PREVALENCE OF SYPHILIS IN WOMEN OF CHILDBEARING AGE AT RAHIMA MOOSA MOTHER AND CHILD HOSPITAL

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

Johannesburg 2022

DECLARATION

I, Filippus Elago Sheetekela, declare that this research report is my own unaided work. It is being submitted for the degree of Master of Medicine MMed at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other University.

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January 2022

DEDICATION

I dedicate this MMed to my late mother Kalorina Jonas for everything I am today, and to my son Christopher Sheetekela.

PRESENTATIONS

Chris Hani Baragwanath Academic Hospital research meeting 01/03/2021

Accepted for a poster presentation at SASOG 2022 26-30 November, Cape Town

ABSTRACT

Background

Syphilis is one of the most common sexually transmitted infections during pregnancy. If left untreated, it can lead to adverse outcomes in pregnancy and congenital syphilis in the new-born. Documented data on the prevalence of syphilis will help strengthen our screening program during pregnancy.

Methods

This was a retrospective analysis of data obtained from a cohort study entitled 'Prospective evaluation of rapid point-of-care test for active syphilis infection among pregnant women' which screened 662 patients and recruited 535 (80.8%) women from the antenatal clinic, gynaecology emergency intake and labour ward. Data were captured into an electronic questionnaire programmed on RedCap and subsequently exported into STATA 14 (Statacorp, College Station, Texas) for statistical analysis. Categorical variables were summarized using frequencies and percentages, whilst continuous variables were described using means (with standard deviations) for normally distributed data and medians (with inter-quartile range (IQR) for non-normally distributed data. Association between variables were evaluated using Wilcoxon signed rank-sum tests and Fischer exact test for continuous and categorical variable respectively. A p-value of <0.05 was considered to be statistically significant.

Results

A total of 526 files out of the 535 (98%) were available for analysis in our study. The mean age of the study patients was 26 years (standard deviation:6.3, range: 18-47). Majority of patients 380 (72.2%) were from the gynaecology unit, while the rest of the participants, 146 (27.8%) women, were from the obstetrics unit. A total of 505 (96%) women had results known for syphilis. Overall, six (1.2%) women tested positive for syphilis, five (1%) were gynaecology patients and one (0.2%) was from obstetrics. The prevalence of syphilis was not significantly different between the two patient groups with a p-value of 0.56. The total number of HIV positive patients was 94 (17.9%).

Conclusion

Syphilis is still a common infection among pregnant patients in South Africa. Current comprehensive antenatal care screening for syphilis should be continued with appropriate

treatment to reduce the incidence of adverse pregnancy outcomes, routine surveillances of gynaecological patients is needed.

Keywords: syphilis, pregnancy

ACKNOWLEDGEMENTS

I would like to express my very great appreciation to Dr A. Wise my supervisor for her patient guidance, enthusiastic and useful critiques of this research work and granting me permission to use data from 'Prospective evaluation of a rapid point-of-care test for active syphilis infection among pregnant women'.

I thank the department of Obstetrics and Gynaecology at RMMCH for all the support towards the study.

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LIST OF ABBREVIATIONS

AHEC- Alfred Hospital Ethic Committee

BBA- Birth Before Arrival

CS- Congenital Syphilis

EDTA- Ethylenediaminetetraacetic acid

HIV- Human Immunodeficiency Virus

HREC- Human Research Ethic Committee

LNMP- Last Normal Menstrual Cycle

MOU- Midwives Obstetrics Unit

NVD- Normal Vaginal Delivery

REDCap- Research Electronic Data Capture

RH- Rhesus Factor

RPR- Rapid Plasma Reagin

RMMCH- Rahima Moosa Mother and Child Hospital

SAJID- Southern African Journal of Infectious Diseases

STI- Sexually Transmitted Infection

USA- United States of America

WHO- World Health Organisation

JOURNAL ARTICLE

Prevalence of syphilis in women of childbearing age at Rahima Moosa Mother and Child Hospital

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Conflict of interest:

The researcher and co-author have no conflict of interest to declare

Prevalence of syphilis in women of childbearing age at Rahima Moosa Mother and Child Hospital

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ABSTRACT

Background: Syphilis is one of the most common sexually transmitted infections during pregnancy. If left untreated, it can lead to adverse outcomes in pregnancy and congenital syphilis in the new-born. Documented data on the prevalence of syphilis will help strengthen our screening program during pregnancy.

Methods: This was a retrospective analysis of data obtained from a cohort study entitled 'Prospective evaluation of rapid point-of-care test for active syphilis infection among pregnant women' which screened 662 patients and recruited 535 (80.8%) women from the antenatal clinic, gynaecology emergency intake and labour ward. Data were captured into an electronic questionnaire programmed on RedCap and subsequently exported into STATA 14 (Statacorp, College Station, Texas) for statistical analysis. Categorical variables were summarized using frequencies and percentages, whilst continuous variables were described using means (with standard deviations) for normally distributed data and medians (with inter-quartile range (IQR) for non-normally distributed data. Association between variables were evaluated using Wilcoxon signed rank-sum tests and Fischer exact test for continuous and categorical variable respectively. A p-value of <0.05 was considered to be statistically significant.

Results: A total of 526 files out of the 535 (98%) were available for analysis in our study. The mean age of the study patients was 26 years (standard deviation:6.3, range: 18-47). Majority of patients 380 (72.2%) were from the gynaecology unit, while the rest of the participants, 146 (27.8%) women, were from the obstetrics unit. A total of 505 (96%) women had results known for syphilis. Overall, six (1.2%) women tested positive for syphilis, five (1%) were gynaecology patients and one (0.2%) was from obstetrics. The prevalence of

syphilis was not significantly different between the two patient groups with a p-value of 0.56. The total number of HIV positive patients was 94 (17.9%).

Conclusion: Syphilis is still a common infection among pregnant patients in South Africa. Current comprehensive antenatal care screening for syphilis should be continued with appropriate treatment to reduce the incidence of adverse pregnancy outcomes, routine surveillance of gynaecological patients is needed.

Keywords: syphilis, pregnancy

INTRODUCTION

Syphilis is one of the most frequent sexually transmitted infections(STIs), caused by the spirochete *Treponema pallidum*. It is a topic of interest, especially in developing nations, and it is estimated that about 10 million people in the world are infected with syphilis(1). Mother to child infection with the bacterium during pregnancy raises the risk of HIV transmission to the child in cases of co-infection(1). If left untreated, active syphilis in pregnancy leads to a poor outcome in more than half of infected individuals, including early pregnancy loss, stillbirth, prematurity, low birth weight, neonatal and congenital disease in the new-born babies(2).

Many countries are now working toward the reduction of syphilis infection and eradication of congenital syphilis. The WHO has two syphilis targets: a 90% reduction in syphilis infection from 2018 to 2030 and 50 or lesser incidences of congenital syphilis per 100 000 live deliveries in 80% of countries(3). In recent years, the discovery of HIV and it's high rate of concurrence with syphilis has emphasised the need to reduce mother to child transmission of the two diseases, this has been successful in a number of countries(4). From the geographic point of view, the overall prevalence of syphilis differs from country to country depending on the socioeconomic status(4). Souza et al have demonstrated that the risk of syphilis was higher in female sex workers working in the low-income area of Brazil, a low educational level was one of the contributing factors(5).

Congenital syphilis (CS) results from transplacental transmission of spirochete *Treponema pallidum* from mother to the fetus. The clinical presentation of CS depends on the gestational age, the immunological response of the fetus, and the stage of maternal infection and treatment(2). Recently, the number of CS has been on the rise. In the USA, the number of CS has increased from 362 to 1306, with 94 stillbirth or early neonatal death between the year 2013 and 2018. The increase in cases has been attributed to inadequate maternal treatment and lack of proper prenatal care(6). Though CS can cause severe fetal abnormalities, most babies born with CS are asymptomatic at birth. Depending on the age at which the infection occurred, CS has been classified into early congenital syphilis (ECS) and late congenital syphilis (LCS). ECS manifest in the first 2 years of life, and LCS manifest over the first 2 decades(2). In ECS most babies do not display any symptoms and those with symptoms are usually non-specific. Clinical manifestations usually includes hepatomegaly, jaundice, rhinitis, generalized lymphadenopathy, and a maculopapular rash(7). LCS is very rare but can occur in about 40% of untreated patients. Clinical presentation includes scarring of the skin and mucous membrane gummas, Saber shin- anterior bowing of the shin, intellectual disability and cranial nerve palsies, interstitial keratitis, and a Hutchinson's triad(2). In South Africa, according to the Congenital Syphilis Quarterly Surveillances Report from 1 July 2017 to December 2020, a total of 794 clinical notifications of CS cases and 11 170 Rapid plasma reagin (RPR) positive results from children and infants less than 2 years were reported. It showed that there was an increase in both clinical notification and RPR positive cases(8).

Therefore, we conducted a secondary analysis of a prospectively recruited cohort study at our hospital in Johannesburg, South Africa to estimate the prevalence of syphilis in pregnant and peripartum women attending the Obstetrics and gynaecology department at Rahima Moosa Mother and Child Hospital; to describe the demographics in the population recruited and; describe the pregnancy outcome in the cohort.

METHODS

We conducted a retrospective review of a prospectively recruited cohort study to investigate the presence of syphilis in venous blood collected from patients between June-December 2018 at Rahima Moosa Mother and Child Hospital (RMMCH).

This was a secondary data analysis of the study 'Prospective evaluation of rapid point of care test for active syphilis infection among pregnant women'. In the initial study, venous blood sample was collected from consenting pregnant or peripartum women (within two weeks of miscarriage, termination of pregnancy or childbirth), aged 18 years or older, attending the Obstetrics and Gynaecology department at RMMCH, Johannesburg, South Africa. Each participant provided 3ml venous blood collected in EDTA tubes for standard syphilis serology test and the index test performed in duplicate by two independent test operators. Ethic approval was obtained from AHEC (#556/17) and the Human Research Ethics Committee (HREC) of the University of the Witwatersrand in South Africa (#M180119).

Setting: The study was conducted in a teaching hospital, namely Rahima Moosa Mother and Child Hospital. The hospital is affiliated with the University of the Witwatersrand and situated in the suburb of Coronationville, Johannesburg, South Africa. The hospital was opened in 1944 and was established for Coloured and Indian people. Currently, the hospital provides services to a large population, including 38.5% non-South African. In 2019 the hospital had 13 974 deliveries, of which 99 (0.7%) were syphilis positive, and 2 266 (16%) were HIV positive. Furthermore, in 2020, the hospital had a total of 16093 deliveries, of which 120 (0.7%) were syphilis positive.

Study entry criteria: All consenting pregnant and peripartum patients (within two weeks of miscarriage, termination of pregnancy or childbirth), aged 18 years or older who were included in the 'Prospective evaluation of a rapid point-of-care test for syphilis infection among pregnant women' study. To be included they were to have not been tested for syphilis

in the current pregnancy. Hence the majority were recruited from the Gynaecology Admission ward as most Obstetrics patients have booked and have known syphilis status.

Sampling and sampling size: This is a retrospective review of a prospectively recruited cohort. A total of 662 patients were screened, and 535 were recruited in the initial study. 526 files were available for analysis in our current study.

Measurements: Data for this study was obtained from a study done at RMMCH 'Prospective evaluation of rapid point of care test for active syphilis infection among pregnant women' in which patients were recruited either through the antenatal clinic, Gynaecology emergence intake, or labour ward. The rapid kit was then compared against a sample sent to the hospital laboratory were an RPR test was done. Participants were approached and provided with relevant information. Informed consent was then taken from the participant, and it was signed once they have agreed. Permission to use the study data was given by Dr A. Wise (PI South Africa) and Prof D. Anderson (PI Australia).

Ethical consideration: Ethical approval was sought and granted by the Human Research Ethics Committee (HREC) of the University of the Witwatersrand. Clearance certificate number M201167. Clearance certificate number for the initial study 'Prospective evaluation of rapid point of care test for active syphilis infection among pregnant women' M180119.
Data analysis: Data was transported from REDCap into STATA 14 (Statacorp, College Station, Texas) for statistical analysis. Descriptive tables were constructed for sociodemographic characteristics and for factors thought to be associated with syphilis. Means (standard deviations) or medians (interquartile ranges) were described for continuous variables. Categorical variables were tabulated, and their frequencies were recorded. To compare unit and patient characteristics, we used the Fisher's exact test for categorical variables and the Wilcoxon rank-sum test for continuous variables.

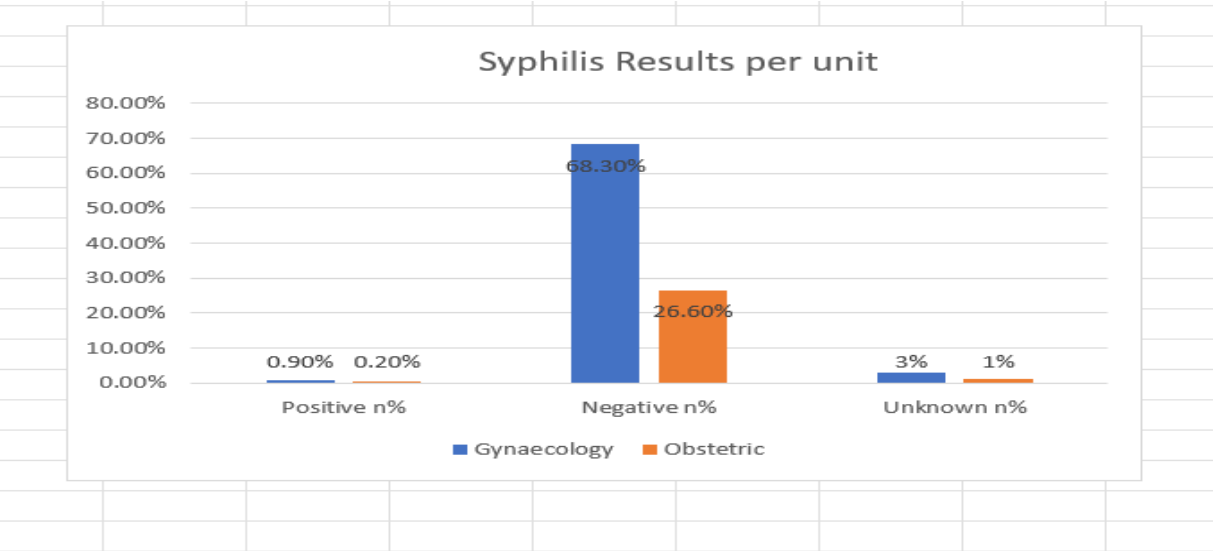
RESULTS

Five hundred and forty-five women were recruited into the primary study conducted between June 2018 and December 2018. Out of these, 286 files and 240 data collecting sheet from the

main study were available for analysis in our study. More than two-thirds of the women (380 women, 72.2%) were from the Gynaecology Unit, while the rest (146 women, 27.6%) were recruited from the Obstetric wards. Six women (1.2%) tested positive for syphilis. Twenty-one patients included in the study had unknown syphilis status as their RPR results were rejected from our laboratory.

Error! Reference source not found. shows the demographics and characteristics of the study participants. The mean age of the study participants was 26 years (standard deviation: 6.3, range: 18 - 47). All the women in the study were pregnant with the median gestational age of 10 weeks (interquartile range: 7 – 23). Two hundred and twenty-five women (42.8%) who were attending the hospital was because of miscarriage. In comparison, 87 women (16.5%) attended because they were in labour. Ninety-four women (17.9%) tested positive for HIV. Only one patient that tested positive for HIV also tested positive for syphilis, representing 1.1% of the HIV population. Some of the data was not available for analysis due to missing files.

IQR- Interquartile range



Unit	Positive n(%)	Negative n(%)	Unknown n(%)
Gynaecology	5 (0.9)	359 (68.3)	16 (3.0)
Obstetric	1 (0.2)	140 (26.6)	5 (1.0)

Figure 1: Syphilis results by unit.

When comparing the patients with known syphilis results recruited from Obstetrics and Gynaecology the p-value was 0.56. The lack of significance could be due to the small sample size. It is interesting to note that the proportion of positive patients recruited in Gynaecology was nearly twice that in Obstetrics.

Table 1: Characteristics of the study population

Characteristic		Overall	Gynaecology	Obstetric	P-value
Age in years (n-=526)	Mean (IQR)	26.1 (6.3)	29 (25-35)	27 (23-33)	0.020
Parity (n=426)	0	116(27.2)	91 (30.1)	25 (20.3)	0.051
	1	128 (30.0)	88 (29.2)	40 (32.5)	
	2	114 (26.8)	84 (27.8)	30 (24.4)	
	3	54 (12.7)	32 (10.6)	22 (17.9)	
	4 +	13 (3.0)	7 (2.5)	6 (4.9)	
Gravidity (n=426)					
	1	109 (25.6)	75 (24.8)	33 (26.8)	0.99
	2	131 (30.8)	95 (31.5)	36 (29.3)	
	3	104 (24.4)	73 (24.2)	31 (25.2)	
	4	58 (13.6)	42 (13.9)	16 (13.01)	
	5 +	24 (5.6)	17 (5.6)	7 (5.7)	
Gestational age in weeks (n=259)	Median (IQR)	10 (7 – 22)	8 (6-12)	36 (29-38)	<0.001
	1	126 (48.6)	91 (35.1)	35 (13.5)	
	2	87 (33.6)	63 (21.1)	24 (19.7)	
	3	36 (13.9)	19 (6.3)	17 (13.9)	
	4+	10 (3.9)	5 (1.7)	5 (4.1)	
Reason for visiting the hospital (n=526)	Miscarriage	225 (42.8)	220 (41.8)	0 (0.0)	<0.001
	Termination	13 (2.5)	12 (2.3)	1 (0.7)	
	Ectopic pregnancy	27 (5.1)	27 (5.1)	0 (0.0)	
	Delivery	87 (16.5)	0 (0.0)	86 (16.3)	
	BBA	34 (6.5)	1 (0.2)	34 (6.5)	
	Other	140 (26.6)	120 (22.8)	18 (3.4)	
HIV status (n=526)	Negative	307 (58.4)	221 (42.0)	84 (65.1)	<0.001
	Positive	94 (17.9))	45 (8.5)	45 (34.9)	
	Unknown	125 (23.7)	114 (21.7)	11 (2.1)	
Blood RPR(n=526)	Negative	499 (94.9)	359 (98.6)	140 (99.3)	1.00
	Positive	6 (1.1)	5 (1.3)	1 (0.7)	
	Unknown	21 (4.0)			

IQR- Interquartile range

Treatment for syphilis

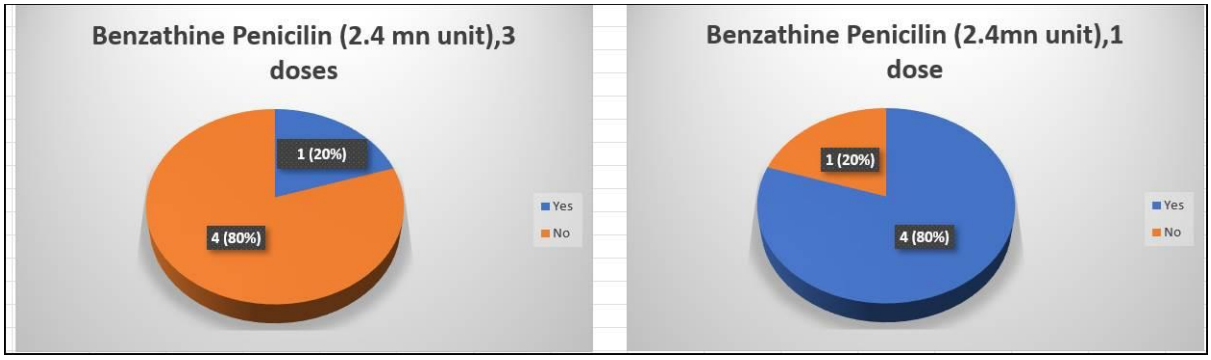


Figure 2: Syphilis treatment offered to the patients

Figure 2 shows the treatment that was offered to the five syphilis positive patients. In total Five patients (83.3%) received Benzathine penicillin (2.4 million units), of these patients one (20%) received the full 3 doses. Four patients had their first dose to referral to their local clinic. One syphilis positive patients had missing documentation on the treatment given and there was no contact information to trace her.

Pregnancy outcomes

Table 2 shows the pregnancy outcomes of all the women by syphilis result. Four syphilis positive women (66.7%) had miscarriages with a p-value of 0.234 between the negative and positive for syphilis, One delivered a live baby and one syphilis positive woman (16.7%) had a stillbirth.

Table 2: Pregnancy Outcome, by syphilis result

Characteristics	**Negative n (%) n=505**	**Positive n (%) n=6**	**Unknown status n (%) n=21**	**Total N=526**
Miscarriage	212 (94.2)	4(1.7)	9 (4.0)	225 (42.7)
Live birth	89 (96.7)	1 (1.1)	2 (2.2)	92 (17.5)
Ectopic pregnancy	27 (100.0)	0 (0.0)	0 (0.0)	27 (5.1)
Neonatal death	1 (100.0)	0 (0.0)	0 (0.0)	1 (0.2)
Preterm delivery	24 (96.0)	0 (0.0)	1 (7.7)	26 (4.9)
Stillbirth	10 (71.4)	1 (7.1)	3 (21.4)	14 (2.7)
Unknown	135 (95.7)	0 (0.0)	6 (4.3)	141 (26.8)

DISCUSSION

Syphilis is a global health problem and very common in women of childbearing age. If left untreated, syphilis infection in pregnancy might lead to adverse outcomes. We carried out this study to determine the prevalence of syphilis at RMMCH among our pregnant or patients within two weeks of miscarriage, termination of pregnancy, or childbirth. This study was conducted to better understand the prevalence of syphilis on an Obstetrics and Gynaecology setting.

In our present study, among the five hundred and twenty-six files available for analysis, 505 patients had known syphilis status of which six patients were positive for syphilis accounting for 1.2% of the whole study population. Year-wise from 2019 to 2020, the incidence of syphilis in our setting has been around 0.7% over the past two years, which shows a uniform and stable trend of syphilis in our setting. These statistics are mostly from our obstetric unit as there are national policies pertaining to HIV and syphilis testing with data capturing in all our obstetric patients presenting for antenatal care (9). In our study, two thirds of the patients that tested positive for syphilis were from our gynaecology department (72.2%), presenting mainly with a miscarriage. Our study correlates with the South African National Antenatal Sentinel HIV and Syphilis prevalence Survey that showed an overall syphilis prevalence of

1.6% in pregnant women. The decline in syphilis was largely attributed to the implementation of syndromic management of STIs from 1994 onwards (10). In comparison, in Beijing, China Xue Zhang et al found an infection rate of 1.4% among pregnant women which was a similar finding as in our study (11). The prevalence of syphilis during pregnancy in the western world ranges between 0.02 to 4.5% in northern Europe and the United States (12). According to the WHO the prevalence of syphilis among pregnant mothers in the United Kingdom ranges between 0.1 to 0.17%, these figures are relatively lower compared to the findings in our study (13). Our study found only one syphilis positive patient that was co-infected with HIV (1.1%). This is in stark contrast with the study by Monjurul H et al. which found a prevalence of co-infection of 5.6% in South Africa, however the numbers in our study are very small (14). Our study found only one syphilis positive patient that was co-infected with HIV. According to the South African Guideline For Maternity Care, every pregnant women should be screened for syphilis, HIV, Rh, Hb during their first antenatal visit. Furthermore, syphilis tests are repeated again at 32 weeks of gestation for all women who tested negative at initial testing and HIV at every ANC visit (15).

Regarding pregnancy outcome in syphilis positive patients, our study found that four of them had miscarriages while one patient had a stillbirth at 27 weeks of gestation, birth weight was 800g. One patient that was unbooked gave birth before arrival (BBA), the birth weight was 3380g. According to De Santis et al. untreated syphilis during pregnancy lead to an adverse fetal outcome in the form of stillbirth, miscarriages, prematurity, low birth weight, neonatal and infant death(2). Our study has demonstrated some of these adverse effects of syphilis in pregnancy, namely stillbirth and miscarriages. C. Duan et al. have indicated that non-latent syphilis was a risk factor for stillbirth, and adequate treatment was the only protective method for stillbirth(16). Similarly it has been demonstrated that adverse birth outcomes are preventable if patients are screened for syphilis and treated in the first trimester(17). During our study, one patient that tested positive for syphilis also tested positive for HIV representing 1.1% of the HIV population in our study. Comparing our findings to other studies in the field of HIV and syphilis especially from Asia, which showed that HIV acquisition was high in patients with syphilis and this was attributed to the syphilitic ulcer, which damages the epithelium and making it easy for HIV transmission(14). A South African study found that pregnant women who are HIV positive had a significantly higher rate (5.6%) of syphilis compared to 2.5% for pregnant women who are HIV negative. The study also

found that pregnant women who are syphilis negative, are 55% less likely to have HIV infection (14).

In terms of treatment, out of six patients that tested positive for syphilis, we had information on five patients regarding their treatment. Of them, one patient received a full dose of penicillin, four patients each received one dose of penicillin and they were referred back to their local clinic to complete treatment. We could not allocate the sixth file with contact information for the patient that tested positive for syphilis and therefore, we do not have treatment information on this patient. The South African Sexually Transmitted Infection Management guideline recommends Benzathine penicillin G 2.4 million units intramuscular once weekly for three consecutive weeks during pregnancy for latent syphilis or latent syphilis of unknown duration. In case of penicillin allergy, Penicillin desensitization was recommended or alternatively, Amoxicillin and Probenecid can be prescribed(18). A 2012 study by C. Yang et al. has demonstrated that a single dose of Benzathine penicillin resulted in a more serological failure than a three-weekly Benzathine penicillin, especially in patients who are co-infected with HIV(19).

Our study could not demonstrate the impact of syphilis in the newborn as most patients that tested positive for syphilis either had a miscarriage or stillbirth. One patient that was syphilis positive delivered a live baby, she received her first dose at 20 weeks of gestation and the last dose at 23 weeks of gestation. According to Sandra R. et al. there is no test which, at birth, will identify the asymptomatic baby with normal long bone examination as definitely infected or uninfected as most infected babies are asymptomatic at birth (20). Review of maternal serology and follow-up of the infant will, over time, indicate whether infection has occurred. A complete diagnostic evaluation is warranted if the child or infant has signs and symptoms of congenital syphilis, if the mother was treated within four weeks of delivery or if maternal treatment was inadequate during pregnancy (20). Currently, there have been reports of country-level shortage of Benzathine penicillin in South Africa which is the recommended treatment to prevent mother-to-child transmission of syphilis (21).

LIMITATION

Our study was conducted in a busy obstetrics and gynaecology unit with more than 10 000 deliveries per year. Our present study has limitations due to its retrospective design, not all files were available for analysis and those that were available did not have all the information required for our data collection. Furthermore, our study was conducted in a regional academic hospital, which in most cases only accepts complicated and high risk patients. Majority of low risk patients are seen at Midwives Obstetrics Unit (MOU), therefore our present study does not represent the whole community population.

RECOMMENDATION

- Most statistics and audits focus more on obstetric patient population than gynaecology unit. I suggest there is more focus on both obstetrics and gynaecology to define the extent of the problem clearly with prospective routine data collection and emphasis on testing and treating.
- Patients with poor obstetric outcome need to be investigated, for syphilis and followed up at a specialist center.
- Larger prospective studies need to be done to better understand the impact of congenital syphilis in our setting.

CONCLUSION

Our study finds a low prevalence of syphilis in our setting and a low seroconversion rate of HIV and syphilis . Majority of patients that tested positive for syphilis are from our gynaecology unit. While we have a routine statistics collection for syphilis from obstetrics, our study suggest that we should have the same for gynaecology as the proportion of affected patients was twice that in obstetrics. Follow-up and good communication with local clinics is needed to ensure follow-up of patients and adequate treatment. Further prospective studies are needed to show the impact of congenital syphilis on the new-born

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I would like to express my very great appreciation to Dr A. Wise my supervisor for her patient guidance, enthusiastic and useful critiques of this research work and granting me

permission to use data from a study ‘Prospective evaluation of a rapid point-of-care test for active syphilis infection among pregnant women’.
I thank the department of Obstetrics and Gynaecology at RHMMCH for all the support towards the study.

DISCLOSURE

The authors report no conflict of interest in this study.

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Appendices

Appendix A: Approved Research Protocol

1.1 INTRODUCTION

Syphilis is one of the most frequent sexually transmitted infections (STIs), caused by a spirochete Treponema pallidum. It is a topic of interest especially in developing nations. About 10 million people in the world are infected by syphilis (1) .Mother to child infection of the bacterial during pregnancy rises the risk of HIV transmission to the child in case of coinfection (1). Many countries are working toward the reduction of Syphilis infection and eradication of congenital Syphilis. The WHO has 2 Syphilis target: 90% reduction in Syphilis infection from 2018 to 2030 and 50 or lesser incidences of CS per 100 000 live deliveries in 80% of countries (2).

1.2 LITERATURE REVIEW

1.2.1 SYPHILIS

Syphilis- a sexually or transplacental acquired infection caused by the bacteria Treponema Pallidum. It is an obligate human pathogen that is recognized by its invasiveness and immune-evasiveness (3). Infected people follow a disease trend which split into Primary, Secondary, Latent, and Tertiary stages that can take up to more than 10 years (3).

In recent years, the discovery of HIV and its high rate of concurrence with Syphilis has put more consideration in reducing mother to child transmission of the two diseases which has been successful in 5 countries: Cuba, Thailand, Belarus, Armenia and the Republic of Moldova (4).

1.2.2 MICROBIOLOGY

Treponema Pallidum belongs to a family of Spirochete which also includes other non-venereal diseases such as Yaws, Endemic Syphilis, and Pinta(5). Because of its multistage clinical presentation, Syphilis has always been a topic of intense discussion in medicine and public health(6). Described since the late 15th century, Syphilis has been known to have an unusual clinical presentation and has been called "the great imitator", sir William Osler famously said "who knows Syphilis, knows medicine"(6).

T. Pallidum is a spirochete, slow-growing, and spiral in shape. Only infect human beings(6). The bacteria has a diameter of 0.10 to 0.18 micrometres and a length of 6 to 20 micrometer (4). Syphilis is transmitted via sexual contact and vertically through the placenta (4). On rare occasions, syphilis may also be transmitted via bloodborne during blood transfusion(6).

1.2.3 GEOGRAPHIC DISTRIBUTION

Overall the prevalence of Syphilis differs from country to country depending on the socioeconomic status. (4). Souza et al, have demonstrated that the risk of Syphilis was higher in FSW working in the low-income area of Brazil Amazon region and low educational level were one of the contributing factors (7).

In Brazil Gomes NCRC et al**,** compared the prevalence of Syphilis among MSM, DU, and people with STDs. The population of MSM showed a high rate of Syphilis infection as compared to other groups (8). A different study done by EKOUEVI et al demonstrated that Syphilis in sub-Sahara Africa including South Africa was on a decreasing trend among the vulnerable people(9). The low prevalence in these key populations was attributed to the irrational use of antibiotics for sexually transmitted diseases (9).

Generally, the spread of Syphilis is mostly common in low-income to middle-income countries (LMICs) as compared to high-income countries(4). According to the EU and EEA annual report on epidemiology, Syphilis has been on increasing trend mostly in MSM and this has been attributed to a higher rate in engaging in risky sexual behaviours (10).

In Africa, a 2018 report on pregnant patients indicated that the prevalence of Syphilis was 6.5% in Southern Africa, 4.6% in Eastern Africa and 4.0% in West Africa(4).

1.2.4 CLINICAL MANIFESTATION

Syphilis is a multistage infection as described by Forrestel et al. It Starts as Primary Syphilis followed by Secondary syphilis, Latent syphilis, and subsequently Tertiary syphilis(6).

Primary Syphilis has classical symptoms of Cancre formation-a painless single lesion with a clear base. (11). Cancre can develop anywhere on the body but mostly on the genitals. The incubation period has an average of 21 days and is associated with Lymphodenopathy, the lesion resolved by itself in one to four months period (12).

Multiple lesions can occur concurrently especially in people living with HIV infection (13).

Secondary Syphilis manifests three to twelve weeks after the disappearance of the cancre or concurrently. Involve systemic dissemination of the Syphilis causing bacteria Spirochete in the blood (6).

This stage involves the development of skin rash, described as "raw ham" or "copper-coloured". The rash extends from a macular to maculopapular rash, folicullar, and sometimes pustular (11). Cutaneous symptoms are associated with generalized non-tender lymphadenopathy and other flu-like symptoms such as fever, headache, fatigue, and muscle ache. Secondary Syphilis lasts about a few weeks to a few months before it resolves with the possibility of relapse. This stage is considered infectious within a 12 months flame after acquisition (13).

Latent Syphilis

The asymptomatic stage where infected people show no symptoms. In the early latent phase (less than 12 months after exposure), there is a risk of relapse to Secondary Sphylis (14).

Tertiary Syphilis

Subdivided into Gummatous syphilis, Cardiovascular syphilis, and Neurosyphilis (12). Tertiary syphilis is not infectious and lasts about 1 to 46 years after exposure(14).

Gummatous syphilis involve the development of necrotic gummatous lesion(14). The lesions affect all body organs but mostly the skin, mucous membrane, and bones(12).

Cardiovascular syphilis manifests about 10 to 30 years after exposure and involves the development of Syphilitic aortitis commonly in the ascending aorta, the most common complication of this form of Syphilis is Aortic regurgitation (11).

Neurosyphilis- This stage affects about 10% of exposed patients and present with multiple neurological manifestation including convulsions. This stage may also cause sensory change, and affect the gastrointestinal and urinary function (12).

1.2.5 CONGENITAL SYPHILIS

Congenital Syphilis (CS) results from transplacental transmission of Spirochete Treponema Pallidum from mother to the fetus. The clinical presentation of CS depends on the gestational age, the immunological response of the fetus, and the stage of maternal infection and treatment (15). Recently, the number of CS has been on a rise. In the USA, the number of CS have increased from 362 to 1306 with 94 stillbirth or early neonatal death between 2013 and 2018. The increase in the number of cases has been attributed to inadequate maternal treatment and a lack of proper prenatal care (16) .

Though CS can cause severe fetal abnormalities, most babies born with CS are asymptomatic at birth. Depending on the age at which the infection occurred, CS has been classified into ECS and LCS. ECS- manifest in the first 2 years of life and LCS manifest over the first 2 decades (15).

In ECS most of the babies do not display any symptoms and those with symptoms are usually non-specific. A clinical manifestation usually includes Hepatomegaly, Jaundice, Rhinitis, generalized Lymphadenopathy, and a Maculopapular rash (17).

LCS is very rare but can occur in about 40% of untreated patients. Clinical presentation includes scarring of the skin and mucous membrane gummas, Saber shin- anterior bowing of the shin, intellectual disability and cranial nerve palsies, interstitial keratitis, and a triad of Hutchinson (15) .

1.3 AIMS AND OBJECTIVES

AIM

To evaluate the prevalence of Syphilis in pregnant or peripartum patients age 18 and older, attending the Obstetrics and Gynaecology department at Rahima Moosa Mother and Child Hospital (RMMCH).

OBJECTIVES

1. To estimate the prevalence of syphilis in pregnant and peripartum women attending the Obstetrics and Gynaecology department at Rahima Moosa Mother And Child Hospital.
2. To describe the demographics in the population recruited.
3. To describe the pregnancy outcome in the cohort.

1.4 METHODS

1.4.1 STUDY DESIGN

This is a retrospective review of a prospectively recruited cohort study to investigate the presence of syphilis in venous blood collected from patients between June-December 2018 at Rahima Moosa Mother and Child Hospital.

Data for this study will be collected from a study 'Prospective evaluation of rapid point of care test for active syphilis infection among pregnant women'.

1.4.2 SETTING

The study was conducted in a teaching hospital Rahima Moosa Mother And Child Hospital. The hospital is affiliated to the University of Witwatersrand and is situated in the suburb of Coronationville, Johannesburg, South Africa. The hospital was opened in 1944 and was established for colored and Indian people. Currently, the hospital provides services to a large

population including 38.5% non-South African. In 2019 the hospital had a total of 13 974 deliveries of which 99 (1%) were syphilis positive and 2 266 (18%) were HIV positive.

1.4.3 STUDY POPULATION

All consenting pregnant or peripartum patients attending the department of Obstetrics and Gynaecology at Rahima Moosa Mother and Child Hospital.

INCLUSION CRITERIA

1. Pregnant or patients within two weeks of miscarriage, termination of pregnancy, or childbirth.
2. Informed consent
3. Age 18 and older

EXCLUSION CRITERIA

No exclusion criteria for this study

1.4.4. SAMPLING AND SAMPLE SIZE

This is a retrospective review of a prospectively recruited cohort in which a total of 662 patients were screened and out of them, 535 were recruited for the study.

1.4.5 MEASUREMENT

Data for this study will be obtained from a study done at Rahima Moosa Mother and Child Hospital 'Prospective evaluation of rapid point of care test for active syphilis infection among pregnant women' in which patients were recruited either through the antenatal clinic, Gynaecology emergency intake, or labour ward. Participants were approached and provided with relevant information, and informed consent was explained to the participant and it was signed once they have agreed.

Permission to use the study data was given by Dr A Wise (PI South Africa) and Prof D Anderson (PI Australia).

SPECIMEN COLLECTION

In the study 'Prospective evaluation of rapid point of care test for active syphilis infection among pregnant women', each participant provided 3ml venous blood collected in EDTA tubes for standard Syphilis serology test and the index test performed in duplicate by two independent test operator. The index test was performed in duplicate by a trained technician at the RMMCH's research laboratory as part of the development of the IgA rapid test kit. A reference sample was sent to the NHLS as part of the standard of care- pregnant women who had not had a syphilis test done as part of the 'booking bloods' were recruited. For the purpose of this study only the results from the NHLS will be used as the rapid test was still undergoing validation.

FOLLOW UP AND RESULTS

Patients with positive results were called back, counselled, and offered treatment as per national guidelines. As per guideline, they received Benzathine Penicillin G 2.4mU i.m one injection weekly for 3 consecutive weeks (18)

DATA CAPTURING AND MANAGEMENT

The investigator will be using RedCap to capture the data.

1.5 ETHICAL CONSIDERATION

- Data will be collected from a study "Prospective evaluation of a rapid point of care test for active syphilis infection among pregnant women. Clearance certificate NO. M180119
- Approval to conduct the study will be obtained from the Human Research Ethics Committee.
- The protocol will be submitted to the postgraduate research committee of the Department of Obstetrics and Gynaecology of the University of Witwatersrand.

- Approval will be sought from the Chief Executive Officer of Rahima Moosa Mother and Child Hospital.
- Consent was obtained from participating patients for the original study
- Any information obtained from the participants files will be kept confidential at all times.
- The study will be registered on the National Health Research Database

1.6 BUDGET

ITEMS	**COST**
Printing of datasheet	R 500
Printing of dissertation	R 200
Total cost	R 700

All printing cost will be paid by the researcher

1.7 TIMELINE AND PROJECT MANAGEMENT

ACTIVITY	**March-June 2020**	**July-Sep 2020**	**Oct-Dec 2020**	**January 2021**	**Feb 2021**	**MARCH 2021**
Mmed submission	X					
Ethic aspect		X				
Postgraduate committee		X				
Permission from CEO		**X**				
Data collection			**X**	**X**		
Data processing				**X**		
Statistical analysis					**X**	

Publication and preparation						**X**
Submission						**X**

1.8 REPORTING

- Feedback will be given to the department of Obstetrics and Gynaecology of the findings of the study.
- The results of the study will be presented to the department
- Dissertation

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Appendix B: Participant Informed Consent Form

Study title: Prospective evaluation of a rapid point-of-care test for active syphilis infection among pregnant women

Study team: Australia - A/Prof Anderson, A/Prof Luchters, Ms Garcia, Ms Mohamed

South Africa - Dr Wise, Prof Lombaard, Dr Technau, ESRU research team

I confirm that I have been informed by the study team member_____, about the nature of the study. I have also read/it was read to me and I understood the information sheet and have had the opportunity to ask questions.

I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected.

I understand that sections of any of my medical records may be looked at by the study team listed above. I am aware that I will have a sample of my blood taken along with other samples that are needed to help look after me, and will answer a short questionnaire. Test results and my age, race, will be anonymously processed into a computerised system. Data will be kept for five years if published or six years if not published, after this period the data will be destroyed.

I know who to contact regarding consent at any time: Dr Wise at 073 152 7513, Dr Technau at 082 687 3633 or Professor Lombaard at 011 470 9090.

I agree to take part in the above-mentioned study. I hereby give consent for my records to be used as per the above-mentioned conditions and for the purposes of research to have an extra tube of blood taken.

Printed name and surname of patient/participant:

Signature: Date:

Printed name of researcher:

Signature Date:

Printed name of witness (if applicable):

Signature Date:

Appendix C: Data collection sheet

Confidential

Prevalence of syphilis in women of childbearing age at Rahima Moosa Mother and Child hospital

Please complete the survey below.

Thank you!

Study number	_____
Age	_____
Parity	_____
Gravidity	_____
Last normal period	◯ Known ◯ Unknown
LNMP	_____
Last normal menstrual period	◯ Sure dates ◯ unsure dates ◯ Unknown date
Unit	◯ Gynaecology ◯ Obstetrics
Pregnancy test	◯ positive ◯ negative
Estimated Gestational Age in Weeks	_____
Method of estimating gestational age	◯ By date ◯ By early ultrasound ◯ by late ultrasound ◯ Palpation
Expected date of delivery	_____
Number of previous miscarriage 1st trimester	_____
Number of previous miscarriage 2nd trimester	_____
Number of previous stillbirths	_____

Number of previous deliveries NVD	_____
Number of previous deliveries C/S	_____
Reason for attendance to hospital	◯ Miscarriage ◯ termination ◯ ectopic pregnancy ◯ delivery ◯ BBA ◯ other
Mode of delivery	◯ NVD ◯ C/section
Date of booking blood	_____
booking blood HIV status	◯ Negative ◯ Positive ◯ Unknown
Booking blood VL	_____
Booking blood CD4	_____
Booking blood HB	_____
RH	◯ positive ◯ Negative
Booking blood RPR	◯ Positive ◯ Negative ◯ unknown
Treatment in syphilis positive	☐ Benzathine penicillin 2.4 units 3 doses ☐ Benzathine penicillin 2.4 unit single dose ☐ Doxycycline ☐ Others ☐ none
Pregnancy outcome	☐ miscarriage ☐ live birth ☐ Ectopic pregnancy ☐ Neonatal death ☐ Small for gestational age ☐ Preterm delivery ☐ Stillbirth ☐ unknown
Features of syphilis in infant	_____

Appendix D: Permission to use the main study

UNIVERSITY OF THE WITWATERSRAND JOHANNESBURG
OBSTETRICS AND GYNAECOLOGY
School of Clinical Medicine

16 December 2020

To whom it may concern

As the South African PI of the study 'Prospective evaluation of a rapid point of care test for active syphilis infection among pregnant women' (M 180119), I give Dr Filippus Elago Sheetekela permission to use the data set for his MMed study 'Prevalence of syphilis in women of child bearing age at Rahima Moosa Mother and Child Hospital.

Regards

Dr Amy Wise

Senior Consultant O&G
Sub-specialist Maternal and Fetal Medicine
Research Co-ordinator MMed/MSc O&G
Department of Obstetrics and Gynaecology
Rahima Moosa Mother and Child Hospital
University of the Witwatersrand

Appendix E: Permission letter from RMMCH

GAUTENG PROVINCE
HEALTH
REPUBLIC OF SOUTH AFRICA

RAHIMA MOOSA MOTHER AND CHILD HOSPITAL

Enquiries : Karen Marshall
Tel : (011) 470 9284
Fax : 086 553 4623
Email : Karen.Marshall@wits.ac.za

TITLE OF RESEARCH PROJECT:
"PREVALANCE OF SYPHILIS IN WOMEN OF CHILDBEARING AGE AT RAHIMA MOOSA MOTHER AND CHILD HOSPITAL"

NAME OF SUPERVISOR:
DR AMY WISE

NAME OF RESEARCHER:
DR FILIPPUS SHEETEKELA

NHRD REF NO: GP_202010_093

Dear Dr Sheetekela,

Permission is granted for you to conduct the research as indicated in the title above.

The terms under which this permission is granted is contained in the Researcher Declaration form that you have signed. Failure to comply with these conditions will result in the withdrawal of such permission.

It is crucial for you to inform the Research Coordinator, Karen Marshall of the actual start and end dates of your study. This could be done by e-mail.

Should the study commence more than 12 months after receipt of this approval letter you will have to go through the process of applying again.

You are strongly advised to keep a signed copy of the declaration form to ensure that the terms of this agreement are complied with at all times.

Yours sincerely,

DR FREW BENSON
ACTING CHIEF EXECUTIVE OFFICER
2020:12:07

ADDRESS: Cnr FUEL & OUDSTHOORN STREET CORONATIONVILLE 2093 / PRIVATE BAG X20 NEWCLARE 2112 JHB

Appendix F: Ethic clearance certificate

UNIVERSITY OF THE WITWATERSRAND JOHANNESBURG

R49 Dr FE Sheetekela

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
CLEARANCE CERTIFICATE NO. M201167

NAME: (Principal Investigator)	Dr FE Sheetekela
DEPARTMENT:	School of Clinical Medicine Department of Obstetrics and Gynaecology Medical School University
PROJECT TITLE:	*Prevalence of syphilis in women of childbearing age at Rahima Moosa Mother and Child Hospital*
DATE CONSIDERED:	2020/11/27
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Dr A Wise
APPROVED BY:	Dr CB Penny, Chairperson, HREC (Medical)
DATE OF APPROVAL:	2021/01/26

This Clearance Certificate is valid for 5 years from the date of approval. An extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office secretariat on the 3rd floor, Phillip Tobias Building, Parktown, University of the Witwatersrand, Johannesburg.

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 submit details to the Committee. **I agree to submit a yearly progress report**. When a funder requires annual re-certification, the application date will be one year after the date when the study was initially reviewed. In this case, the study was initially reviewed in **November** and therefore reports and re-certification will be due in the month of **November** each year. Unreported changes to the study may invalidate the clearance given by the HREC (Medical).

Signature of Principal Investigator — Date: 15/12/2020

Appendix G: Journal guideline for SAIDJ

Overview

The author guidelines include information about the types of articles received for publication and preparing a manuscript for submission. Other relevant information about the journal's policies and the reviewing process can be found under the about section. The **compulsory cover letter** forms part of a submission and must be submitted together with all the required **forms.** All forms need to be completed in English.

Original Research Article

An original article provides an overview of innovative research in a particular field within or related to the focus and scope of the journal, presented according to a clear and well-structured format.

Word limit	3500 words (excluding the structured abstract and references)
Structured abstract	250 words to include a Background, Methods, Results and Conclusion
References	50 or less
Tables/Figures	no more than 7 Tables/Figure
Ethical statement	should be included in the manuscript
Compulsory supplementary file	ethical clearance letter/certificate

Original Research Article full structure

Title: The article's full title should contain a maximum of 95 characters (including spaces).

Abstract: The abstract, written in English, should be no longer than 250 words and must be written in the past tense. The abstract should give a succinct account of the objectives,

methods, results and significance of the matter. The structured abstract for an Original Research article should consist of four paragraphs labelled Background, Methods, Results and Conclusion.

- Background: Summarise the social value (importance, relevance) and scientific value (knowledge gap) that your study addresses.
- Methods: Clearly express the basic design of the study, and name or briefly describe the methods used without going into excessive detail.
- Results: State the main findings.
- Conclusion: State your conclusion and any key implications or recommendations.

Do not cite references and do not use abbreviations excessively in the abstract.

Introduction: The introduction must contain your argument for the social and scientific value of the study, as well as the aim and objectives:

- Social value: The first part of the introduction should make a clear and logical argument for the importance or relevance of the study. Your argument should be supported by use of evidence from the literature.
- Scientific value: The second part of the introduction should make a clear and logical argument for the originality of the study. This should include a summary of what is already known about the research question or specific topic, and should clarify the knowledge gap that this study will address. Your argument should be supported by use of evidence from the literature.
- Conceptual framework: In some research articles it will also be important to describe the underlying theoretical basis for the research and how these theories are linked together in a conceptual framework. The theoretical evidence used to construct the conceptual framework should be referenced from the literature.
- Aim and objectives: The introduction should conclude with a clear summary of the aim and objectives of this study.

Research methods and design: This must address the following:

- Study design: An outline of the type of study design.

- Setting: A description of the setting for the study; for example, the type of community from which the participants came or the nature of the health system and services in which the study is conducted.
- Study population and sampling strategy: Describe the study population and any inclusion or exclusion criteria. Describe the intended sample size and your sample size calculation or justification. Describe the sampling strategy used. Describe in practical terms how this was implemented.
- Intervention (if appropriate): If there were intervention and comparison groups, describe the intervention in detail and what happened to the comparison groups.
- Data collection: Define the data collection tools that were used and their validity. Describe in practical terms how data were collected and any key issues involved, e.g. language barriers.
- Data analysis: Describe how data were captured, checked and cleaned. Describe the analysis process, for example, the statistical tests used or steps followed in qualitative data analysis.
- Ethical considerations: Approval must have been obtained for all studies from the author's institution or other relevant ethics committee and the institution's name and permit numbers should be stated here.

Results: Present the results of your study in a logical sequence that addresses the aim and objectives of your study. Use tables and figures as required to present your findings. Use quotations as required to establish your interpretation of qualitative data. All units should conform to the **SI convention** and be abbreviated accordingly. Metric units and their international symbols are used throughout, as is the decimal point (not the decimal comma).

Discussion: The discussion section should address the following four elements:

- Key findings: Summarise the key findings without reiterating details of the results.
- Discussion of key findings: Explain how the key findings relate to previous research or to existing knowledge, practice or policy.
- Strengths and limitations: Describe the strengths and limitations of your methods and what the reader should take into account when interpreting your results.

- Implications or recommendations: State the implications of your study or recommendations for future research (questions that remain unanswered), policy or practice. Make sure that the recommendations flow directly from your findings.

Conclusion: Provide a brief conclusion that summarises the results and their meaning or significance in relation to each objective of the study.

Acknowledgements: Those who contributed to the work but do not meet our authorship criteria should be listed in the Acknowledgments with a description of the contribution. Authors are responsible for ensuring that anyone named in the Acknowledgments agrees to be named. Refer to the acknowledgement structure guide on our *Formatting Requirements* page.

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Appendix H: Plagiarism declaration

University of the Witwatersrand, Johannesburg

School of Clinical Medicine

Senate Plagiarism Policy

Declaration by Students

I Filippus Elago Sheetekela (student number: 2325265) am a student registered for Mmed (Obstetrics and Gynaecology).

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