Review of the use of Cervical Cerclage at Charlotte Maxeke Johannesburg Academic Hospital

This is 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

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20 DECEMBER 2022

DECLARATION

I NEO MALETE declare that this Research Report is my own work. It is being submitted for the Degree of Master of Medicine at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at any other University.

NMalete

(Signature of candidate)

____20_____day of December_____2022_____

DEDICATION

This research is dedicated to my ever-supportive wife Aliziwe, my parents and my family at large.

PUBLICATION

This research is expected to be published in Journal of Women's Health.

ABSTRACT

Objective

The aim of the study was to review the use of transvaginal cervical cerclages at Charlotte Maxeke Johannesburg Academic Hospital (CMAJH) for the period 1 June 2016 to 1 June 2017.

Methods

This is a retrospective review of 39 transvaginal cervical cerclages. The data collected included maternal demographic and pregnancy characteristics, previous pregnancies and outcomes, indications for the cerclages, antenatal and maternal complications, and neonatal outcomes. STATA software version 16 (Stata Corporation, USA) was used to analyse the data.

Results

There were 39 transvaginal cerclages, 28 (72%) of which were history-indicated (HI) and 11 (28%) ultrasound-indicated (UI). The overall live-born rate was 26/39 (67%) Seventy-one percent (20/28) and 55% (6/11) of history and ultrasound indicated cerclages culminated in livebirth respectively however there were no statistical significance in terms of effectivity in preventing preterm birth between the two types of cerclages (p-value = 0.446>0.05). There was higher incidence of PPROM in the ultrasound compared to the history indicated cerclage group (45.4% vs 10.7%) with a p-value= <0.05. The incidence of UTI in the entire cohort was 12.8%. No significant difference in the neonatal outcomes in (APGAR, FSB, and stillbirth) were found in the two groups (p-value=0.43, 0.99, and 0.29 >0.05 respectively).

Conclusion

Transvaginal cervical cerclage remains an important intervention for preventing pre-term labour secondary to cervical incompetence. The use of cervical cerclage in this study resulted in a significant number of live birth rates and good neonatal outcomes regardless of the indications for the cervical cerclage.

Keywords: Cervical incompetence, transvaginal cerclage, pregnancy

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ACOG: American college of obstetrics and gynaecology

APH: Antepartum haemorrhage

APLS: Antiphospholipid syndrome

ART: Antiretroviral Treatment

ARV: Antiretroviral

BMI: Body Mass Index

CEO: Chief Executive Officer

CMJAH: Charlotte Maxeke Johannesburg Academic Hospital

DES: Diethylstilboestrol

FSB: Fresh stillborn

GA: Gestational age

HI: History indicated cerclage

HIV: Human Immunodeficiency Virus

IUFD: Intrauterine fetal death

LLETZ: Large loop excision of the transformation zone

NICU: Neonatal intensive care unit

POH: Poor obstetric history

PPROM: Preterm prelabour rupture of membranes

PTB: Preterm birth

RH: Rhesus

RPR: Rapid plasmin reagin

T1: First trimester

T2: Second trimester

TVUCL: Transvaginal ultrasound cervical length

UI: Ultrasound indicated cerclage

UTI: Urinary tract infection

VS: Versus

W: Weeks

JOURNAL ARTICLE

REVIEW OF THE USE OF CERVICAL CERCLAGE AT CHARLOTTE MAXEKE JOHANNESBURG ACADEMIC HOSPITAL

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There were 39 transvaginal cerclages, 28 (72%) of which were history-indicated (HI) and 11 (28%) ultrasound-indicated (UI). The overall live-born rate was 26/39 (67%).

Seventy-one percent (20/28) and 55% (6/11) of history and ultrasound indicated cerclages culminated in livebirth respectively, however there were no statistical significance in terms of effectivity in preventing preterm birth between the two types of cerclages (p-value = 0.446>0.05). There was however higher incidence of PPROM in the ultrasound compared to the history indicated cerclage group (45.4% vs 10.7%) with a p-value= <0.05. The incidence of UTI in the entire cohort was 12.8%. No significant difference in the neonatal outcomes in (APGAR, FSB, and stillbirth) were found in the two groups (p-value=0.43, 0.99, and 0.29 >0.05 respectively).

Conclusion

Transvaginal cervical cerclage remains an important intervention in the prevention of pre-term labour secondary to cervical incompetence. The use of cervical cerclage in this study resulted in a significant number of live birth rates and good neonatal outcomes regardless of the indications for the cervical cerclage.

Keywords: Cervical incompetence, transvaginal cerclage, pregnancy

INTRODUCTION

Cervical insufficiency complicates around 1% of the obstetric population [1]. The management of cervical insufficiency has created a clinical dilemma, firstly because there is no strict consensus on the diagnostic criteria and secondly, because of the lack of clear criteria for the group of patients more likely to benefit from intervention. Furthermore different settings have different management protocols for the same condition [2]. Cervical insufficiency is thought to be a pathophysiological mechanism resulting in pre-term labour. Despite novel technologies and advances in medical science, pre-term labour remains one of the leading global causes of perinatal deaths and was found to be responsible for 35% of 2.5 million neonatal deaths in 2018 [3]. South Africa has a prematurity birth rate of 15%. [4]

Cervical cerclage and progesterone are the two main preventative treatment for preterm birth however the two interventions can be used in patient identified to be at risk [1]. Cervical cerclage has been part of obstetrics practice for over a century,

however , the role of cervical cerclage and its indications remain ill-defined and most controversial, leading to wide variations in practice across different clinical settings [1]. This lack of clarity surrounding cervical cerclage contributes to the uncertainty in identifying those patients who need it and are most likely to benefit from its use (those with true cervical insufficiency or who are at increased risk of early preterm delivery) [3].

The most commonly used criteria for the diagnosis of cervical insufficiency is a combination of risk factors or/and cervical ultrasound findings [1]. There is some evidence that suggests that transvaginal cervical cerclage offers better outcomes in the management of women at risk of preterm delivery who present a shortened cervix on ultrasound [1]. Based on the above, a study assessing outcomes of cervical cerclage in an academic hospital was warranted. Such information will contribute to the existing knowledge on the role of cervical cerclage in preventing pre-term births related to cervical insufficiency by sharing experience from an academic institution from a limited resource setting. The aim of the study was to review the use and outcomes of transvaginal cervical cerclages at Charlotte Maxeke Johannesburg Academic Hospital over a one-year period (1 June 2016 to 1 June 2017).

MATERIAL AND METHODS

This is a retrospective descriptive review of clinical records of patients diagnosed and managed for cervical incompetence at Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) in Gauteng province, South Africa. CMJAH, a central hospital, is a referral centre for four districts and six regional hospitals. The hospital also accepts direct referrals from clinics and Midwives' Obstetric Units (MOUs).This hospital conducts over 9000 deliveries per annum. This hospital has a dedicated clinic that manages women with a history of pregnancy losses. Details of pregnant women who had undergone elective transvaginal cerclage during the period from 1 June 2016 to 1 June 2017 were identified through gynecological and labour ward theatre record books. Inclusion criteria was all pregnant women who had undergone elective transvaginal cerclage during the period from 1 June 2016 to 1 June 2017. All pregnant women who underwent elective transvaginal cerclage outside the period from 1 June 2016 to 1 June 2017, twin pregnancy, and emergency cerclage and combined use of cerclage and progesterone were excluded from the study. A specially designed data collecting tool was used to collect the following variables : basic pregnancy data (maternal age, gravidity, parity, booking blood, current and past pregnancy outcomes), pre-existing

medical conditions, indications for transvaginal cerclage, cervical ultrasound findings before the insertion of cerclage, complications, and neonatal parameters such as (birthweight, APGAR Score and NICU admissions). Institutional approval for the study was granted by the Chief Executive Officer of CMJAH and ethics clearance was obtained from the Human Research Ethics Committee of the University of the Witwatersrand, study number M180761.

The data was captured in an Excel spreadsheet and analysed using STATA software version 16. The study applied descriptive statistics, frequencies and percentages, and measures of central tendencies mean, median, and mode to summarise the data collected. Fisher's exact test assessed the difference between History-indicated group and Ultrasound-indicated group. Continuous variables were described using medians. A p-value of $\alpha<0.05$ was used to compare the level of significance.

RESULTS

A total number of 48 transvaginal cerclages were inserted during the one-year study period. Nine (18.8%) cases were excluded because of missing records. Five (10.4%) records were incomplete however the records were included since they had enough data points to enable analysis. Thus a total number of 39 records were analysed.
Four (10.3%) out of the 39 cases of transvaginal cerclages where done by consultants and the remaining 35 (89.7%) by registrars with consultants as assistants during the procedures. Seven (17.9%) were Shirodkar and the remaining 32 (82.1 %), McDonald cerclages.

The average age of the patients was 29 (range 19-39) years with a median gravidity and parity of five (range 2-8) and two (range 0-4) respectively. None of the patients were smokers. Nine patients (23.1%) were HIV positive and all were on treatment. Three patients (6.3%) were on treatment for asthma and a further three (6.3%) for hypertension. Five (12.8%) had a previous history of caesarean section delivery, and none of the patients had a previous history of large loop excision of transformation zone or other forms of cervical surgery. A total of 18 patients (46.2%) had a previous history of miscarriage, five (27.8%) of which were in the first trimester and the remaining 13 (72.2%) during the second trimester. A total of 19 patients (48.7%) had a previous history of pre-term delivery. Five out of 39 (12.8%) patients had cerclages inserted in

the previous pregnancies, two out of the five patients (5.1%) had cervical cerclages inserted on two or more occasions, however, only one patient out of the five patients (2.5%) had successful cerclage from the previous pregnancies. Only three out of the 39 (7.7%) tested positive for antiphospholipid syndrome. The three were among the five patients who had a history of first trimester miscrarriages. There were no significant differences between women who had cerclages based on history or ultrasound with respect to all the above parameters (P value > 0.05). The above information is summarized in Table 1 below.

Table 1. Patient demography

	History Indicated N=28	**Ultrasound Indicated N=11**	**Total N=39**
Age (years) (mean)	33	33	33
Gravidity (median)	4	6	5
Parity (median)	2	2	2
HIV positive on treatment	6 (21.4%)	3 (27.2%)	9 (23.1%)
Rh	28 (100%)	11 (100%)	39 (100%)
Smoking	0	0	0
Asthma	1 (3.5%)	2 (18.1%)	3 (7.6%)
Diabetes	0	0	0
Hypertension	2 (7.1%)	1 (9.1%)	3 (2.5%)
APLS	3 (10.7%)	0	3 (7.7%)
Previous miscarriage First trimester miscarriage **One** **Two** **Three or more**	 3 (10.7%) 1 (3.5%) 1 (3.5%)	 1 (9.0%) - 2 (9.0%)	 4 (10.2%) 1 (2.5%) 3 (7.6%)
Previous second trimester miscarriage **One** **Two** **Three or more**	 1 (3.5%) 2 (7.1%) 10 (35.7%)	 - 2 (18.1%) 5 (45.4%	 1 (2.5%) 4 (10.2%) 15 (38.4%)

Previous cervical cerclage			
One	2 (7.1%)	1 (9.0%)	3 (7.6%)
Two	1 (3.5%)	1 (9.0%)	2 (5.1%)
Three or more			
Outcome of previous cerclage			
Failed	2 (7.1%)	2 (18.1%)	4 (10.3%)
successful	1 (3.5%)	-	1 (2.5%)
Previous Pre-term delivery (37 weeks)			
No	17 (63.3%)	3 (22.2%)	20 (53.9%)
Yes	11 (36.7%)	8 (77.8%)	19 (46.2%)
Previous caesarean section	5 (17.9%)	-	5 (12.8%)
Previous LLETZ or Cone Biopsy	-	-	-

In terms of complications (Table 2), more than half of the patients experienced complications 24/39 (61.6%), the majority of which occurred after 24 weeks 18/39 (46.2%) compared to 6/39 (15.4%) for less than 24 weeks. Miscarriage was the only complication that occurred before 24 weeks while UTI occurred in 5/39 (12.8%) and PPROM in 8/39 (20.5%). There was no statistical difference in terms of the risk of miscarriages between the HI and UI group, however, there was a higher incidence of PPROM in the UI group compared to the HI group (p-value= 0.028).

Table 2: Antenatal complications

	History Indicated N=28	**Ultrasound Indicated N=11**	**Total N=39**	**P-value**
Antenatal complications after 24 weeks				
PPROM	3 (10.7%)	5 (45.4%)	8 (20.5%)	0.028
APH	3 (10.7%)	-	3 (7.6%)	>0 .05
UTI	4 (14.3%)	1 (9.0%)	5 (12.8%)	

GDM	1 (3.5%)	-	1 (2.5%)	
PIH	1 (3.5%)	-	1 (2.5%)	
Antenatal Complications before < 24 weeks gestation				
Miscarriages				
Inevitable	2 (7.1%)	1 (9.0%)	3 (7.7%)	>0.99
missed miscarriage	3 (10.7%)	-	3 (7.7%)	

Table 3 and 4 is a summary of pregnancy and neonatal outcomes. Majority of the women delivered live babies 26/39 (66.7%) and only 6/39(15.4%) had miscarriages. Gestational age at delivery was known in 34/39 (87.2%) of the cases with 8/39 (20.5%) less than 28 weeks, 15/39 (38.5%) between 28-37 weeks and 11/39 (28.2%) more than 37 weeks. Among the women who delivered live babies (26/39, 66.7%), 17/26 (65.4%) and 9/26 (34.6%) had normal vaginal delivery and caesarean section respectively. Of the normal deliveries, 15/17 (88.2%) had spontaneous labour while 2/17 (11.8%) were induced. Most of the Caesarean sections were emergencies, 7/39 (17.9%) and only 2/39 (5.1%) women had elective Caesarean delivery. The indications for emergency Caesarean sections were foetal distress in 4/7(57.1%) and antepartum haemorrhage secondary to abruptio placenta in 3/7 (42.9%). There was however no difference in terms of mode of delivery, gestational age at delivery, or neonatal outcomes between the HI and UI cerclages.

Table 3: Delivery outcomes

	History Indicated N=28	**Ultrasound Indicated N=11**	**Total N=39**	**P-value**
Mode of delivery (n %)				
Unknown	5 (17.8%)	_	5 (12.8%)	
Caesarean section (emergencies)	3 (10.7 %)	4 (36.4%)	7 (17.9%)	
Caesarean section (elective)	2 (7.1%)	-	2 (5.1%)	**0.31**
Vaginal (spontaneous)	16 (57.1%)	7 (63.6%)	23 (59.1%)	
Vaginal (induction)	2 (7.1%)	-	2 (5.1%)	

Gestational age of delivery (n %)				
Less than 24 weeks	5 (13.1%)	1(9.1%)	6(15.4%)	0.99
Between 24-27 weeks	2 (7.1%)	-	2 (5.1%)	
28-37weeks	10 (35.7%)	5 (45.5%)	15 (38.5%)	
Over 37weeks	10 (35.7%)	1 (9.1%)	11 (28.2%)	
Unknown	5 (17.9%)	-	5 (12.8%)	

Table 4: Known birth outcomes > 24 weeks

	History Indicated N=28	**Ultrasound Indicated N=11**	**Total N=39**	**P-value**
Live born #	20 (71.4%)	6 (54.5%)	26 (66.7%)	0.45
Neonatal ICU admission	2 (7.1%)	4 (36.4%)	6 (15.4%)	0.29
Apgar 5min	9 (0-10)	9 (0-10)	9 (0-10)	0.43
Fresh still birth#	2 (7.1%)	0	2 (7.1%)	0.99

Gestational age > 24 weeks

Discussion

This study reviewed the use and outcomes of cervical cerclages in a central/tertiary hospital situated in Gauteng Province, South Africa. The main aim of inserting cervical cerclage is to decrease perinatal mortality and morbidity by reducing the rate of pre-term labour and prematurity [1]. The cerclages in this study were inserted either based on the history of a patent that was suggestive of cervical incompetence defined as history of a painless cervical dilatation with preterm midtrimester loss or preterm delivery [3] or a finding of short cervix (defined as cervical lengths of less than 25mm) on transvaginal (TV) ultrasound [5]. These above are the most common criteria used to select pregnant women requiring intervention [6]. The MRC/RCOG working party on cervical cerclage reported that cervical cerclages were more beneficial in women with a history of three consecutive spontaneous second-trimester miscarriages due to cervical incompetence in the absence of other known causes as well as in women with a history

of three or more spontaneous pre-term births [2]. Instead of using three history of three history of three miscarriages and three preterm labour, the study included patients who has history of two or more preterm births or two or more consecutive midtrimester miscarriages due to cervical incompetence or combination of history of midtrimester miscarriages and preterm births in absence of other known causes. These was done to ensure that no patients who needs intervention is missed.

An ultrasound-indicated cerclage may be considered for women who have a history of spontaneous loss or pre-term birth at less than 34 weeks gestation if the cervical length in a current singleton pregnancy is noted to be less than 25 mm before 24 weeks of gestation. It is important to note that this recommendation is invalidated without a history of pre-term birth [5].

Our ultrasound-indicated group had their cerclages inserted before 24 weeks, and the history-indicated group had their cerclages inserted on average at 13 weeks. The above finding is in line with international practice. Ultrasound-indicated and physical examination-indicated cerclages should be placed before 24 weeks gestation [7]. Women undergoing a history-indicated cerclage procedure should have placement between 12-14 weeks gestation [8].

Majority of the cerclages in this study were MacDonald and only few were Shirodkar.. Both MacDonald and Shirodkar techniques have comparative efficacy in preventing preterm labour, however Shirodkar has been associated with more maternal morbidity [8.9]. Furthermore due to the relative ease of placement and removal of the McDonald's cerclage, the McDonald technique tends to be used more frequently [9].

Most of the cerclages (89%) in this study were inserted by registrars (assisted by consultants) and consultants were the primary surgeons in only 10.3% of the cases. The above is similar to the findings from a study conducted in Nigeria where most of the cerclages were inserted by senior registrars [10]. The advantage of this arrangement is that it enable the transfer of skill from consultants to the trainees. Consultants supervision reduces the chances of incorrect placement of cerclages by juniors and reduces the intraoperative complications that might occur.

One third of the patient delivered live babies however, although there was no statistical significance (p value 0.45) there was a higher rate of live births of 20/28 (71.4%) in the HI group compared to 6 out of 11 (55%) in UI group. The live birth rate

in this study is lower than the more than 90% livebirth rate for the history indicated group reported in other studies [11.12]. The low live birth rate can be attributed to multiple factors, among those being, the unknown birth outcomes of five out of 28 (17.9%) in the HI group and a higher rate of PPROM in the UI group (which might have resulted in foetal loss).

The live birth rate of 6/11(55%) for the UI population is also lower when compared to the live birth rates of 88-100% reported in studies conducted in developed countries [13.14]. This difference is likely a reflection of availability of resources that are available for the care of extremely low and low birth weight. NICU management is commonly not offered to neonates weighing less than 800g in our setting.

Just slightly over a quarter of the patients (25.6%) delivered at less than 34 weeks. This figure was higher in the UI (45.4%) group compared to the HI (17.7%) group. This findings is different from a meta-analysis by Berghella et al [13] which showed reported pre-term delivery of 23% for HI and 17% for UI in pre-term labour < 34 weeks. A study done in Tygerberg Hospital reported a lower pre-term rate of 43% and 33% in HI and UI respectively for less than 34 weeks [15]. This finding is difficult to explain because the incidence of UTI between the two groups although numerically higher in the ultrasound group did not reach statistical significance. One possible explanation could be incorrect attribution of patient' losses to cervical incompetence when there were other causes of the midtrimester loses because of inaccurate history talking.

History taking remains a significant part of the screening for the cervical incompetence however some studies have recommended inclusion of routine cervical length screening among strategies directed as reducing the incidence of preterm labour [13]. While ultrasound require resources and expertise, the long term benefits outweighs the cost [14]. Our study (albeit the small numbers) suggest that history indicated cerclages is beneficial and therefore should be considered in areas where there is lack resources of expertise to perform trans-vaginal ultrasound.

The vaginal delivery rate in this study was 24/39 (64%), and the caesarean section rate was 9/39 (23%). These results are almost similar to the study done in Tygerberg hospital [15] and consistent with other published data [14]. The Caesarean section findings in both studies are comparable to the national and local provincial rates of about 25% in South Africa [16]. Caesarean section delivery rate was 17.8% for the HI

group and 36% for the UI group. Our findings are slightly higher than the Cochrane figures of 14% for the history-indicated group and 28% for the ultrasound-indicated group [18.19]. This is not surprising as Cochrane is a based on meta-analysis of number of studies from different settings and populations.

This research includes about 20/28 (71%) of live births in the history-indicated group, and six out of 11 (55%) of live births in the ultrasound-indicated group. The total live births in these groups was 67%. From this current study, overall neonatal survival is almost similar to the systematic review which reported a neonatal survival rate of 71% [15]. The slightly lower live-born rate in this study could have been because of the miscarriages and stillbirths. Four out of 39 (10.2%) of deliveries in this current study were either induced or underwent an elective caesarean section while some patients experienced complications such as APH, GDM, etc., all of which might have reduced the chance of successful spontaneous vaginal delivery.

The most important complication identified in this current study was pre-term pre-rupture of membranes (PPROM) responsible for 8/39 (20.5%) of the total complications. ACOG [20] reported a rate of 0.18-18% of PPROM complications. Other studies reported a rate of PPROM of between 3-65% in the UI group and 17.7% in the HI group [12, 21]. Our rate falls within the reported ranges. The rate of PPROM in our study might be linked to UTI which complicated five out of 39 (12.8%) of pregnancies after 24 weeks. We suspect that the high rate of UTI also contributed to the lower live-birth rate .Screening for possible infections such as UTI is an important intervention since this condition has been associated with PPROM and pre-term labour [1]. A meta-analysis done by Ehsanipoor *et* al. showed that risk factors such as evidence of infection and obstetric history influence the outcome of cervical cerclage [22].

The trend towards a high rate of PPROM in the UI group compared to the HI group (p-value =0.028) might suggests that ultrasound was better than history in identifying patients with true cervical incompetence compared to history. A meta-analysis on UI cervical cerclage showed a decrease in pre-viable pre-term birth at less than 24 weeks, pre-term birth, and perinatal mortality [23]. Another meta-analysis of trials using individual patient-level data showed no decrease in pre-term birth in patients with an incidental finding of the short cervix of less than 25mm between 16 and 24 weeks of gestation without prior history of pre-term birth [24,25]. However, for predicting preterm

labour in women with a history of pre-term delivery, cervical screening using trans-vaginal ultrasound remains a safe option and a gold standard [26].

Limitations

There were nine missing files and five files with incomplete information, which is a common weakness in retrospective studies. Missing data might have an influence on the study's findings. The sample size was comparable to other retrospective studies from developing countries. However, despite the above limitations, this study provides recent data on the outcomes of trans-cervical cerclage for the management of cervical incompetence from the perspective of a developing country with a limited resources. The detailed history on the antenatal card about previous obstetric history, miscarriages, delivery complications, and recorded outcomes gave this study good strength.

Conclusion

The use of transvaginal cervical cerclage in pregnant women diagnosed with cervical incompetence remains an important preventive measure for pre-term labour. Ultrasound has a better chance than a history of picking up women with true cervical incompetence compared to history. In general, using cervical cerclage is associated with improved pregnancy outcomes such as live birth rates and neonatal outcomes. Proper patient data filling system could have improved the quality of the results of our study.

Conflict of interest: None

Contributorship: NM conceptualised, collected data and wrote the manuscript. Both authors contributed in the analysis. HL reviewed the manuscript.

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Covering letter, the covering letter is important. To help the Editors in their preliminary evaluation, please indicate why you consider the paper suitable for publication.

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The title should be concise and informative, accurately indicating the content of the article

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The list of authors should include all those who can legitimately claim authorship. This is all those who:

1. Made a substantial contribution to the concept or design of the work; or acquisition, analysis or interpretation of data,
2. Drafted the article or revised it critically for important intellectual content,
3. Approved the version to be published,
4. Each author should have participated sufficiently in the work to take public responsibility for appropriate portions of the content.

Authors should meet the conditions of all of the points above. When a large, multicentre group has conducted the work, the group should identify the individuals who accept direct responsibility for the manuscript. These individuals should fully meet the criteria for authorship. Acquisition of funding, collection of data, or general supervision of the research group alone does not constitute authorship, although all contributors who do not meet the criteria for authorship should be listed in the Acknowledgments section. Please refer to the CMJE authorship guidelines for more information on authorship.

Authors should meet the conditions of all of the points above. When a large, multicentre group has conducted the work, the group should identify the individuals who accept direct responsibility for the manuscript. These individuals should fully meet the criteria for authorship.

Acquisition of funding, collection of data, or general supervision of the research group alone does not constitute authorship, although all contributors who do not meet the criteria for authorship should be listed in the Acknowledgments section. Please refer to the CMJE authorship guidelines for more information on authorship.

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Appendix B: Approved research Protocol

Review of the use of Cervical Cerclage at Charlotte Maxeke Johannesburg Academic Hospital

This is a research protocol submitted to the Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, in partial fulfillment of the requirements for the degree

of

Master of Medicine in Obstetrics and Gynaecology

Reseacher name :Dr Neo Malete

MBBCH (WITS)

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Approved research Protocol -TITLE- Review of the use of Cervical Cerclage at Charlotte Maxeke Johannersburg Academic Hospital

1. Background

Cervical insufficiency complicates around 1% of the obstetric population[1]. The management of cervical insufficiency has created a clinical dilemma, firstly because there is no strict consensus on diagnostic criteria and secondly, because there is a lack of clear criteria for a group of patients who are more likely to benefit from the intervention. Furthermore, different management protocols exist for the management of the same problem in different settings[1]. Cervical insufficiency is thought to be one of the pathophysiological mechanisms leading to preterm labour. Despite novel technologies and advancements in medical science, preterm labour remains one of the major challenges in obstetrics. Preterm birth contributes between 7 and 11 % of all deliveries and is responsible for about 35% of neonatal deaths[2].

Cervical cerclage and progesterone are the two interventions that are used to treat cervical insufficiency. Cervical cerclage has been part of obstetric practice for over a century; however, the role of cervical cerclage and its indications remain ill-defined and controversial and has led to wide variations in practice in different clinical settings[1]. This lack of clarity regarding cervical cerclage contributes to the uncertainty in the identification of patients who need and are likely to benefit from its use (i.e. those with true cervical insufficiency or at an increased risk of early preterm delivery)[3].

2. Definition

Cervical insufficiency does not have a consistent definition, but is usually characterized by painless dilatation and shortening of the cervix before the 37th week of gestation in the absence of preterm labour[4]. This condition usually occurs in the second or early third trimester, resulting in membrane prolapse, premature rupture of the membranes, midtrimester pregnancy loss, or preterm birth[1, 4]. The underlying pathology is the

inability of a woman to support a full-term pregnancy due to a functional or structural defect in the cervix[5].

3. The Pathogenesis of cervical insufficiency

The pathogenesis of cervical insufficiency remains unclear however, this condition is believed to be associated with cervical trauma and congenital urogenital abnormalities. Diagnosis is often made retrospectively in a woman with an anatomically normal cervix[7]. Studies have shown that up to 85% of the dry weight of the cervix is collagen. Petersen and Uldbjerg examined cervical collagen in non-pregnant women with previous cervical insufficiency and found that the median cervical hydroxyproline concentrations were significantly lower than those of parous women without cervical insufficiency[1]. The causes of this have yet to be ascertained, but this seems to be a key factor in understanding the mechanism of cervical failure in such cases[1]. The cervix also plays a role in protecting pregnancy from ascending infections. This is a function of the cervical mucous barrier[6]. Data suggest that 80% of cases of acute cervical insufficiency may be associated with intra-amniotic infection associated with an ascending urogenital infection and disruption of the cervical mucosa barrier[1].

4. Incidence

The incidence of cervical insufficiency in the general obstetric population is reported to vary between approximately 1/100 and 1/2000. The incidence is about 3-4 % if women with singleton gestation, prior spontaneous preterm birth, and current transvaginal cervical ultrasound of less than 25mm are labelled as having cervical insufficiency. There are wide variations in estimating the incidence of cervical insufficiency most likely due to real biological differences between study populations, criteria used to establish the diagnosis and bias reporting between general practitioners and referral centres[7]. In Denmark, from 1980 to 1990, cervical insufficiency was diagnosed in 4.6 per 1000 pregnant women, and it is estimated to occur in 8% of women with recurrent mid-trimester losses[1]. The risk of recurrence of cervical insufficiency has about 30%[8]. This stresses the importance of prevention as cervical insufficiency is associated with an increase in perinatal mortality.

5. Risk factors for cervical insufficiency[1, 6, 8]

A number of risk factors have been found to have a strong association with cervical insufficiency. The most commonly reported risk factors are[1, 6, 8]:

5.1 The classic history of recurrent mid-trimester pregnancy loss.

5.2 A previous preterm pre-labour rupture of membranes at less than 32 weeks.

5.3 A prior pregnancy with a cervical length measurement of less than 25 mm prior to 27 weeks of gestation

5.4 Any history of prior cervical trauma (e.g. repeated therapeutic abortion, repetitive cervical dilatation, cone biopsy, cervical tears and lacerations, trachelectomy, loop electrosurgical excision procedure).

5.5 Mother having been exposed to diethylstilbestrol in utero

5.6 Maternal risk factors, the presence of a congenital uterine anomaly or maternal connective tissue disease or abnormalities.

5.7 In the pregnancy index, findings indicative of possible cervical insufficiency includes cervical funneling, cervical shortening, and overt cervical dilatation.

5.8 Even in the absence of funneling, the cervical length determined by ultrasound to be < 25 mm prior to 27 weeks increases the risk of pregnancy loss or preterm birth[1, 6, 8].

5.9 Polycystic ovarian syndrome has been suggested as a risk factor for cervical insufficiency, especially in women of South Asian or Black origin according to recent studies[9].

5.10 Smoking[1, 6, 8]

The challenge with all the above risk factors is that their usage in clinical practice does not always accurately identify the group of women who end up with pregnancy loss or preterm labour.

6. Types of cervical cerclage

Cervical cerclage can be classified into three groups based on indications:

6.1. Elective cerclage

This is based on a patient report or documented evidence of painless dilatation of the cervix culminating to second trimester loss or a history of multiple preterm births. Alternatively, women who are found to have short cervix on transvaginal ultrasound screening are also candidates for elective cervical cerclage.

This type of cerclage is inserted after a transvaginal ultrasound that shows evidence of a short cervix in the second trimester. The standard cut off cervical length for this indication is either less than 25mm in length or 15mm at less than 24 weeks. In addition, the patients must also have pre-existing risk factors for preterm birth. The Mcdonald or Shirodka sutures method can be used.

6.2. Emergency cervical cerclage

This is a rescue cerclage offered to women presenting with dilatation of the cervix with or without bulging of membranes.

6.2.1 Techniques of insertion

Described techniques include the Shirodkar and McDonald style suture, most commonly using a braided mersilene tape or a loop nylon suture. There are no randomised data to support one technique or one suture material over another. Both techniques have been associated with an increased in the caesarean section rate[1, 9]. The reason behind this finding is not very clear. In the McDonald approach, the suture is inserted as close as possible to the junction of the cervix with the vagina, without dissecting tissue planes[1, 10]. This differs from the Shirodkar approach in that a Shirodkar suture follows a subepithelial approach. The suture is inserted above the junction of the cervix and the vagina with the dissection of the bladder and rectum; this allows for higher placement of the suture,closer to the internal cervical os, than the McDonald approach[1, 9, 10]. There are other two forms of cerclage stated as double cerclage. The first one simply involves the insertion of two cervical cerclages in an attempt to buttress the cervix more strongly. This type of approach has not shown any benefit[1, 11]. In the second type of double cerclage, a second occlusive suture is placed at the external os to retain the mucous plug and help the cervix maintain its properties as a barrier to infection. At present, only limited data regarding this is available[1].

6.3 Route of insertion

This is done either through laparotomy or laparoscopy[10, 12, 13]. The cerclage can be placed before conception or at the end of first trimester after aneuploidy screening. This type of cerclage is reserved for women with multiple previous preterm births or late second trimester losses and failed transvaginal cerclage, or for women with a history of extensive cervical surgery and minimal cervical tissue remaining. Transabdominal cerclage allows a high level of cervico-isthmic junction placement.

7. Diagnosis of cervical insufficiency

There is no diagnostic test for cervical insufficiency. However, many tests have been reported or are used (assessment of the cervical canal width by hysterosalpingogram, assessment of the ease of insertion of cervical dilators [size 9 Hegar] without resistance, the force required to withdraw an inflated Foley catheter through the internal os, the force required to stretch the cervix using an intracervical balloon) none of these meet the criteria required for a diagnostic test[1, 6]. Part of the diagnosis is based upon the exclusion of other causes of preterm delivery or mid-trimester pregnancy loss[1, 6]. In clinical practice, transvaginal ultrasonography is increasingly used as a demonstrably valid and reproducible method of cervical assessment, and cervical shortening correlates with the risk of preterm delivery[6].

Without a reliable diagnostic test, it becomes necessary to screen for or to predict the likelihood of cervical insufficiency. This process is based upon the identification and recognition of key risk factors in women history and in the index[1]. It is within this context that ultrasound performs much better in the diagnosis of suspected cervical insufficiency.

8. Complications of cervical cerclage[1, 12, 14]

8.1 Puerperal pyrexia- clinical trials have shown double risk in patient with cerclage.
8.2 Increase in medical intervention.
8.3 Increased use of tocolytic agents and hence more hospital admissions.
8.4 Higher rates of Caesarean sections.
8.5 Premature rupture of membranes, premature labour.
8.6 Cervical lacerations at delivery.
8.7 Haemorrhage.

8.8 Cervical dystocia.

9. Removal of cerclage

In general, cerclage is removed electively at 36 to 38 weeks of gestation. Cerclage can be removed without using anaesthesia or using only short acting narcotics like fentanyl administered intravenously[1, 15]. The onset of premature labour unresponsive to tocolysis and/or a strong suspicion of sepsis are indications for the emergency removal of the cerclage.

Meta-analysis has shown an increased neonatal mortality rate with delayed removal of cerclage with sepsis as the principal cause. Based on these findings, a policy of removal of cerclage within 48 hours (allowing time for corticosteroid administration if appropriate) is advocated[16]. C-reactive protein estimation can be used as a predictor of chorioamnionitis following preterm membrane rupture and may therefore aid the decision between immediate or delayed (< 48 hours) suture removals[1, 16].

10. Problem statement

There is no standard diagnostic criterion for cervical insufficiency and this has led to wide variation in diagnosis and management. The most commonly used criteria to diagnose cervical insufficiency are either a combination of risk factors (discussed previously) or/and cervical ultrasound findings. The second challenge is the option of the insertion technique. There is some evidence that suggests that transvaginal cervical cerclage offers better outcomes in the management of women at risk of preterm delivery who have a shortened cervix on ultrasound[1]. However, the above findings are based on differences in the population studied, the type of suture used (Shirodkar vs McDonald) and additional therapies, e.g. (antibiotics and tocolysis)[1, 6] . Based on the above, a study focusing on indications and outcomes of cervical cerclage insertion in an academic hospital is warranted. Such information will contribute to the existing knowledge on cervical insufficiency through the sharing of experience from an academic institution situated in limited resource setting.

10.1 Purpose of study

The aim of the study is to investigate indications and outcomes of elective transvaginal cervical cerclage at Charlotte Maxeke Johannesburg Academic Hospital over a one-year period (1 June 2016 to 1 June 2017).

10.2 Objectives

10.2.1 To investigate/criteria used for inserting transvaginal cervical cerclage within the study institution.

10.2.2 To investigate the types of maternal complications associated with cervical cerclage insertion in the study population.

10.2.3 To asses fetal outcomes following the insertion of cervical cerclage (gestational age at delivery, mode of delivery, birth weight, APGAR SCORE, NICU admissions and reasons of admissions).

11. Methods

11.1 Setting

The study will be conducted at the Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) in the Department of Obstetrics and Gynaecology. CMAJH is a quaternary hospital providing service to the surrounding primary and secondary healthcare facilities. The department conducts around 9700 deliveries per annum. The department of obstetrics also runs the high-risk clinics including the poor obstetric history clinic (POH). Patients who need to be inserted or who are inserted with a transvaginal cervical cerclage are seen by obstetric specialists and followed up in this clinic.

11.2 Study design

This will be a retrospective cross-sectional study analysis using the medical history records of women who were inserted transvaginal cervical cerclage in CMAJH for a period of 1 year between 1st June 2016 to 1st June 2017. This will be also looking at the indications and criteria used to insert the cerclage.

11.3 Study population

The study population will comprise of all the women who were inserted the transvaginal cervical cerclage and neonates born to these women at CMJAH during the time period from 1 June 2016 and 1 June 2017.

11.4 Exclusion criteria

11.4.1 Twin pregnancy

11.4.2 Emergency cerclage insertions

11.4.3 Transabdominal cerclage

11.4.4 Combined use of cerclage and progesterone

11.5 Data collection

Pregnant women who were inserted the elective transvaginal cerclage during the study period will be identified through the gynae theatre and labour ward theatre record books. These women will be retrieved from their medical records and the data relevant to the study question will be retrieved.

This data will include:

- Maternal age,
- gravity,
- parity,
- Rh, RPR and HIV status,
- Pre-existing medical conditions,
- Previous pregnancy outcomes (miscarriages, livebirth, IUFD),
- indications for transvaginal cerclage,
- ultrasound findings of cervix before the insertion of cerclage,
- surgeon inserting the cerclage (consultant or registrar),
- maternal complications associated with the insertion of cerclage(anaesthetic, surgical, sepsis),
- gestational age at delivery,
- route of delivery and
- whether patient was induced or not.

Data specific to neonatal outcomes will focus on birthweight and APGARS Score, NICU admissions and reasons thereof. The expected number of patients records to be retrieved are estimated to be around 50-60 patients.

11.6 Data analysis

The data will be entered in an Excel spreadsheet and the data analysis will be conducted using the STATA software with the help of a statistician. Categorical variables will be described using frequencies and percentages whereas continuous variables will be described using and medians. Percentages will be used to describe the criteria used for inserting transvaginal cervical cerclage and to describe the maternal complications associated with cervical cerclage in the study population whilethe medians and percentages will be used for the evaluation of fetal outcomes following the insertion of cervical cerclage.

11.7 Limitations

This is a retrospective study and is at risk of all the challenges facing retrospective data retrieval. Inability to access some of the required data, incomplete data, etc., are some of the challenges hence, loss of some data might be encountered. Sample size can be affected since this is retrospective study.

11.8 Ethical issues

This study will commence with the approval of the Post Graduate Committee and Human Research Ethics Committee of the University of the Witwatersrand. Permission to conduct the study will be requested from the CEO of CMJAH and head of the Department of Obstetrics and Gynaecology at CMJAH.

In order to maintain confidentiality, all women in this study will remain anonymous with each patient allocated a study number on the spread sheet. Details of the women will be available to the researcher and supervisor.

12. Timing

	Nov	Dec	Jan	Feb	Mar	Apr	May	June	July	Aug	Sep
Literature review	X	X									
Preparing protocol			X	X	X						
Protocol						X					
Ethics application						X					
Data collection						X	X				
Data analysis								X			
Writing up thesis									X	X	
Writing up paper											X

13. Funding

The only costs that will be incurred in the study will be stationary and data capturing expenses. These costs will be covered by the researcher.

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APPENDIX C: Data Collection Sheet

STUDY NUMBER:	**DATE:**
1.DEMOGRAPHIC DATA	**AGE** (in years): ____ **BMI** (number): _____ **GRAVIDITY** (number):____ **PARITY** (number):_____ **Rh STATUS** **Positive** ☐ **Negative** ☐ **Unknown** ☐ **HIV STATUS** **Positive** ☐ **Negative** ☐ **Unknown** ☐ **ARVs** **Yes** ☐ **No** ☐ **SMOKING** **Yes** ☐ **No** ☐ **If YES, number of cigarettes per day:**_____
2. MEDICAL HISTORY(Do you now have or have you ever had): Hypertension	**Yes** ☐ **No** ☐
Diabetes	**Yes** ☐ **No** ☐
Connective tissue disease	**Yes** ☐ **No** ☐
Asthma	**Yes** ☐ **No** ☐
Other (please specify)	**Yes** ☐ **No** ☐

3. SURGICAL HISTORY

History of Caesarean **Yes** ☐ **No** ☐

If YES, number of caesareans:_____

History of Gynaecological surgery **Yes** ☐ **No** ☐

History of Large LOOP **Yes** ☐ **No** ☐

Excision of Transformation Zone(LLETZ) **Yes** ☐ **No** ☐

History of CONE biopsy **Yes** ☐ **No** ☐

4. MISCARRIAGE & PRETERM LABOUR

First Trimester (<13wks) ☐ **If YES, number:___**	**Second Trimester (13wks – 23wks)** ☐ **If YES, number:___**

Preterm Birth (24wks – 27wks) ☐ **If YES, number:___**	**Preterm Birth (28wks – 33wks)** ☐ **If YES, number:___**	**Preterm Birth (34wks – 36wks)** ☐ **If YES, number:___**

5. PREVIOUS CERCLAGE

Yes ☐ **No** ☐

If YES, number:_____

Indication of current cerclage **Yes** ☐ **No** ☐

If YES, cervical length(Ultrasound):___

Type of Cerclage:

McDonald ☐

Shirodkar ☐

Abdominal ☐

Screening for infection done? **Yes** ☐ **No** ☐

If YES, organism and site? Yes ☐ No ☐

Surgeon who inserted the cerclage:
Consultant ☐ Registrar ☐

Complications associated with Cerclage:

Anaesthetic ☐ Surgical ☐

If ANY, please specify: _____

_____

_____

Sepsis Yes ☐ No ☐

If YES, please specify: _____

6. PREGNANCY OUTCOME

Gestational age of delivery: _____

Mode of delivery:

Spontaneous ☐
Induction ☐
Indication for ☐
induction ☐
Caesarean Section

If Caesarean Section, indicate in: Birth Weight ☐

Gender ☐

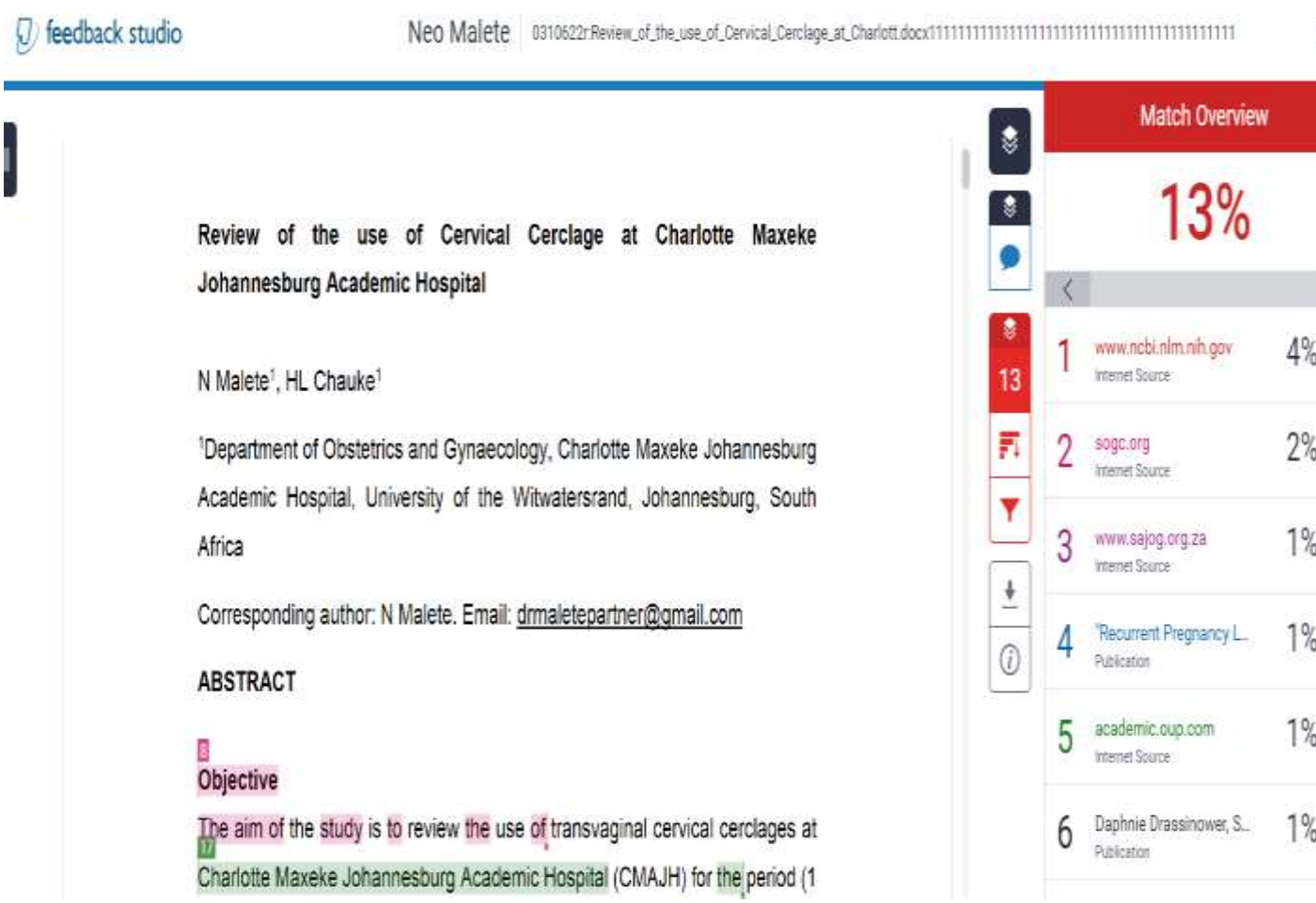
APGAR:

1 minute ☐ 5 minutes ☐ 10 minutes ☐

NICU Admission: Yes ☐ No ☐

If YES, indication for admission: _____

Appendix D: Turnitin



Appendix E: Letter of approval from the 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
28th June 2018

Dear Dr. N. Malete

STUDY TITTLE: Review of the Use of Cervical Cerclage at Charlotte Maxeke Johannesburg Academic Hospital.

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: 29/06/2018

(Approved) / not approved

Ms G. Bogoshi
Chief Executive Officer
DATE: 02.07.2018

Appendix F: Human Research Ethics Committee Clearance Certificate

UNIVERSITY OF THE WITWATERSRAND JOHANNESBURG

R14/49 Drs N Malete, L Chauke and F Retief

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
CLEARANCE CERTIFICATE NO. M180761

NAME: (Principal Investigator)	Drs N Malete, L Chauke and F Retief
DEPARTMENT:	School of Clinical Medicine Department of Obstetrics and Gynaecology Chris Hani Baragwanath Academic Hospital
PROJECT TITLE:	Review of the use of cervical cerclage at Charlotte Maxeke Johanesburg Academic Hospital
DATE CONSIDERED:	27/07/2018
DECISION:	Ap[proved unconditionally
CONDITIONS:	
SUPERVISOR:	Drs L Chauke and F Retief
APPROVED BY:	Dr CB Penny, Chairperson, HREC (Medical)
DATE OF APPROVAL:	27/11/2018

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 3rd floor, Phillip V Tobias Building, Parktown, University of the Witwatersrand, Johannesburg.
I/We fully understand the conditions under which I am/we are authorised 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 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 of the meeting when the study was initially reviewed. In this case, the study was initially reviewed in **July** and will therefore reports and re-certification will be due early in the month of July each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).

Principal Investigator Signature

29 november 2018
Date

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

Appendix G: Plagiarism Form

UNIVERSITY OF THE WITWATERSRAND JOHANNESBURG

FACULTY OF HEALTH SCIENCES

PLAGIARISM DECLARATION TO BE SIGNED BY ALL HIGHER DEGREE STUDENTS

SENATE PLAGIARISM POLICY: APPENDIX ONE

I NEO MALETE (Student number: 0310622R) am a student registered for the degree of Obstetrics and Gynaecology in the academic year 2017

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: 23/9/2021