baseline, (6) Mothers general health during delivery and (7) maternal placental syndrome with an hypertensive event. *'Backward conditional'* progressive stepwise model with removal at P<0.05, retained in the final analysis, three factors. HIV-RNA viral load at baseline > 50 copies/ml [AOR=2.7; 95%CI: 1.2-6.3; P=.017], mothers general health during delivery [AOR= 4; 95%CI: 4.0: 1.8-9.1; P=.001] and inconclusively, maternal placental syndrome characterized by hypertensive [AOR=0.1; 95%CI: 0.0-1.0; P = .052].

Table 5

Multivariate analysis of risk factors associated with adverse pregnancy outcomes

Variable	AOR (95% CI)	P Value
Full model		
IRIS		
Yes	1.6 (0.4-5.8)	0.508
No	1.0	
Marital status		
Single	1.4 (0.5-3.6)	0.529
Married	1.0	
Separated	2.4 (0.5-11.5)	0.259
Widowed	-	1.000
Opportunistic infections		
Yes	1.8 (0.7-4.5)	0.200
No	1.0	
CD4 counts at baseline		
<350	0.5 (0.1-1.8)	0.293
>350	1.0	
HIV viral load at baseline		
> 50 copies/ml	2.8 (1.1-7.2)	0.036
< 50 copies/ml	1.0	
MPS		
Yes	0.1 (0.0-1.0)	0.048
No	1.0	
Mothers General health during delivery		
Sick	3.2 (1.3-7.9)	0.014
Not Sick	1.0	
Reduced model		
HIV viral load at baseline		
> 50 copies/ml	2.7 (1.2-6.3)	0.017
< 50 copies/ml	1.0	
MPS		
Yes	0.1 (0.0-1.0)	0.052
No	1.0	
Mothers General health during delivery		
Sick	4.0 (1.8-9.1)	0.001
Not Sick	1.0	

DISCUSSIONS

This study has demonstrated that, maternal HIV immune reconstitution inflammatory response syndrome increases the incidence risk of adverse pregnancy in ART naïve women. HIV-infection among pregnant women has been linked with multiple *adverse pregnancy outcomes as* compared to non-infected which was due to use of ART (12).

Similarly, a study on the association between maternal HIV among ART treated women and perinatal outcome including neonatal mortality showed some positive association (OR=1.1, 95%ci 0.63-1.93) (13).

In another study, among women initiating ART in pregnancy, HAART use was associated with higher odds of preterm delivery (AOR, 1.4; 95% CI, 1.2, 1.8), SGA (AOR, 1.5; 95% CI, 1.2, 1.9), and SB (AOR, 2.5; 95% CI, 1.6, 3.9) (14). However, these studies are not related to this they did not focus on the immune reconstitution inflammatory response syndrome.

The findings support that, other factors other than maternal HIV-IRIS predict the adverse pregnancy outcomes. Maternal health during pregnancy which may be due to IRIS is associated with adverse pregnancy outcomes. Excess adverse pregnancy outcomes in HIV-infected ART naïve pregnant women is not primarily explained by the associated opportunistic infections due to IRIS but was strongly associated with HIV-RNA-loads of > 50 copies/ml at baseline, and possibly, any form of hypertensive disorder during pregnancy or maternal placental syndrome, similar to a study done in Haiti (15).

Presence of any hypertensive disorder during pregnancy, although being protective at reduced model for adverse pregnancy outcomes, was at the borderline and seemingly predicted the outcome but not conclusive as a risk factor associated with adverse pregnancy outcomes (AOR=0.1, 95% CI: (0.0-1.0); P=.052). Similar to this finding, in a systematic review and meta-analysis study, no single test of hypertensive disorder was a strong independent predictor of an adverse pregnancy outcome. The most promising prediction was with multivariable models, especially when oxygen saturation, or chest pain/dyspnea were included, just at borderline showing other inter-related clinical courses (16,17). In another cohort study, there was a mixed prediction of both protective and significant association for adverse pregnancy and birth outcomes: decreased risk of LGA (OR 0.65, 0.51-0.83), with a recommendation that; hypertensive disorder should be combined with other maternal characteristics, medical and obstetric history when calculating an individualized adjusted risk for adverse pregnancy complications(18).

Mother's general health was highly significant for adverse pregnancy outcomes in this prospective cohort study. There are mechanisms thought to account for the synergy between neonatal mortality outcome and infections during pregnancy and delivery that lead to neonatal mortality by affecting proper fetal growth and development. Regarding this, women who were defined as 'sick' had four times incident of adverse pregnancy outcomes compared to women who were not defined as sick within the same periods of time[OR=4 ; 95%CI:1.8-9.1; P=.001], which is reflective to a case control study done in Jimma University on determinants of adverse pregnancy outcomes where; mothers who had illness during current pregnancy had seven times risk of adverse birth outcome [AOR=7.22, 95% CI:1.65-31.58] (19). This finding compare well with study examining maternal characteristics associated with adverse pregnancy outcomes(20).

HIV-RNA viral load of > 50 copies/ml at the baseline during the first trimester among

the HIV positive ART naïve women was found to be associated almost three times with adverse pregnancy outcomes as compared to HIV-RNA viral load of < 50 copies/ml. This was in regard to being a risk factor for IRIS identification which was the main predictor variable for adverse pregnancy outcomes. This correlates with another USA based study on burden of viral load which showed that, extent of HIV replication during pregnancy, as represented by plasma HIV RNA viral load, predicted an adverse pregnancy outcome; the risk of pregnancy loss for those with $\log_{10}$ viral load >4.00 before pregnancy ended was 1.59 (95% confidence interval (CI): 0.99, 2.56) times as high as the risk for women whose $\log_{10}$ viral load was ≤1 (21). In a study, which although compared HIV positive women and HIV negative women, there was a significantly higher risk of low birth weight (RR 2.29, 95% CI 1.34–3.92; *P* =0.03) and prematurity (<37 weeks) (RR 1.93, 95% CI 1.35–2.77; *P* =0.0003). It concluded that, HIV-infected women, particularly those who are symptomatic, are at a higher risk of adverse pregnancy outcomes (22).

The study indicates that adverse pregnancy outcomes were significantly associated with opportunistic infections OR= 2.3; 95%CI: (1.1-4.8); P=.013) in bivariate analysis, but it did not predict neonatal mortality outcome in multivariate level. This imitates a conference paper by Charlene and Megan, 2017. This fact of opportunistic infections predicting adverse pregnancy outcomes is commensurate with mother's general well-being at delivery in this study which shows a four-fold prediction rate for adverse pregnancy outcomes at logistic regression, reduced model.

CONCLUSION

Adverse pregnancy outcome was associated with maternal HIV immune reconstitution inflammatory response syndrome but was insignificant after adjusting for the potential confounders at the multivariate analysis since multiple logistic regressions revealed that; Maternal placental syndrome characterized by hypertensive event although not conclusive, Mothers General health during delivery and plasma HIV-RNA viral load at baseline of above 50 copies/ml as independent factors associated with adverse pregnancy outcomes.

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