Masters of medicine

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Timing of onset and severity of pre-eclampsia in HIV positive pregnant women on antiretroviral therapy compared to HIV negative pregnant women

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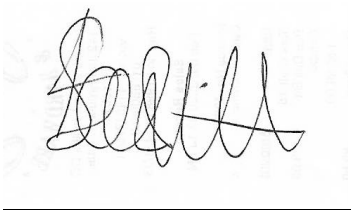
Both authors were involved in conceptualizing the study. Dr I. Small-Smith collected the data, did the data analysis and wrote the first draft of the manuscript.

Both authors contributed to the final write-up.



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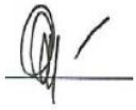

Dr. C Mnyani
Supervisor

Dedication

I dedicate this Masters to my husband, Nick and our daughter, Mila.
Thank you for being so understanding and supportive.

Presentations

04/07/2018: Oral presentation at Charlotte Maxeke Johannesburg Academic Hospital

Abstract

Background: The association between pre-eclampsia, HIV infection and antiretroviral therapy (ART) is poorly understood. Little is known about the timing of onset and severity of disease in HIV-positive patients on ART.

Objective: To compare the timing of onset and severity of pre-eclampsia amongst HIV-positive pregnant patients on ART and HIV-negative pregnant patients. Secondary outcomes included maternal and neonatal outcomes.

Methods: A retrospective record review of patients with pre-eclampsia who delivered at Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) between 1 July and 31 December of 2017 was done.

Results: Of the 100 patients enrolled in the study, 79% were HIV-negative and 21% were HIV-positive. HIV-positive patients had an earlier gestational age of onset of pre-eclampsia, 30±5 weeks vs. 32.5±4.9 weeks ($p<0.05$), and consequently an earlier gestation at delivery compared to HIV-negative patients, 31.3±4.5 weeks vs. 34±4.9 weeks ($p<0.05$). The incidence of severe pre-eclampsia was similar in the two groups with a odds ratio (OR) of 1.08 (95% confidence interval (CI) 0.38 - 3) There was no difference in maternal outcomes, but neonatal outcomes were poorer in the HIV-positive group with fewer live births with an OR of 0.24 (CI 0.06 - 0.86), and more intrauterine fetal deaths with an OR of 7.92 (CI 1.57 - 39.67).

Conclusion: In this study, HIV-positive pregnant patients on ART had earlier onset of pre-eclampsia. There was no statistical difference in severity of disease and maternal outcomes but HIV-positive patients had poorer neonatal outcomes. Further studies are needed to confirm these findings.

Acknowledgements

I would like to thank CMJAH and the Department of Obstetrics and Gynaecology for allowing me to access their data, as well as my supervisor, Dr Mnyani, for her ongoing support and advice

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List of abbreviations

AZT	Zidovudine
ART	Antiretroviral therapy
ARDS	Acute inflammatory distress syndrome
CMJAH	Charlotte Maxeke Johannesburg Academic Hospital
DIC	Disseminated intravascular coagulopathy
GA	Gestational age
HELLP	Haemolysis elevated liver enzymes, low platelets
HIV	Human immunodeficiency virus
HPT	Hypertension
IRIS	Immune reconstitution inflammatory syndrome
IUGR	Intrauterine growth restriction
LMIC	Low and middle income countries
MAP	Mean arterial pressure
mTOP	Medical termination of pregnancy
WHO	World health organization

Introduction

The association between pre-eclampsia, HIV infection and antiretroviral therapy (ART) is poorly understood. Hypertensive disorders of pregnancy are the second leading cause of maternal deaths in South Africa with a maternal mortality ratio (MMR) of 24 deaths per 100 000 live births reported in 2017. They are second only to non-pregnancy related infections, largely HIV-related, with a MMR of 32 deaths per 100 000 live births reported in the same year. (1) South Africa has a high HIV prevalence rate among pregnant women and this has plateaued at around 30% for the past 13 years. (2) Since 2015, the country's HIV guidelines recommend ART initiation for all HIV positive patients from the time of HIV diagnosis. The National Antenatal Sentinel HIV survey in 2017 found that 98.2% of HIV-positive pregnant women attending antenatal clinics in the public sector were on ART. (2)

Literature on the link between hypertensive disorders of pregnancy and HIV infection remains inconsistent. The pathophysiology of pre-eclampsia, a complication of hypertension in pregnancy, is complex. Defective placental invasion and immunological abnormalities are thought to be the initial insult, which is then followed by a systemic inflammatory response. (3) HIV infection causes immune suppression while ART causes reconstitution of the immune system and thus it is thought that the immune response related to the development of pre-eclampsia would be modified in HIV-positive pregnant women. In the absence of treatment, HIV infection has been hypothesized to decrease the risk of pre-eclampsia as the immune response is minimized or inhibited. As the immune system reconstitutes with ART, the risk of pre-eclampsia is then hypothesized to return to the same as in HIV-negative women or even increase with an immune reconstitution inflammatory syndrome (IRIS)-like phenomena. (4) Two large meta-analyses published in 2014 and 2016 failed to show a link between HIV infection and hypertensive disorders of pregnancy. (4) Suy et al., in a large study done in Spain, however showed an increased risk of pre-eclampsia in HIV-positive women when compared to HIV-negative women (OR 4.3; 95% CI 1.9-9.0; $p<0.001$) and highlighted ART usage prior to pregnancy as a risk factor for the development of pre-eclampsia. (5)

South African data are limited, but a large study with 2 266 participants, done in the Western Cape showed a significant decrease in the incidence of gestational hypertension and pre-eclampsia in HIV-positive women, with 4.8% of HIV-positive and 7.9% of HIV-negative women being affected by the disease ($P<0.01$). There was no difference in incidence of pre-eclampsia between the 200 HIV-positive women on ART and the 865 women on Zidovudine (AZT) monotherapy. (6) The authors also found no difference in incidence when the HIV-positive women were stratified according to a CD4 count of above and below 350 cells/mm^3. Another study done in Cape Town, comparing spontaneous and medically induced preterm delivery in HIV-positive and HIV-negative women, showed no difference between rates of pre-eclampsia in the two groups. (7) Women who received more than four weeks of ART were however more likely to develop severe pre-eclampsia. ($p=0.007$) (7)

The majority of studies report on the incidence of pre-eclampsia, with limited data on the severity of pre-eclampsia and outcomes in pregnant women with HIV infection. (5,6,8,9) Hence the aim of this study was to assess the timing of onset and severity of pre-eclampsia in HIV-positive women on ART compared to HIV-negative women.

Methods

Study setting

This study was conducted at Charlotte Maxeke Johannesburg Academic Hospital (CMJAH), in South Africa, an academic hospital that offers tertiary and quaternary services. The obstetrics department at CMJAH is a referral unit for primary healthcare clinics, district and regional hospitals in the area. There are approximately 9 600 deliveries a year, with a caesarean section rate of around 45%. The antenatal clinic sees about 2 200 patients per month, with a 30% HIV prevalence amongst pregnant women, in keeping with national levels. High-risk obstetrics patients, who include all hypertensive patients, are seen in the antenatal clinic.

Study design

A retrospective record review was done of maternity case records of patients with a diagnosis of pre-eclampsia admitted to CMJAH from 1 July to 31 December 2017. The inclusion criteria were pregnant women with a singleton pregnancy, known HIV status and on ART if HIV-positive. The primary outcomes compared were timing of onset and severity of pre-eclampsia, and the secondary outcomes assessed were maternal and neonatal outcomes.

Pre-eclampsia was defined as hypertension occurring at or after the 20^{th} week of pregnancy with one or more of the following: proteinuria, maternal organ dysfunction or uteroplacental dysfunction as diagnosed by intrauterine growth restriction (IUGR). IUGR was defined according to the International Society of Ultrasound in Obstetrics and Gynaecology (ISUOG) guidelines which is an estimated fetal weight below the 3^{rd} centile for gestation or abnormal foetal Doppler ultrasound (10). Evidence of severe pre-eclampsia was defined by criteria that necessitated immediate delivery. (11) These included uncontrolled maternal blood pressure despite antihypertensive agents, maternal pulse oximetry below 90% or pulmonary oedema unresponsive to initial diuretics, progressive deterioration in liver function, glomerular filtration rate (GFR), haemolysis or platelet count, placental abruption and reversed end diastolic flow in the umbilical artery Doppler and stillbirth. We also included intra-uterine growth restriction (IUGR) as a marker of severe disease.

Data were analyzed using the STATA software (version 11). Categorical variables were describes using percentages and continuous variables were described using means and standard deviations (SD). Odds ratios with a confidence interval of 95% were used to compare outcomes and a p-value of <0.05 was seen to be significant. The Human Research Ethics Committee of the University of the Witwatersrand and the chief executive officer (CEO) of CMJAH granted ethics approval for the study (ref. no. M180831).

Results

A total of 100 patients were enrolled in this study and the majority, 79%, were HIV-negative and 21% were HIV-positive. Table 1 shows the demographics of the patients included in the study.

Table 1: Patient demographics stratified by HIV status, n=100

	Overall	HIV negative N=79	HIV positive N=21	P value
Booked, n (%)				
Yes	88	68 (86.1)	20 (95.2)	0.34
No	12	11 (13.9)	1 (4.8)	
Age at booking, (Mean years±SD)	29.3±6.5	28.9±6.6	30.7±6	0.28
Gravidity				
Median	2	2	3	0.06
IQR	1-3	1-3	2-4	
Parity				
Median	1	1	1	0.08
IQR	0-2	0-2	1-2	
Gestation at booking, (mean weeks±SD)	20.6±7.7	20.7±7.4	20±8.1	0.70
MAP† at booking, (mean mmHg±SD)	103±21.2	104.8±17.8	103±20.7	0.74
Chronic hypertension, n (%)	26	20 (25.3)	7 (33.3)	0.21
Diabetes, n (%)	3	3 (0.03)	0 (0)	
Previous preterm delivery/mTOP‡ secondary to hypertension, n (%)	13	10 (12.7)	3 (14.3)	0.83
Previous intrauterine fetal death/early neonatal death*, n (%)	16	12 (15.2)	4 (19)	0.45

*IQR – interquartile range
†MAP: mean arterial pressure;
‡mTOP: medical termination of pregnancy
It was not specified in the patient records whether these perinatal losses were related to hypertensive disease of pregnancy

Most patients (88%) had accessed antenatal care, with an overall mean gestation at booking of 20.6±7.7 weeks.

Height and weight measurements, which allowed for a body mass index (BMI) calculation, were recorded for 61% of the study participants. Of these, the average BMI was 30.1kg/m^2±6, being 31.3 kg/m^2±6.2 in the HIV-negative group and 28.7 kg/m^2±4.5 in the HIV-positive group, p=0.13.

Table 2 presents details of HIV diagnosis and treatment among the HIV-positive patients. Of the 21 HIV-positive patients, 13 (61.9%) patients were initiated on ART before the index pregnancy while eight (38.1%) were initiated during pregnancy. Most of the patients (n=19, 90,5%) were on the Tenofovir, Emtricitabine and Efavirenz (TEE) fixed-dose combination. The majority of patients had a baseline CD4 count above 350 cells/mm^3 (66.7%, n=14) and 52.4% (n=11) had a viral load of <100 copies/ml at the time of diagnosis of pre-eclampsia. It was not possible to calculate the median viral load as the majority of patients had a viral load of <100 copies/ml and was recorded as undetectable with no actual value given.

Table 2: Details of HIV diagnosis and treatment among HIV-positive pregnant patients, n=21

Timing of HIV diagnosis and ART initiation, n%	
Before pregnancy	13 (61.9)
During pregnancy	8 (38.1)
≥ 12 weeks on ART at delivery	4 (50)
< 12 weeks on ART at delivery	4 (50)
CD4 (cells/mm^3), n (%)	
≥ 350	14 (66.7)
< 350	5 (23.8)
Unknown	2 (9.5)
Mean±SD	549.3±236.4
Median	515
Viral load (copies/ml)*, n (%)	
≥1000	1 (4.8)
101-999	4 (19)
≤100	11 (52.4)
Unknown	2 (9.5)

*Viral load at or near diagnosis of pre-eclampsia

The mean gestational age at onset of pre-eclampsia was 30±5 weeks in the HIV positive patients and 32.5±4.9 weeks in the HIV negative patients. ($p<0.05$). Overall, there were 68 patients who had features of severe pre-eclampsia, which included 54 (78%) of the HIV-negative patients and 14 (66.7%) of the HIV-positive patients. (OR 0.88, 95% CI 0.38 - 3)

Table 3: Timing of onset and evidence of severe features of pre-eclampsia in HIV-negative and HIV-positive women, n=100

	Total	HIV neg (n=79)	HIV pos (n=21)	P value	Comparison with 95% confidence interval
Gestational age at diagnosis (mean weeks ±SD)	32±5	32.5±4.9	30±5	<0.05	Difference -2.5 (-4.89, -0.10)
Early onset (<34 weeks) (%)	58 (58)	42 (53.2)	16 (76.2)	0.08	OR 2.62 (0.88, 7,97)
Signs of severity of preeclampsia	68 (68)	54 (78.3)	14 (66.7)	0.88	OR 1.08 (0.38, 3)

The most common features of severity were haematological complications which included thrombocytopaenia or evidence of haemolysis and/or disseminated intravascular coagulopathy (DIC) (34%), evidence of IUGR (28%) and renal dysfunction (22%). There was no statistically significant difference between the HIV-positive and HIV-negative patients.

The mean gestational age of onset of preeclampsia was 31.8±5.9 weeks in patients with CD4 counts of <350cells/mm^3 compared to 29.1±4.5 in patients with a CD4 count of ≥350 cells/mm^3. (p=0.30). Patients with CD4 counts of ≥350 cells/mm^3 were 1.6 times more likely to have early onset disease and 0.86 times more likely to have evidence of severe disease compared to patients with CD4 counts <350 cells/mm^3 but the results were not statistically significant. (p=0.86)

The overall mean gestational age at delivery was 33.1±4.8 weeks. The mean age at delivery was 34±4.9 weeks in HIV-negative patients and 31.3±4.5 weeks in HIV-positive patients (p<0.05).

Table 4: Neonatal and maternal outcomes stratified by HIV status

	Total	HIV-negative (n=79)	HIV-positive (n=21)	P value	Comparison and 95% confidence interval
Neonatal outcomes					
Gestational age at delivery, mean weeks±SD	33.1±4.8	34±4.9	31.3±4.5	<0.05	Difference -2.7 (-5.0, -0.35)
Delivery <34 weeks n (%)	47	34 (43)	13 (61.9)	0.13	OR 2.15 (0.78, 5.86)
Alive n (%)	87	72 (91.1)	15 (71.1)	<0.05	OR 0.24 (0.06, 0.86)
IUFD n (%)	8	3 (3.8)	5 (23.8)	<0.05	OR 7.92 (1.57, 39.67)
Maternal outcomes n (%)					
Death	2	2(2.5)	0	0.08	OR 1.38 (0.06, 29.99)
High care admission	65	54 (68.4)	11 (52.4)	0.17	OR 0.51 (0.18, 1.37)
ICU admission	3	3 (3.8)	0	0.65	OR 0.51 (0.02, 10,23)

There were 15/21 (71.1%) live births in the HIV-positive patients compared to 72/79 (91.1%) in the HIV-negative patients (OR 0.24, 95% CI 0.78 - 5.86). Of the HIV positive patient, 5/21 (23.8%) had intrauterine fetal deaths compared to 3/79 (3.8%) in the HIV negative group. (OR 7.92, 95%CI 1.57 - 39,67). There were three fresh stillbirths and two early neonatal deaths which were secondary to delivery for maternal indications, for fetuses weighing less than 1kg, with no statistical difference between HIV positive and HIV negative patients. (p=0.47). There were two maternal deaths and three maternal ICU admissions, all in HIV-negative patients.

The gestational age at delivery was 32±5.2 weeks in the patients with CD4 counts of <350 cells/$mm^3$and 30.8±5 weeks in the patients with CD4 counts of ≥350 cells/mm3 (p=0.67). There was one (20%) IUFD in the patients with CD4 counts of <350 cells/mm3 and four (28.3%) in the patients with CD4 counts of ≥350 cells/mm3, O.R 0.62. (CI 0.05 - 7,46)(p=0.71)

Discussion

In this study, HIV-positive patients on ART had an earlier gestational age at onset of pre-eclampsia and consequently an earlier gestation at delivery when compared to HIV-negative patients. HIV-negative and HIV-positive patients had similar incidence of severe pre-eclampsia, with no significant difference in risk factors for pre-eclampsia such as chronic hypertension, diabetes, primigravidity, advanced maternal age and/or increased BMI. (12) Even though the two maternal deaths and three ICU admissions were all in HIV negative women, there was no statistically significant difference in maternal outcomes between the two groups. Neonatal outcomes were significantly poorer in the HIV positive group with less live births and more intrauterine fetal deaths.

The cause of the difference in gestational age at onset of pre-eclampsia between HIV-positive and HIV-negative women is not known but it is hypothesized to be secondary to the immune reconstitution like effect that happens with ART. This is in keeping with the findings of Suy et. al and Tooke et. al that highlights ART usage as a risk factor for the development of pre eclampsia (5,7) but there is no evidence comparing gestational age of onset of pre eclampsia.

Among the HIV-positive patients in our study, the majority had CD4 counts above 350 cells/mm^3 and suppressed viral loads. There was no significant difference in severity of pre-eclampsia and timing of onset of pre-eclampsia and when stratified by CD4 count but the numbers were small. This is in contrast to a study done by Kalumba et al. in 2012 looking at the rate of HIV/AIDS (and CD4 levels) in women with pre-eclampsia compared to a control group. They showed an association between a low median CD4 count and development of pre-eclampsia. (13) In their study, a median CD4 count of 208 cells/mm^3 was associated with a lower risk of pre-eclampsia compared to a median CD4 count of 304 cells/mm^3. This suggests that women with advanced immune suppression have a decreased risk of pre-eclampsia. A study done in the United Kingdom in 2002 also suggested that immune reconstitution was associated with a higher risk of pre-eclampsia as they found higher rates of pre-eclampsia in HIV-positive women on ART compared to HIV-positive women not on treatment and HIV negative women. (14) They also noted unusually severe forms of pre-eclampsia in the HIV positive patients on ART. There are

limited data in other studies looking at the severity of pre eclampsia and maternal outcomes in pregnant women with HIV infection.

The 47% overall rate of delivery prior to 34 weeks in this study is comparable to the 41% rate quoted in a study done at three tertiary hospitals in South Africa in 2018. (15) That study aimed to describe maternal and perinatal outcomes in low and middle income countries (LMIC) and showed that rates and complications of pre eclampsia in South Africa was much higher than other LMIC despite access to tertiary health care.

Neonatal outcomes are in keeping with findings from the study by Suy et al. and Wimalasundera et al. which showed a higher incidence of fetal deaths in HIV infected patients on ART compared to HIV negative patients. (5,14) This is in contrast to the AmRo study which aimed to compare pregnancy outcomes in HIV positive women and HIV negative women. That study showed no significant difference in perinatal mortality when comparing HIV negative patients and HIV positive patients on antiretroviral treatment. Even though they did not specifically compare fetal death in patients with pre eclampsia, their study did not show a significant difference in incidence of pre eclampsia. (16) Nathan et al. showed South African stillbirth rates in women with pre-eclampsia to be 17.7% which is higher than the 11% found in this study which combines the eight intrauterine fetal deaths and the three fresh stillbirths. Because of the sample size in this study, we are unable to say if the neonatal outcomes are specifically in patients with pre-eclampsia or whether it is attributed to HIV status and ART. Neonatal outcomes from this study were favorable in patients with CD4 counts $\geq$ 350 cells/mm^3 compared to patients with CD4 counts < 350 cells/mm^3, but this difference was not significant.

Although the sample size from this study was small, the findings of earlier gestational age of onset of pre eclampsia would prompt us to recommend higher vigilance in HIV positive patients for the development of early onset pre-eclampsia. All pregnant patients should ideally undergo comprehensive first trimester screening for pre eclampsia and considered for low dose Aspirin as a mean of preventing early onset disease. (17) There is currently no evidence for HIV as a risk factor when considering low dose Aspirin but further studies are needed to evaluate the benefits of this. (18)

<u>Limitations</u>

The limitations of this study were the small sample size, the fact that is was retrospective study and that CD4 counts and viral load analysis were not available for all patients. The external validity of the study would be limited by these factors and therefore further studies would be needed to confirm the findings. Because of the small sample size, we were unable to stratify data according to viral load and duration of time on ART, hence more studies are needed to see if duration of ART and levels of immune reconstitution affects outcomes in patients with pre-eclampsia.

Conclusion

Our study found that HIV positive pregnant patients on ART have earlier onset of pre-eclampsia, but similar severity of disease compared to HIV-negative women. There was a higher incidence of adverse maternal outcomes in HIV-negative women, but this could be due to the higher number of negative women in the study. There were poorer neonatal outcomes in HIV-positive women, with a higher incidence of intrauterine fetal deaths and stillbirths.

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Appendix A: Approval protocol

MMed research proposal

Title: Timing of onset and severity of pre- eclampsia in HIV positive pregnant women on antiretroviral therapy compared to HIV negative pregnant women

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List of abbreviations

AFI	Amniotic fluid index
ARDS	Acute respiratory distress syndrome
ART	Antiretroviral therapy
ARVs	Antiretrovirals
BMI	Body mass indexa
BP	Blood pressure
CMJAH	Charlotte Maxeke Johannesburg Academic Hospital
DIC	Disseminated intravascular coagulopathy
EFW	Estimated fetal weight
GA	Gestational age
HAART	Highly active antiretroviral therapy
HELLP	Haemolysis, elevated liver enzymes, low platelets
HIV	Human immunodeficiency virus
HLA	Human Leucocyte Antigen
HPT	Hypertension
HREC	Human Resource Ethics Committee
ICU	Intensive care unit
IUGR	Intrauterine growth restriction
IRIS	Immune reconsitution inflammatory syndrome
NHRD	National Health Research Database
PMTCT	Prevention of mother-to-child transmission of HIV
WHO	World Health Organization

1. Introduction

South African has very high burden of pre-eclampsia and HIV infection and thus there are a large number of pregnant patients affected by both these disease entities. There is conflicting information around how HIV infection affects the development of pre-eclampsia. There are also limited data in the era of widespread availability of antiretroviral therapy (ART) on how the extent of immune compromise associated with HIV infection affects the timing of onset, severity and progression of pre-eclampsia.

2. Background and literature review

Pre eclampsia is the most common medical complication of pregnancy in South Africa (1) and is defined as hypertension and proteinuria, or hypertension and end organ dysfunction with or without proteinuria that develops after the 20th week of pregnancy. (2) The spectrum of disease ranges from mild to severe and the sequela are multisystemic, resulting in significant maternal and perinatal morbidity and mortality.

The incidence of pre-eclampsia varies world-wide from 2-10% and the World Health Organization (WHO) estimates that rates are up to 7 times higher in developing countries compared to the developed world due to inadequate access to obsterics care and the need for better screening and treatment of hypertensive disorders. (3,4) South Africa has a high burden of hypertensive disease of pregnancy and thus sees a high number of complications. According to the data collected from the 2016 Saving Mothers report, hypertensive disease of pregnancy is the second biggest cause of maternal mortality in South Africa with a

rate of 24/100 000 live births, second only to non-pregnancy related infections which are 32/100 000 live births. (1) It is important to note that maternal mortality related to hypertensive disease is increasing (RR=1.12, 95% CI 0,93–1,36; p=0,21) despite the overall improvement in the maternal mortality rate. (RR=0.52, 95% CI 0,41-0,61; p< 0,001). This highlights the need for ongoing research and understanding around hypertensive disorders of pregnancy.

Pre-eclampsia is a spectrum of disease that can be classified from mild to severe. It can also be classified according to gestational age of onset with 34 weeks used to distinguish between early and late onset disease. Increasing evidence is showing that there are distinct etiological differences between early and late onset pre-eclampsia. Early onset pre-eclampsia is related to a more severe form of disease with worse fetal and maternal outcomes and seems to be largely placenta mediated. In late onset or the milder form, cardiovascular and metabolic maternal risk factors seem to play a larger role. (5)

Pre-eclampsia is a progressive disorder and can lead to multi organ failure and death. Maternal complications include renal and liver dysfunction, haematological abnormalities, pulmonary oedema and cerebral complications. Fetal complications result from hypo perfusion which results in intrauterine growth restriction. The majority of fetal complications result from preterm delivery and abruptio placenta. (6)

South Africa also has the highest rates of HIV infection in the world with prevalence in pregnant women attending antenatal clinics estimated to be 30,8%

in 2015. (7) Rates in the Gauteng province and in Johannesburg are in keeping with the national average and also estimated to be around 30%. HIV infection results in destruction of the immune system with $CD4^+$ cell depletion as the virus replicates and compromises cell mediated immunity. The body becomes progressively more susceptible to opportunistic infections. With combination ART, immune function is gradually restored.

The South African National HIV guidelines of 2017 are based on the WHO guidelines (8) and recommend antiretroviral treatment for all HIV positive patients in South Africa. (9) As all pregnant women are routinely tested for HIV at booking, with repeat tests throughout pregnancy for those who test negative, all pregnant women who are HIV positive should be started on treatment at diagnosis. This has been the case since 2013 when South Africa adopted the WHO prevention of mother-to-child transmission (PMTCT) B+ guidelines where all HIV positive women were started on ART irrespective of HIV count.

Pre-eclampsia and its pathogenesis

The pathophysiology of pre-eclampsia is complex and involves both fetal and maternal factors. Two stages of pathology have been postulated with defective placental invasion and immunological abnormalities being the initial fault, which is then followed by a systemic inflammatory stress response. (5)

Immunologically, patients with pre eclampsia show a similar response to patients with graft vs host disease, with an increase in natural killer cells and an unusual combination of human leukocyte antigen (HLA) expression. (5) This activation of

the maternal immune system is thought to then result in abnormal placental implantation and hypoperfusion. The ischemic placenta releases antiangiogenic factors into the blood, which causes widespread endothelial and platelet dysfunction. This activates a systemic inflammatory response characterised by oxidative stress and pro inflammatory cytokines that leads to increased vascular reactivity. (5) This mechanism is thought to be multifactorial with immunological, genetic and environmental factors contributing.

As HIV causes immunesuppression and antiretroviral medication causes reconstitution of the immune system, it is thought that this immune response related to development of preeclampsia would be modified. HIV infection has been hypothesised to decrease the risk of hypertensive disorders of pregnancy as the immune and inflammatory state is minimised or inhibited. As the immune system reconstitutes with ART, the risk of hypertensive disorders are then hypothesised to return to the same as in HIV negative women or even increase with a immune reconsitution inflammatory syndrome (IRIS) like -phenomena . (6)

The association between HIV and pre-eclampsia

There is inconsistent literature around the association between pre-eclampsia, HIV infection and ART. A meta-analysis and systemic review done in 2014 shows no significant association between HIV infection and hypertensive disorders of pregnancy. (6) The authors however highlighted the high level of bias and a low quality of the studies. Confounding factors were only accounted for in 19% of the studies and outcomes were not clearly stipulated.

Another meta analysis published in 2016 also failed to show an association between HIV positive women on ART and pre eclampsia but ART usage and regimes varied amongst studies cited. (4)

Frank et al. published a large study with a cohort of 2600 women in 2006, which looked at all pregnant women who delivered in Soweto over a 9-month period in 2002. (10) They hypothesised that untreated HIV positive pregnant women had a lower risk of pre-eclampsia than HIV negative women but this study failed to show any association. In contrast to the studies which show no association between pre-eclampsia and HIV infection are studies done which shows an increased risk of pre-eclampsia in HIV negative women. Suy et al. showed an increase in pre-eclampsia in HIV positive women when compared to HIV negative women and highligted ART use prior to pregnancy as a risk factor. (11) This is in keeping with the study done by Wimalasundera et al. which showed HIV positive women on triple therapy to have a higher incidence of preeclampsia when compared to HIV positive women who were not using antiretrovirals (ARVs). (12) They, however showed no difference between pre-eclampsia in HIV positive women on ART vs. HIV negative women with similar rates of pre-eclampsia in these groups of women. This in contrast to the Suy et al. study, which showed an increase risk in HIV positive women treated with ART before pregnancy when compared to HIV negative women. (11,12)

Exposure and outcomes were reversed in a retrospective case control study done in KwaZulu-Natal, South Africa. Kalumba et al. compared rates of HIV infection in women with pre-eclampsia to rates of HIV in a control group and showed women

in the pre eclamptic group to be 0,62 times as likely to be HIV positive. (OR=0,62, 95% CI: 0,47-0,82, p=0,001). (13) In 2007, a large prospective study was done in Paarl in the Western Cape. This study showed a significant increase in gestational hypertension and pre-eclampsia in HIV positive women (P<0.01). (14) Overall, 80% of HIV positive women received Zidovudine monotherapy in pregnancy with single dose Nevirapine intrapartum and 18% of women received triple therapy ART. They found no difference in incidence of pre-eclampsia in these groups (p=0,24). They also divided the HIV positive group using a $CD4^+$ count of 350 and found no significant difference.

Limitations of previous studies

The widespread availability of ARVs has changed the disease profile of women living with HIV. It is a rapidly evolving field with international guidelines around ART usage changing rapidly over the last 20 years. During the Frank et al. study, there was no routine access to ART during pregnancy and South African national guidelines only stipulated that all pregnant women receive a single dose of Nevirapine in labour for PMTCT. (10) Other older studies also had different regimens of ART usage for patients depending on guidelines at the time. (4,13–15) This is markedly different from current guidelines that stipulate that all pregnant women receive ART from the time of diagnosis. (7) Use of ARVs during pregnancy and the development of pre-eclampsia, or lack thereof, is highlighted as an important confounding variable in all previous studies. In previous studies, different ART regimens were used and thus the effect of ARVs cannot be accurately determined.

There is also a shortage of data on level of immune suppression and the association with pre-eclampsia. (13,14) Kalumba et al. showed an association between a low median CD4 count and development of pre-eclampsia. (12) In their study, a median CD4 count of 208 cells/mm^3 was associated with a lower risk of pre-eclampsia compared to a median CD4 count of 304 cells/mm^3. This suggests that women with advanced immune suppression have a decreased risk of pre-eclampsia. Similar to these findings, Wimalasundera et al. in their study also suggested that immune reconstitution was associated with a higher risk of pre-eclampsia. (12) During the Frank et al. study, CD4 count testing was not routinely done and thus could not compare the risk of pre-eclampsia and risk of immune suppression. Measurement of CD4 counts and viral loads has become standard of care in HIV disease profiling and monitoring of patients' response to ART. A systematic review of the effect of HIV infection and ART on the risk of pre-eclampsia, published in 2016, concluded that results are conflicting and that more accurate CD4 count and viral load monitoring is needed to further analyse the association. (4)

The majority of studies also only comment on the incidence and development of pre-eclampsia and there are limited data looking at the severity of pre-eclampsia in pregnant women with HIV infection. Wimalasundera et al. noted unusually severe pre-eclampsia in HIV positive women on ART with complications such as HELLP syndrome (haemolysis, elevated liver enzymes and low platelets) and intrauterine fetal deaths being more common.(11) A study done in Cape Town, in 2016, showed that more than four weeks of ART usage increased HIV positive

women's risk of developing early onset pre-eclampsia. (15) The investigators however found no correlation with CD4 counts.

Rationale for the study

Given the inconsistent data on the incidence of pre-eclampsia in HIV positive women compared to HIV negative women and the limited data on severity of disease in women living with HIV, there is a need for a study to address these gaps in knowledge especially in the era of widespread availability of ART.

Definitions

The International Society of the Study of hypertension's definition to classify women with pre-eclampsia will be used. (2)

Hypertension is classified as:

- Blood pressure (BP) greater than or equal to 140mmHg systolic or greater than or equal to 90mmHg diastolic on at least two occasions 4 hours apart
- BP greater than or equal to 160mmHg systolic or 110mmHg diastolic on a single occasion

Pre-eclampsia is hypertension that occurs at or after the 20th week of pregnancy along with one or more of the following:

- Proteinuria (Spot Protein:Creatinine (PR:CR) 0,03 or 1+ on dipstick)
- Maternal organ dysfunction :
    - Renal insufficiency (Creatinine >90 µmol/L)

- Liver involvement (elevated transaminases – at least twice upper limit of normal)
- Neurological complication (such as eclampsia, blindness, stroke, hyperreflexia or persistant visual scotomata)
- Haematological complications (platelets <150x10^3/mL, disseminated intravascular coagulopathy (DIC), haemolysis)

• Uteroplacental dysfunction as diagnosed by fetal growth restriction

Early onset pre-eclampsia is defined as pre-eclampsia before 34 weeks gestation.

Fetal complications of severity include intrauterine fetal demise and non reassuring fetal testing including growth restriction. (2,16)

3. Study aim and objectives

3.1 Aim:

To determine whether there is a difference in the timing of onset and severity of pre-eclampsia between HIV negative and HIV positive pregnant women on ART.

3.2 Objectives:

3.2.1 To describe the demographics of HIV positive and HIV negative pregnant women diagnosed with pre-eclampsia during the study period.

3.2.2 To compare the timing of onset and severity of pre-eclampsia in HIV positive women on ART compared to HIV negative women.

3.2.3 To compare complications and obstetric outcomes in HIV positive and HIV negative women with pre-eclampsia.

4. Methods

4.1 Study setting

The study will be done at Charlotte Maxeke Johannesburg Academic Hospital (CMJAH), an academic hospital that offers tertiary and quaternary services. The obstetrics department at CMJAH manages high-risk pregnancies on a referral and walk-in basis, and has approximately 7500 deliveries per annum. All pregnant women are routinely tested for HIV and the HIV prevalence reflects that in the general population. The hospital is based close to the Johannesburg city centre and thus serves a large proportion of foreign patients and refugees, with 48% of patients seen in the obstetrics department being non-South Africa.

4.2 Study design

This will be a retrospective record-review study.

4.3 Study population

All pregnant patients diagnosed with pre-eclampsia and managed at CMJAH admitted between 1 July and 31 December 2017 will be included in the study. An estimated sample size which is calculated based on the weekly number of patients admitted with pre-eclampsia amounts to 8 patients x 26 weeks = 208 patients.

Inclusion criteria: Women with pre-eclampsia, with or without chronic hypertension; known HIV status and on ART if HIV positive; singleton pregnancy

Exclusion criteria: pregnant women with unknown HIV status; multiple pregnancies, molar pregnancies and trisomal abnormalies; and HIV positive women not on ART.

4.4 Data collection:

All patients diagnosed and admitted with pre-eclampsia during the study period will be identified. Patients details will be collected from registers in the antenatal ward and a list of all patients with diagnosis of 'hypertension' or 'pre-eclampsia' will be collected. The registers in high care and theatre, the antenatal clinic admission book and the post natal wards admission book will also be studied to attempt to make the list as complete as possible.

Patients' files will then be retrieved from the records department and all relevant data will be captured onto a standardised data sheet (See Appendix A). Patients who do not meet the requirements for a diagnosis of pre-eclampsia will be excluded. The following data will be collected: demographics; HIV status and treatment details for HIV positive women; timing of diagnosis of pre-eclampsia and management during pregnancy; complications related to pre-eclampsia and obstetric outcomes.

The patient's gestational age will be calculated using an early ultrasound, done at less than 23 weeks, if available, or the date of the last normal menstrual period if certain. Late ultrasound or booking palpation will be used if the date of the last normal menstrual period is uncertain and there is no early ultrasound.

The collected data will be entered onto the REDCap™ data capture programme.

5. Data Analysis

Data will be analysed using STATA software. Descriptive data will be analysed to determine the prevalence of variables, means and medians. Any association between these variable and the various outcomes will be analysed using analytical statistics and logistic regression. These statistics will employ a p value of 0.05, odd ratios and 95% confidence intervals.

6. Dissemination of results

Results will be submitted to the post-graduate committee and the Human Resource Ethics committee (HREC) by means of a written report. Additionally, results will be presented at local and international meetings, academic research days or conferences, and will also be submitted for publication in a peer-reviewed journal.

7. Ethics

Ethics approval will be obtained from the University of the Witwatersrand's Human Research Ethics Committee before the start of the study and before any records are accessed. Permission to conduct the study will also be obtained from the CMJAH chief executive officer. Patients' anonymity will be ensured by assigning all patients a study number during data collection and analysis. Study numbers will be correlated with folder numbers and dates of birth in a separate folder that only the researcher and the supervisor will have access to.

8. Timing of study

	Mar 18	Apr 18	May 18	Jun 18	Jul 18	Aug 18	Sep 18	Oct 18	Nov 18	Dec 18	Jan 19	Feb 19	Mar 19	Apr 19
Literature review														
Protocol														
Ethics														
Data Collection														
Write up														

9. Funding

Limited costs are anticipated in this study and all costs will be funded by the researcher. Below is an estimation of the budget:

	Price	**Number**	**Total**
Photocopies for protocol	R0.80	25 x 9	R180.00
Photocopies for ethics	R0.80	5 x 25 25 x 2	R140.00
Photocopies for write up	R0.80	100 x 10	R800.00
Publication fee	R1500.00	2	R3000.00
Total			R4120.00

10. Limitations

This study is a retrospective record review and data in patient records may be incomplete. Missing files will be traced to make the data as complete as possible.

Confounding variables such as race, chronic disease and body mass index (BMI), which have been show to influence the development of pre-eclampsia, will be accounted for.

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Appendix B: Data collection tool

Patient details

Study no		
Age at booking		
Gravidity		
Parity		
GA at booking		By dates
		By Early ultrasound
		By Late ultrasound
		By palpation

Obstetrics hx	Previous caesar and indication	
	Previous preterm delivery related to hypertension	
	Previous medical termination of pregnancy related to hypertension	
	Previous intrauterine fetal death/ early neonatal death	

Chronic HPT	Yes	No
GA at diagnosis of HPT		

HIV

Positive	Negative

If HIV positive:

Timing of HIV diagnosis	Before pregnancy	During pregnancy
		Gestational age:
CD4 testing during pregnancy:	Result	Gestational age
Viral load testing during pregnancy:	Result	Gestational age:
ART initiation	Before current pregnancy	Current pregnancy
ART regimen:		Duration of treatment at time of delivery:

Other:

Details of diagnosis of pre-eclampsia

Gestational age		By sure dates
		By early ultrasound
		By late ultrasound
		By palpation
BP		
Proteinuria	Dipstick	
	Pr:Cr ratio	
	24 hour urine	

EFW		
Umbilical RI		
MCA		
AFI		
IUGR	Yes	No

Details at worst deterioration

Gestational age			
BP			
Agent and dosage	**Aldomet**		
	Amlodipine		
	Other		
	MgSO4	Loading	Completed
Proteinuria	Dipstick		
	Pr:Cr ratio		
	24 hour urine		

EFW		
Umbilical RI		
MCA		
AFI		
IUGR	Yes	No

Laboratory results

	Admission	Worst (gestational age)
Hb		
Platelets		
Urea		
Creatinine		
AST		
ALT		
Other:		

Delivery

Gestation			
Indication for delivery	**Maternal**		**Fetal**
	Uncontrolled HPT	Imminent eclampsia	Fetal distress
	HELLP syndrome	Abruptio placenta	Intrauterine growth restriction on ultrasound
	Acute kidney injury	Pre eclampsia 34/40	
	Eclampsia	Pre eclampsia 37/40	
	Other:		
Labour	Spontaneous		Induced
Mode of delivery	NVD		C/S
Evidence of abruptio	Clinical		Confirmed
IUGR	Yes		No
Birth weight			
Birth outcome	Alive/stillbirth/intrauterine fetal death/early neonatal death/late neonatal death		
Other:			

Complications

Pulmonary oedema	Yes	No
Signs of imminent eclampsia	Yes	No
Eclampsia	Yes	No
ICU admission	Yes	No
Indications for admission to ICU		
Obstetrics high care admission	Yes	No
Indications for admission to obstetrics high care area		
Acute kidney injury	Yes	No
Dialysis	Yes	No
Transfusion of blood products	Yes	No

Special investigations:

Chest X-Ray	Yes	No
Details:		

Echocardiogram	Yes	No
Details:		

CT Brain	Yes	No
Details:		

CTPA/VQ scan	Yes	No
Details:		

Other special investigations:

Discharge details

Nr of days admitted		
Nr of days post-delivery on discharge		
Treatment		
Follow up	Local clinic	Other

Other:

Appendix C: Ethics clearance certificate

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

R14/49 Dr Ine Small-Smith

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M180831

NAME: (Principal Investigator)	Dr Ine Small-Smith
DEPARTMENT:	Obstetrics and Gynaecology Charlotte Maxeke Johanessburg Academic Hospital
PROJECT TITLE:	Timing of onset and severity of pre-eclampsia in HIV positive pregnant women on antiretroviral therapy compared to HIV negative pregnant women
DATE CONSIDERED:	31/08/2018
DECISION:	Approved Unconditionally
CONDITIONS:	
SUPERVISOR:	Coceka Mnyeni
APPROVED BY:	Doctor CB Penny, Chairperson, HREC (Medical)
DATE OF APPROVAL:	22/10/2018

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office Secretary on the Third Floor, Faculty of Health Sciences, Phillip Tobias Building, 29 Princess of Wales Terrace, Parktown, 2193, University of the Witwatersrand. I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to resubmit the application to the Committee. **I agree to submit a yearly progress report**. The date for annual re-certification will be one year after the date of convened meeting where the study was initially reviewed. In this case, the study was initially reviewed in **August** and will therefore be due in the month of **August** each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).

Principal Investigator Signature

10.08.2019
Date

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

Appendix D: Ethics approval CMJAH CEO

GAUTENG PROVINCE
HEALTH
REPUBLIC OF SOUTH AFRICA

CHARLOTTE MAXEKE JOHANNESBURG ACADEMIC HOSPITAL

Enquiries:
Ms. N. Mzila
Office of the Clinical Director
Email:Nolwazi.Mzila@gauteng.gov.za
Tell: (011): 488-4812
17 August 2018

Dear Dr. I. Small - Smith

STUDY TITTLE: Timing of the Onset and Severity of Pre - Eclampsia in HIV Positive Pregnant Women on Antiretroviral Therapy Compared to HIV Negative Pregnant Women.

Permission to conduct the above mentioned study is provisional approved. Your study can only commence once Ethics approval is obtained. Please forward a copy of your Ethics Clearance Certificate as soon as the study is approved by the Ethics Committee for the CEO's office to give you the final approval to conduct the study.

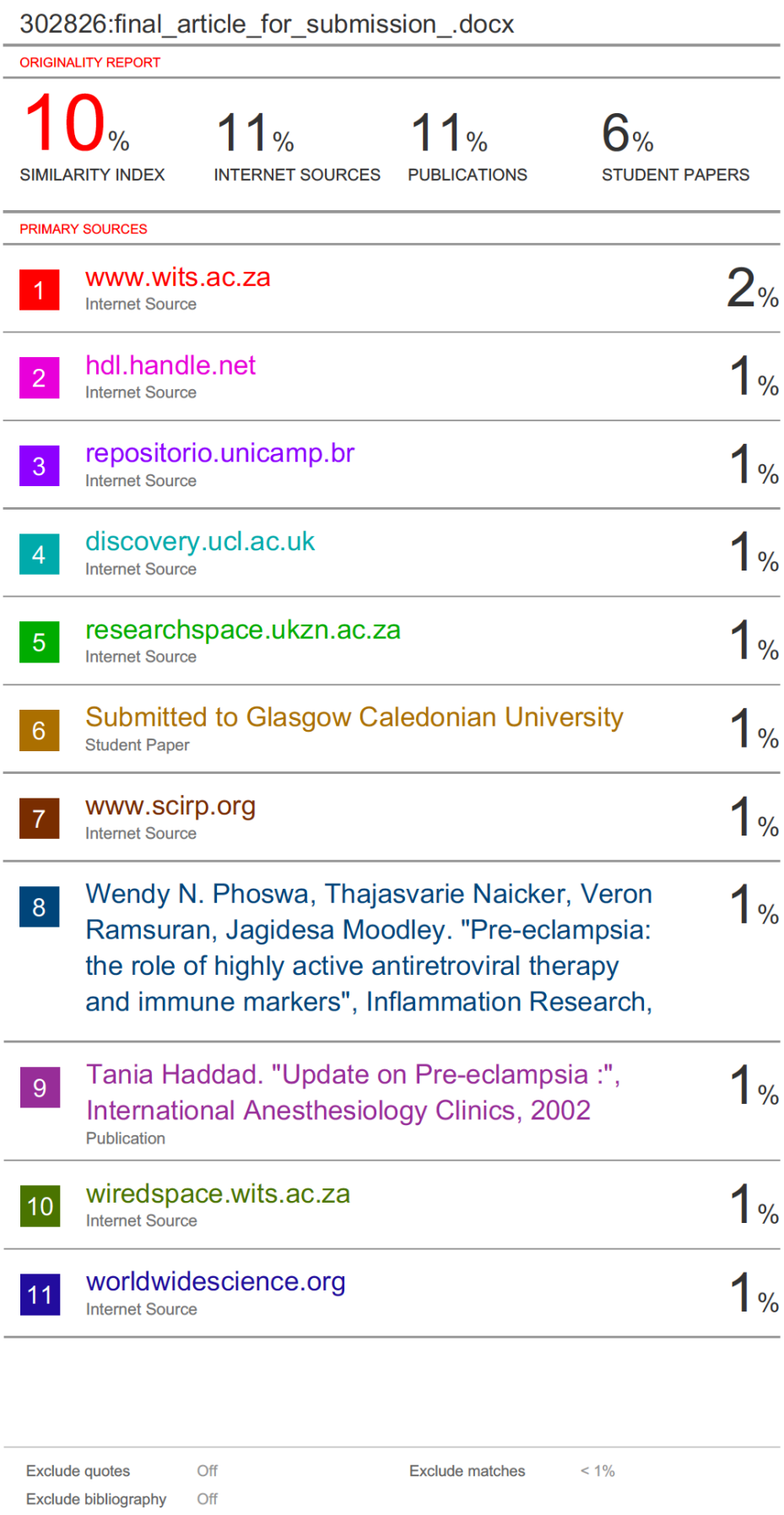
Supported / ~~not supported~~

Dr. M.I. Mofokeng
Clinical Director
DATE: 17/08/2018

Approved / not approved

Ms. G. Bogoshi
Chief Executive Officer
DATE: 20.08.2018

Appendix E: Turnit in report



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Appendix F: Plagiarism declaration

PLAGIARISM DECLARATION TO BE SIGNED BY ALL HIGHER DEGREE STUDENTS

SENATE PLAGIARISM POLICY: APPENDIX ONE

I I. Small-Smith (Student number: 302826) am a student registered for the degree of Masters of Medicine in Obstetrics and gynaecology in the academic year 2020.

I hereby declare the following:

- I am aware that plagiarism (the use of someone else's work without their permission and/or without acknowledging the original source) is wrong.
- I confirm that the work submitted for assessment for the above degree is my own unaided work except where I have explicitly indicated otherwise.
- I have followed the required conventions in referencing the thoughts and ideas of others.
- I understand that the University of the Witwatersrand may take disciplinary action against me if there is a belief that this is not my own unaided work or that I have failed to acknowledge the source of the ideas or words in my writing.
- I have included as an appendix a report from "Turnitin" (or other approved plagiarism detection) software indicating the level of plagiarism in my research document.

Signature: _____ Date: 10.12.2020

1

Appendix G: SAJOG author guidelines

Author Guidelines

Please view the Author Tutorial for guidance on how to submit on Editorial Manager.

To submit a manuscript, please proceed to the SAJOG Editorial Manager website: http://www.editorialmanager.com/sajog

To access and submit an article already in production, please see the guidelines here.

Author Guidelines

Please take the time to familiarise yourself with the policies and processes below. If you still have any questions, please do not hesitate to ask our editorial staff (tel.: +27 (0)21 532 1281, email: submissions@samedical.org).

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When submitting a Research article to the SAJOG, the submitting author must agree to pay the APC should the article be accepted for publication. The APC is payable when your manuscript is editorially accepted and before production commences for publication. The submitting author will be notified that payment is due and given details on the available methods of payment. Prompt payment is advised; the article will not enter into production until payment is received.
Queries can be directed to claudian@samedical.org

Authorship

Named authors must consent to publication. Authorship should be based on: (i) substantial contribution to conceptualisation, design, analysis and interpretation of data; (ii) drafting or critical revision of important scientific content; or (iii) approval of the version to be published. These conditions must all be met for an individual to be included as an author (uniform requirements for manuscripts submitted to biomedical journals; refer to www.icmje.org)

If authors' names are added or deleted after submission of an article, or the order of the names is changed, all authors must agree to this in writing.

Please note that co-authors will be requested to verify their contribution upon submission. Non-verification may lead to delays in the processing of submissions.

Conflicts of interest

Conflicts of interest can derive from any kind of relationship or association that may influence authors' or reviewers' opinions about the subject matter of a paper. The existence of a conflict – whether actual, perceived or potential – does not preclude publication of an article. However, we aim to ensure that, in such cases, readers have all the information they need to enable them to make an informed assessment about a publication's message and conclusions. We require that both authors and reviewers declare all sources of support for their research, any personal or financial relationships (including honoraria, speaking fees, gifts received, etc) with relevant individuals or organisations connected to the topic of the paper, and any association with a product or subject that may constitute a real, perceived or potential conflict of interest. If you are unsure whether a specific relationship constitutes a conflict, please contact the editorial team for advice. If a conflict remains undisclosed and is later brought to the attention of the editorial team, it will be considered a serious issue prompting an investigation with the possibility of retraction.

Research ethics committee approval

Authors must provide evidence of Research Ethics Committee approval of the research where relevant. Ensure the correct, full ethics committee name and reference number is included in the manuscript.

If the study was carried out using data from provincial healthcare facilities, or required active data collection through facility visits or staff interviews, approval should be sought from the relevant provincial authorities. For South African authors, please refer to the guidelines for submission to the National Health Research Database. Research involving human subjects must be conducted according to the principles outlined in the Declaration of Helsinki. Please refer to the National Department of Health's guideline on Ethics in Health research: principles, processes and structures to ensure that the appropriate requirements for conducting research have been met, and that the HPCSA's General Ethical Guidelines for Health Researchers have been adhered to.

Protection of rights to privacy

Research Participants

Information that would enable identification of individual research participants should not be published in written descriptions, photographs, radiographs and pedigrees unless the information is essential for scientific purposes and the patient (or parent or guardian) has given informed written consent for publication and distribution. We further recommend that the published article is disseminated not only to the involved researchers but also to the patients/participants from whom the data was drawn. Refer to Protection of Research Participants. The signed consent form should be submitted with the manuscript to enable verification by the editorial team.

Other individuals

Any individual who is identifiable in an image must provide written agreement that the image may be used in that context in the SAJOG.

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Ethnic/race classification

Use of racial or ethnicity classifications in research is fraught with problems. If you choose to use a research design that involves classification of participants based on race or ethnicity, or discuss issues with reference to such classifications, please ensure that you include a detailed rationale for doing so, ensure that the categories you describe are carefully defined, and that socioeconomic, cultural and lifestyle variables that may underlie

perceived racial disparities are appropriately controlled for. Please also clearly specify whether race or ethnicity is classified as reported by the patient (self-identifying) or as perceived by the investigators. Please note thatit is not appropriate to use self-reported or investigator-assigned racial or ethnic categories for genetic studies.

Continuing Professional Development (CPD)

SAJOG is an HPCSA-accredited service provider of CPD materials. Principal authors can earn up to 15 CPD continuing education units (CEUs) for publishing an article; co-authors are eligible to earn up to 5 CEUs; and reviewers of articles can earn 3 CEUs. Each month, SAJOG also publishes a CPD-accredited questionnaire relating to the academic content of the journal. Successful completion of the questionnaire with a pass rate of 70% will earn the reader 3 CEUs. Administration of our CPD programme is managed by Medical Practice Consulting. To complete questionnaires and obtain certificates, please visit MRP Consulting

Manuscript preparation

Preparing an article for anonymous review

To ensure a fair and unbiased review process, all submissions are to include an anonymised version of the manuscript. The exceptions to this requirement are Correspondence, Book reviews and Obituary submissions.

Submitting a manuscript that needs additional blinding can slow down your review process, so please be sure to follow these simple guidelines as much as possible:

• An anonymous version should not contain any author, affiliation or particular institutional details that will enable identification.
• Please remove title page, acknowledgements, contact details, funding grants to a named person, and any running headers of author names.
• Mask self-citations by referring to your own work in third person.

General article format/layout

Submitted manuscripts that are not in the correct format specified in these guidelines will be returned to the author(s) for correction prior to being sent for review, which will delay publication.

General:

• Manuscripts must be written in UK English (this includes spelling).
• The manuscript must be in Microsoft Word or RTF document format. Text must be 1.5 line spaced, in 12-point Times New Roman font, and contain no unnecessary formatting (such as text in boxes). Pages and lines should be numbered consecutively.
• Please make your article concise, even if it is below the word limit.
• Qualifications, full affiliation (department, school/faculty, institution, city, country) and contact details of ALL authors must be provided in the manuscript and in the online submission process.
• Abbreviations should be spelt out when first used and thereafter used consistently, e.g. 'intravenous (IV)' or 'Department of Health (DoH)'.
• Numbers should be written as grouped per thousand-units, i.e. 4 000, 22 160.
• Quotes should be placed in single quotation marks: i.e. The respondent stated: '...'
• Round brackets (parentheses) should be used, as opposed to square brackets, which are reserved for denoting concentrations or insertions in direct quotes.

If you wish material to be in a box, simply indicate this in the text. You may use the table format –this is the only exception. Please DO NOT use fill, format lines and so on.

SAJOG is a general specialist obstetrics and gynaecology journal, therefore for articles involving genetics, it is the responsibility of authors to apply the following:

- Please ensure that all genes are in italics, and proteins/enzymes/hormones are not.
- Ensure that all genes are presented in the correct case e.g. TP53 not Tp53.

** NB: Copyeditors cannot be expected to pick up and correct errors wrt the above, although they will raise queries where concerned.

- Define all genes, proteins and related shorthand terms at first mention, e.g. '188del11' can be glossed as 'an 11 bp deletion at nucleotide 188.'
- Use the latest approved gene or protein symbol as appropriate:
o Human Gene Mapping Workshop (HGMW): genetic notations and symbols
o HUGO Gene Nomenclature Committee: approved gene symbols and nomenclature
o OMIM: Online Mendelian Inheritance in Man (MIM) nomenclature and instructions

o Bennet et al. Standardized human pedigree nomenclature: Update and assessment of the recommendations of the National Society of Genetic Counselors. J Genet Counsel 2008;17:424-433: standard human pedigree nomenclature.

Preparation notes by article type

Research

Guideline word limit: 3 000 words (excluding abstract and bibliography)

Research articles describe the background, methods, results and conclusions of an original research study. The article should contain the following sections: introduction, methods, results, discussion and conclusion, and should include a structured abstract (see below). The introduction should be concise – no more than three paragraphs – on the background to the research question, and must include references to other relevant published studies that clearly lay out the rationale for conducting the study. Some common reasons for conducting a study are: to fill a gap in the literature, a logical extension of previous work, or to answer an important question. If other papers related to the same study have been published previously, please make sure to refer to them specifically. Describe the study methods in as much detail as possible so that others would be able to replicate the study should they need to. Where appropriate, sample size calculations should be included to demonstrate that the study is not underpowered. Results should describe the study sample as well as the findings from the study itself, but all interpretation of findings must be kept in the discussion section. The conclusion should briefly summarise the main message of the paper and provide recommendations for further study.

• May include up to 3 illustrations or tables.
• A max of 20 - 25references

Structured abstract

• This should be no more than 250words, with the following recommended headings:
o Background: why the study is being done and how it relates to other published work.
o Objectives: what the study intends to find out
o Methods: must include study design, number of participants, description of the research tools/instruments, any specific analyses that were done on the data.
o Results: first sentence must be brief population and sample description; outline the results according to the methods described. Primary outcomes must be described first, even if they are not the most significant findings of the study.
o Conclusion: must be supported by the data, include recommendations for further study/actions.
• Please ensure that the structured abstract is complete, accurate and clear and has been approved by all authors. It should be able to be intelligible to the reader without referral to the main body of the article.
• Do not include any references in the abstracts.

Here is an example of a good abstract.

Scientific letters/short reports

These are shorter length, scholarly research articles of no more than 1500 words, and include case reports.

Guideline word limit: 1 500 words

• Abstract: Structured, of about 150 words, with the following recommended headings: Background, Objectives, Methods, Results, and Conclusion.
• May include only one illustration or table
• A maximum of 8 references

Editorials

Guideline word limit: 1 000 words

These opinion or comment articles are usually commissioned but we are happy to consider and peer review unsolicited editorials. Editorials should be accessible and interesting to readers without specialist knowledge of the subject under discussion and should have an element of topicality (why is a comment on this issue relevant now?) There should be a clear message to the piece, supported by evidence.

Please make clear the type of evidence that supports each key statement, e.g.:

• expert opinion
• personal clinical experience

• observational studies
• trials
• systematic reviews.

Review articles

Review articles should always be discussed with the Editor prior to submission.

Guideline word limit: 4 000 words

These are welcome, but should be either commissioned or discussed with the Editor before submission. A review article should provide a clear, up-to-date account of the topic and be aimed at non-specialist hospital doctors and general practitioners. They should be aligned to practice in South and/or sub-Saharan Africa and not a précis of reviews published in the international literature

Please ensure that your article includes:

• Abstract: unstructured, of about 100-150 words, explaining the review and why it is important
• Methods: Outline the sources and selection methods, including search strategy and keywords used for identifying references from online bibliographic databases. Discuss the quality of evidence.
• When writing: clarify the evidence you used for key statements and the strength of the evidence. Do not present statements or opinions without such evidence, or if you have to, say that there is little or no evidence and that this is opinion. Avoid specialist jargon and abbreviations, and provide advice specific to southern Africa.
• Personal details: Please supply your qualifications, position and affiliations and MP number (used for CPD points); address, telephone number and fax number, and your e-mail address; and a short personal profile (50 words) and a few words about your current fields of interest.

Correspondence (Letters to the Editor)

Guideline word limit: 400 words

Letters to the editor should relate either to a paper or article published by the SAJOG or to a topical issue of particular relevance to the journal's readership

• May include only one illustration or table
• Must include a correspondence address.

Obituaries

Guideline word limit: 400 words

Should be offered within the first year of the practitioner's death, and may be accompanied by a photograph.

Illustrations/photos/scans

• If illustrations submitted have been published elsewhere, the author(s) should provide evidence of consent to republication obtained from the copyright holder.
• Figures must be numbered in Arabic numerals and referred to in the text e.g. '(Fig. 1)'.
• Each figure must have a caption/legend: Fig. 1. Description (any abbreviations in full).
• All images must be of high enough resolution/quality for print.
• All illustrations (graphs, diagrams, charts, etc.) must be in PDF form.
• Ensure all graph axes are labelled appropriately, with a heading/description and units (as necessary) indicated. Do not include decimal places if not necessary e.g. 0; 1.0; 2.0; 3.0; 4.0 etc.
• Each image must be attached individually as a 'supplementary file' upon submission (not solely embedded in the accompanying manuscript) and named Fig. 1, Fig. 2, etc.

Tables

• Tables should be constructed carefully and simply for intelligible data representation. Unnecessarily complicated tables are strongly discouraged.
• Embed/include each table in the manuscript Word file - do not provide separately as supplementary files.
• Number each table in Arabic numerals (Table 1, Table 2, etc.) consecutively as they are referred to in the text.
• Tables must be cell-based (i.e. not constructed with text boxes or tabs) and editable.
• Ensure each table has a concise title and column headings, and include units where necessary.

• Footnotes must be indicated with consecutive use of the following symbols: * † ‡ § ¶ || then ** †† ‡‡ etc.

Do not: Use [Enter] within a row to make 'new rows':

Rather:
Each row of data must have its own proper row:
Do not: use separate columns for n and %:
Rather:
Combine into one column, n (%):
Do not: have overlapping categories, e.g.:
Rather:
Use <> symbols or numbers that don't overlap:

References

NB: Only complete, correctly formatted reference lists in Vancouver style will be accepted. If reference manager software is used, the reference list and citations in text are to be unformatted to plain text before submitting..

• Authors must verify references from original sources.
• Citations should be inserted in the text as superscript numbers between square brackets, e.g. These regulations are endorsed by the World Health Organization,[2] and others.[3,4-6]
• All references should be listed at the end of the article in numerical order of appearance in the Vancouver style (not alphabetical order).
• Approved abbreviations of journal titles must be used; see the List of Journals in Index Medicus.
• Names and initials of all authors should be given; if there are more than six authors, the first three names should be given followed by et al.
• Volume and issue numbers should be given.
• First and last page, in full, should be given e.g.: 1215-1217 not 1215-17.
• Wherever possible, references must be accompanied by a digital object identifier (DOI) link). Authors are encouraged to use the DOI lookup service offered by CrossRef:
o On the Crossref homepage, paste the article title into the 'Metadata search' box.
o Look for the correct, matching article in the list of results.
o Click Actions > Cite
o Alongside 'url =' copy the URL between { }.
o Provide as follows, e.g.: https://doi.org/10.7196/07294.937.98x

Some examples:

• Journal references: Price NC, Jacobs NN, Roberts DA, et al. Importance of asking about glaucoma. Stat Med 1998;289(1):350-355. http://dx.doi.org/10.1000/hgjr.182
• Book references: Jeffcoate N. Principles of Gynaecology. 4th ed. London: Butterworth, 1975:96-101.
• Chapter/section in a book: Weinstein L, Swartz MN. Pathogenic Properties of Invading Microorganisms. In: Sodeman WA, Sodeman WA, eds. Pathologic Physiology: Mechanisms of Disease. Philadelphia: WB Saunders, 1974:457-472.
• Internet references: World Health Organization. The World Health Report 2002 - Reducing Risks, Promoting Healthy Life. Geneva: WHO, 2002. http://www.who.int/whr/2002 (accessed 16 January 2010).
• Legal references
• Government Gazettes:
National Department of Health, South Africa. National Policy for Health Act, 1990 (Act No. 116 of 1990). Free primary health care services. Government Gazette No. 17507:1514. 1996.
In this example, 17507 is the Gazette Number. This is followed by :1514 - this is the notice number in this Gazette.
• Provincial Gazettes:
Gauteng Province, South Africa; Department of Agriculture, Conservation, Environment and Land Affairs. Publication of the Gauteng health care waste management draft regulations. Gauteng Provincial Gazette No. 373:3003, 2003.
• Acts:

South Africa. National Health Act No. 61 of 2003.
• Regulations to an Act:
South Africa. National Health Act of 2003. Regulations: Rendering of clinical forensic medicine services. Government Gazette No. 35099, 2012. (Published under Government Notice R176).
• Bills:
South Africa. Traditional Health Practitioners Bill, No. B66B-2003, 2006.
• Green/white papers:
South Africa. Department of Health Green Paper: National Health Insurance in South Africa. 2011.
• Case law:
Rex v Jopp and Another 1949 (4) SA 11 (N)
Rex v Jopp and Another: Name of the parties concerned
1949: Date of decision (or when the case was heard)
(4): Volume number
SA: SA Law Reports
11: Page or section number
(N): In this case Natal - where the case was heard. Similarly, (C) woud indicate Cape, (G) Gauteng, and so on.
NOTE: no . after the v
• Other references (e.g. reports) should follow the same format: Author(s). Title. Publisher place: Publisher name, year; pages.
• Cited manuscripts that have been accepted but not yet published can be included as references followed by '(in press)'.
• Unpublished observations and personal communications in the text must not appear in the reference list. The full name of the source person must be provided for personal communications e.g. '...(Prof. Michael Jones, personal communication)'.

From submission to acceptance

Submission and peer-review

To submit an article:
• Please ensure that you have prepared your manuscript in line with the SAJOG requirements.
• All submissions should be submitted via Editorial Manager
• The following are required for your submission to be complete:
o Anonymous manuscript (unless otherwise stated)
o Author Agreement form
o Manuscript
o Any supplementary files: figures, datasets, patient consent form, permissions for published images, etc.
• Once the submission has been successfully processed on Editorial Manager, it will undergo a technical check by the Editorial Office before it will be assigned to an editor who will handle the review process. If the author guidelines have not been appropriately followed, the manuscript may be sent back to the author for correcting.

Peer Review Process

All manuscripts are reviewed initially by the Editor-in-Chief and only those that meet the scientific and editorial standards of the journal, and fit within the aims and scope of the journal, will be sent for external peer review. Each manuscript is reviewed by two reviewers selected on the basis of their expertise in the field. A double blind review process is followed at SAJOG.
Authors are expected to receive feedback from reviewers and an editorial decision within approximately 6 weeks of submission. The time period of the entire review process may vary however depending upon the quality of the manuscript submitted, reviewers' responses and the time taken by the authors to submit the revised manuscript.
Manuscripts from review may be accepted, rejected or returned to the author for revision or resubmission for review. Authors will be directed to submit revised manuscripts within two months of receiving the editor's decision, and are requested to submit a point by point response to the reviewers' comments. Manuscripts which authors are requested to revise

and resubmit will be sent for a second round of peer review, often to the original set of reviewers. All final decisions on a manuscript are at the Editor's discretion

Production process

The following process should usually take between 4 - 6 weeks:

1. An accepted manuscript is passed to a Managing Editor to assign to a copyeditor (CE).
2. The CE copyedits in Word, working on house style, format, spelling/grammar/punctuation, sense and consistency, and preparation for typesetting.
3. If the CE has an author queries, he/she will contact the corresponding author and send them the copyedited Word doc, asking them to solve the queries by means of track changes or comment boxes.
4. The authors are typically asked to respond within 1-3 days. Any comments/changes must be clearly indicated e.g. by means of track changes. Do not work in the original manuscript - work in the copyedited file sent to you and make your changes clear.
5. The CE will finalise the article and then it will be typeset.
6. Once typeset, the CE will send a PDF of the file to the authors to complete their final check, while simultaneously sending to the 2nd-eye proofreader.
7. The authors are typically asked to complete their final check and sign-off within 1-2 days. No major additional changes can be accommodated at this point.
8. The CE implements the authors' and proofreader's mark-ups, finalises the file, and prepares it for the upcoming issue.

Changing contact details or authorship

Please notify the Editorial Department of any contact detail changes, including email, to facilitate communication.

Errata and retractions

Errata

Should you become aware of an error or inaccuracy in yours or someone else's contribution after it has been published, please inform us as soon as possible via an email to publishing@samedical.org,including the following details:

- Journal, volume and issue in which published
- Article title and authors
- Description of error and details of where it appears in the published article
- Full detail of proposed correction and rationale

We will investigate the issue and provide feedback. If appropriate, we will correct the web version immediately, and will publish an erratum in the next issue. All investigations will be conducted in accordance with guidelines provided by the Committee on Publication Ethics (COPE).

Retractions

Retraction of an article is the prerogative of either the original authors or the editorial team of SAMA. Should you wish to withdraw your article before publication, we need a signed statement from all the authors.

Should you wish to retract your published article, all authors have to agree in writing before publication of the retraction.

Send an email to publishing@samedical.orgincluding the following details:

- Journal, volume and issue to which article was submitted/in which article was published
- Article title and authors
- Description of reason for withdrawal/retraction.

We will make a decision on a case-by-case basis upon review by the editorial committee in line with international best practices. Comprehensive feedback will be communicated with the authors with regard to the process. In case where there is any suspected fraud or professional misconduct, we will follow due process as recommended by the Committee on Publication Ethics (COPE), and in liaison with any relevant institutions.

When a retraction is published, it will be linked to the original article.

Indexing

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guaranteed a global and African audience:

- DOAJ
- AIM
- AJOL
- EBSCO
- EMBASE
- Scopus
- Crossref
- Sabinet
- Emerging Sources Citation Index (Web of Science)

Sponsored supplements

Contact the managing editor (claudian@samedical.org) for information on submitting ad hoc/commissioned supplements, including guidelines, conference/congress abstracts, etc.