A retrospective review of pregnancy outcomes in patients who had a cervical cerclage at Chris Hani Baragwanath Academic Hospital between January 2013 and December 2014

Dr Gift Thabo Dingiswayo

Master of Medicine candidate (Mmed)

Student no: 1030824

Supervisor: Dr Coceka Nandipha Mnyani

A research report submitted to the Faculty of Health Sciences, University of the Witwatersrand, in partial fulfilment of the requirements for the degree of Master of Medicine in Obstetrics and Gynaecology MMed (O&G)

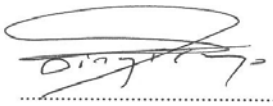
Johannesburg, 2019

DECLARATION

I, Gift Thabo Dingiswayo, declare that this research report is my own work.

It is being submitted for the degree of Master of Medicine in Obstetrics and Gynaecology 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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06 day of September 2019

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DEDICATION

I dedicate this research report to my late mother, father and sister, my siblings, my daughter Leano Nwabisa and my partner.

PRESENTATIONS ARISING FROM THIS RESEARCH PROJECT

1. Chris Hani Baragwanath Academic Hospital department of Obstetrics and Gynaecology research meeting on 13th June 2016

2. University of Cape Town department of Obstetrics and Gynaecology research day 11 August 2017 at Groote Schuur Hospital

ABSTRACT

Preterm delivery is an important cause of neonatal morbidity and mortality worldwide. It has been shown in some studies that compared with no treatment, cervical cerclage reduces the incidence of preterm delivery in women at risk of recurrent preterm delivery, but with no significant reduction in perinatal mortality or neonatal morbidity. The main issues regarding the use of cervical cerclage include patient selection, timing and method of insertion.

A retrospective review of hospital records of patients who had a cervical cerclage inserted between 01 January 2013 and 31 December 2014, at Chris Hani Baragwanath Academic Hospital, was conducted. A total of 142 patients were included in the study. A history of two or few spontaneous second trimester miscarriages were found in 72% of patients who had a cerclage inserted. The mean gestational age at insertion of cerclage and removal was 16±5.8 and 34.3±4.2 weeks, respectively. Just over a half, 53%, of the cerclages were done by junior staff. Delivery after 34 weeks gestation occurred in 67.6 % (n=96) of patients and the mean gestational age at delivery was 35.3±4.8 weeks. No significant association was found between the surgeon's experience and pregnancy outcomes. The majority of patients might have been overtreated owing to the fact that only a third of patients had a history of three or more spontaneous second trimester miscarriages. More than half of the women had one or more live children born at term, suggesting that cervical insufficiency might be an acquired condition.

Delivery after 38 weeks was found in half of the patients, reflecting less stringent selection and criteria for cerclage insertion. Larger studies are needed to evaluate findings from this study.

ACKNOWLEDGMENTS

The following people are acknowledged for making this research report possible

- My supervisor Dr CN Mnyani
- The Clerks at medical records in Chris Hani Baragwanath Academic Hospital

CONTENTS

LIST OF ABBREVIATIONS

ACOG= American College of Obstetricians and Gynecologists

APLS = Antiphospholipid syndrome

CHBAH = Chris Hani Baragwanath Academic Hospital

CI = Confidence interval

CL= Cervical length

ELCS = Elective caesarean section

EMCS= Emergency caesarean section

HAART = Highly active antiretroviral treatment

HIV= Human immunodeficiency syndrome

HREC= Human research ethics committee

MO= Medical officer

NHLS = National health laboratory services

OR= Odds ratio

POHC = Poor obstetric history clinic

RCOG = Royal College of Obstetricians and Gynaecologists

RR= Relative risk

SD= Standard deviation

SLE= Systemic lupus erythematosis

TVUS = Transvaginal ultrasound

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CHAPTER ONE- INTRODUCTION

1.1 BACKGROUND

Cervical incompetence, now called cervical insufficiency (CI), is said to complicate 1% of pregnancies in the general population and 8% of pregnancies in women who have had recurrent mid-trimester pregnancy loses.[1] Establishment of the true incidence of cervical insufficiency is hampered by its inconsistent definition. It is defined as "the history of painless dilatation of the cervix resulting in second or early third trimester delivery, and the passage without resistance of size nine Hegar dilator (9mm).[1-2]

Preterm delivery is an important cause of neonatal morbidity and mortality worldwide. The use of cervical cerclage for the prevention of pregnancy loses in women with history of recurrent second trimester loses or second trimester dilatation was reported in the 1950s by Drs Shirodkar and McDonald, however the first cervical cerclage was first performed in 1902.[2-4] The benefit of cervical cerclage still remains controversial to date.[1-3] The main issues regarding the use of cervical cerclage include patient selection, timing and method of insertion. Randomised controlled trials done on the use of cervical cerclage showed conflicting results partly due to poor design of these studies.[5]

Indication for cervical cerclage is broadly divided into three categories: history-indicated, ultrasound-indicated and rescue cerclage. Cervical cerclage is now used for prevention of recurrent spontaneous preterm delivery.[5] There is no conclusive evidence from randomized controlled trials that inserting a cervical cerclage in women perceived to be at risk of preterm delivery or second trimester pregnancy loss attributed to cervical factors, reduces the risk of pregnancy loss, preterm term labour or morbidity associated with preterm delivery. [14]

In the literature review; the literature on patient selection, indications, methods, timing of insertion/removal and adjuvant therapies will be reviewed.

1.2 PROBLEM STATEMENT

It has been shown in some studies that compared with no treatment, cervical cerclage reduces the incidence of preterm delivery in woman at risk of recurrent preterm delivery.[1,16] The studies however show no statistically significant reduction in perinatal mortality or neonatal morbidity, and uncertain long-term infant outcomes.[1,16] There is also no solid consensus in the literature about the management of recurrent pregnancy losses related to cervical insufficiency, i.e. which women would benefit from a cerclage, the timing of insertion, optimal surgical technique and outcomes of these patients.

1.3 JUSTIFICATION

Preterm delivery is an important cause of neonatal morbidity and mortality worldwide. It has been shown in some studies that compared with no treatment; cervical cerclage reduces the incidence of preterm delivery in woman at risk of recurrent preterm delivery and no significant reduction in perinatal mortality or neonatal morbidity. It is important to determine which group of patients should benefit from cervical cerclage and optimal method of insertion. Hence the aim of this study was to evaluate patient selection, surgical technique and obstetric outcomes in patients with a history suggestive of cervical insufficiency, and had a cervical cerclage inserted at Chris Hani Baragwanath Academic Hospital (CHBAH).

CHAPTER TWO

2. LITERATURE REVIEW

2.1 Physiology of labour

During a normal pregnancy, the cervix remains firm and closed, while the uterus expands to accommodate the growing fetus and the placenta. It is thought that throughout pregnancy "pro-pregnancy" factors help to inhibit myometrial contractions until near term where "pro-labour" factors begin to mediate remodelling of the cervix.[2,6] Progesterone is the principal 'pro-pregnancy factor' and it decreases uterine sensitivity to oxytocin.[6] It also has a negative regulatory effect upon many of the proteins that are responsible for modulation of cervical ripening.[6] Prostaglandins on the other hand are 'pro-labour factors' and are crucial in initiation of labour.[6] They are important for initiation of cervical effacement and dilatation, and also for stimulation of uterine contractions. Prostaglandins are believed to promote proteolysis in the cervix, and fetal membranes and induce myometrial contractility.[2]

2.2 Pathogenesis of spontaneous preterm labour and mid trimester pregnancy loses

Common pathways are shared between term and preterm labour, and these include cervical ripening, uterine contractions and rupture of membranes.[2] Contrary to term labour which is physiological, preterm labour is as a result of pathological activation of these pathways.[2] Anatomical, immunological, biochemical, endocrinological and clinical changes are part of the common pathways of parturition.[2] Studies have been conducted on anatomical and clinical events; the other changes are still poorly understood.[2]

Cervical factors

The cervix is composed mainly of fibrous tissue and smooth muscle, and near term, the cervix changes from a rigid and closed structure to a soft and distensible organ.[2] The process of cervical ripening is initiated after conception and continues throughout pregnancy and the puerperium.[6] Rapid progression of cervical shortening is demonstrated in women who later experience spontaneous preterm labour.[6]

2.3 History and method of cervical cerclage

In 1955, Shirodkar described a method of cervical cerclage with insertion of a purse string suture around the cervix at 14 weeks gestation, requiring dissection of the bladder and rectum from the cervix allowing placement of a nonabsorbable suture above the cardinal ligaments.[3] McDonald described his simpler method two years later, in 1957. The McDonald method involved placing a purse string suture just distal to the vesicocervical reflection and posteriorly, just distal to the vaginal-rectal reflection in three or four bites with no dissection of the bladder or rectum.[4]

The two methods described above are still commonly used. Both methods require regional anaesthesia either spinal or epidural anaesthesia. There is a lack of evidence to support a specific method for cervical cerclage. The systematic review of data from four randomised control trials revealed slight significant difference in mean gestational age of delivery in those who had a McDonald's cerclage compared to those who had a Shirodkar cerclage inserted 36.3±4.7 vs 35.0±5.3 ($p<0.02$), however, on adjusting for confounders using logistic regression modeling, no significant difference in PTB < 33 weeks was found between the two groups (OR, 0.55; 95% CI, 0.2 to 1.3).[7] Harger JH performed a review of 251 who had cerclages inserted, to compare morbidity and success rate of Shirodkar and McDonald techniques.[8] No statistically significance fetal survival rate was found between both groups (87% vs 78% $p>.05$). Success rates were found to be equivalent in both techniques and investigators have favoured McDonald cerclage owing to easy insertion and removal.[8]

Evidence from a retrospective cohort study of 60 women who underwent a history- or ultrasound-indicated cerclage suggests that the mean delivery age with a Shirodkar was more advanced than with a McDonalds (37.1±3.3 versus 34.8±4.9 gestational weeks, p=0.033), but no significant differences were found in neonatal morbidity.[9] In a randomised controlled trial involving 106 women who had a cervical cerclage inserted based on cervical length (CL) of <25mm between 16 and 26 gestational age, who were randomised into Shirodkar\McDonald method and bedrest, Otsuki K et al concluded that Shirodkar cerclage might reduce the occurrence of threatened preterm delivery (11.4% vs 20.6% p=0.019)[10]

2.4 Cervical length assessment

High rates of successful pregnancy outcomes in women with poor obstetric history attributed to CI have not consistently been supported by results from randomised controlled trials. This might be attributed to suboptimal patient selection which is essentially based on obstetric history. Transvaginal sonographic measurement of cervical length (CL) might be a more effective way of identifying high risk groups.[11] A short mid-pregnancy cervical length is associated with high risk of spontaneous preterm delivery. According to the Royal College of Obstetricians and Gynaecologists (RCOG) guidelines on cervical cerclage, ultrasound-indicated cerclage should be offered if the CL is less than 25mm before 24 weeks gestation in women with a history of one or more spontaneous mid-trimester losses.[1]

Owen J et al conducted a randomised controlled trial to assess cerclage for prevention of recurrent preterm delivery in 302 women with singleton pregnancies, cervical length of less than 25 mm detected from serial transvaginal ultrasounds done between 16 and 21 weeks of gestation and a history of spontaneous preterm labour between 17 and 33 weeks of gestation. Patients were randomly assigned to having a cerclage if the CL was <25mm.[12] Results of this randomized controlled trial showed reduction of

preterm delivery in the cerclage group versus the control group (6.1% versus 14%; p =0.03). There was also a reduction in perinatal mortality (8.8% versus 16%; p =0.046) by insertion of a cervical cerclage in women with a cervical length <25 mm and prior spontaneous preterm birth, but did not prevent birth at less than 35 weeks unless the CL was <15mm.[12]

In a 2004 randomised controlled trial by To MS et al involving 253 women with a CL of <15mm, randomised to cerclage or expectant management, similar results of preterm delivery before 33 weeks was found in both groups (22% in cerclage group versus 26% in the control group, p=0.44), with no significant difference in perinatal or maternal morbidity. In women with a short cervix, insertion of a Shirodkar suture did not substantially reduce the risk of early preterm delivery.[11]

There is a strong suggestion from studies that serial sonographic cervical length assessment may help to differentiate between women with prior history of second trimester loss or preterm labour who might need intervention and those who might be managed conservatively.[1] Serial CL screening is indicated for women with prior spontaneous preterm delivery.[1]

2.5 Timing of insertion and removal of cervical cerclage

In the literature review, no studies on the optimal timing of cervical cerclage insertion were found. Most studies advocate insertion of history-indicated cerclage between 12 and 14 weeks of gestation and up to 24 weeks for ultrasound- or physical examination-indicated cerclage.[1,5,7,8] The RCOG guidelines on cervical cerclage recommend history-indicated cerclage to be inserted between 12- and 14-weeks gestation.[1] The American College of Obstetricians and Gynecologists (ACOG) practice bulletin 142 recommends 13 to 14 weeks for history indicated cervical cerclage.[16]

A retrospective cohort study on obstetric outcomes of emergency cerclage versus elective cerclage showed no differences regarding mean gestation age at delivery in both groups 36.1±3 weeks (emergency group) vs 35.6±3 weeks (elective group), p=0.70.[17] Ciavattini et al assessed the effectiveness of emergency cerclage versus conservative management in improving obstetric and neonatal outcomes in women with clinically evident CI. The study findings support the use of emergency cerclage in women up to 24 weeks gestation with up to 5cm dilatation of the cervical os when no signs of infection or active contractions are present.[18]

There are also no studies in the literature directly comparing elective removal and emergency removal (i.e. in labour) of the cerclage. A retrospective cohort by Alabi J et al, involving 296 women who had either history- or ultrasound-indicated cerclage, to determine the time interval between elective removal of cervical cerclage to the onset of spontaneous labour found that the mean gestational age at cerclage insertion was 15.7±1 weeks, removal was 36.7±1.10 weeks and gestational age at spontaneous labour was 39.0±1.94 weeks. The mean interval was 14 days between cervical cerclage removal and spontaneous labour.[19]

A systematic review involving six studies, to evaluate the incidence of cervical lacerations with cerclage removal planned before labour (36-37 weeks gestation) compared to after the onset of labour, showed 8.9% (32\359) overall incidence of cervical lacerations.[18] The elective removal group and removal in labour group had incidences of 6.4% (23\280) and 11.4% (9\79) respectively p=0.70.[20]

2.6 Cervical cerclage compared with no treatment

The majority of studies were underpowered to demonstrate an effect on perinatal outcome. A surrogate marker for improved outcome used in studies is the reduction in rates of preterm delivery. The evidence for use of cervical cerclage to treat cervical insufficiency is

conflicting. Two small randomised controlled trials found no benefit of an elective cerclage to high risk women compared with expectant management. Lazar P et al randomised 506 women at moderate risk of preterm delivery to cerclage group vs control group, using a complex scoring system; differences in both groups was not statistically significant.[13] A study by Rush RW et al involving 194 women at high risk of preterm delivery who were randomised to cerclage or not, assessed the effect of cervical cerclage on pregnancy outcomes and found no evidence that cervical cerclage either prolonged gestation or improved survival.[14]

The RCOG working committee conducted a multicentre randomised controlled trial to assess whether cervical cerclage in women deemed to be at increased risk of cervical insufficiency prolongs pregnancy and thereby improves fetal and neonatal outcome. In this trial involving 1292 women, overall preterm delivery rate found was 28% and there were fewer deliveries before 33 weeks gestation in cerclage group, 13% vs 17% in the control group, p=0.03. The benefit was found in women with a history of three or more late miscarriages or preterm delivery and there was an important beneficial effect in 1 out of 25 cases.[15]

A 2012 Cochrane review including 3328 women from 12 randomised controlled trials assessed whether the use of cervical cerclage in singleton pregnancies at high risk of pregnancy loss, based on history and/or ultrasound finding of short cervix and/or physical exam, improves subsequent obstetric care and fetal outcomes. Cervical cerclage was compared with no treatment and the review found no statistically significant difference in perinatal deaths – 8.4 % (cerclage group) vs 10.7 % (control group), p=0.78, and neonatal morbidity 9.6 % (cerclage group) vs 10.2% (control group), p= 0.95.[5]

2.7 Indomethacin as adjunct to cerclage

The evidence for routine use of indomethacin as tocolytic therapy in patients undergoing cervical cerclage is insufficient. A retrospective cohort involving 101 women who underwent ultrasound-indicated cervical cerclage concluded that administration of indomethacin is not associated with a decrease in spontaneous preterm delivery before 35 weeks gestation, in women who received 48 hours of indomethacin compared to those who did not (39% vs 34%, p=.164).[21] No randomised controlled trials were found directly assessing the effect of prophylactic tocolysis in patient undergoing cerclage.

In summary, cervical cerclage has been shown to be of some benefit in reducing preterm deliveries before 35 weeks. The main issues regarding the use of cervical cerclage is lack of a targeted population that evidence of benefit has been shown, and when and how the cerclage should be inserted. Studies done were poorly designed and results are conflicting.

CHAPTER THREE – METHODS

3.1 STUDY DESIGN

This was a retrospective review of hospital records of patients who had a cervical cerclage inserted between 01 January 2013 and 31 December 2014.

Study Aim

The aim of this study was to evaluate patient selection, surgical technique and obstetric outcomes in patients with a history suggestive of cervical insufficiency, and had a cervical cerclage inserted at Chris Hani Baragwanath Academic Hospital (CHBAH) between January 2013 and December 2014.

Objectives of the study:

- To describe patient selection and criteria for cervical cerclage.
- To evaluate obstetric outcomes, i.e. gestational age at delivery, birth weight, mode of delivery, neonatal morbidity and mortality in patients who had a cervical cerclage inserted based on history and/or ultrasound assessment of cervical length.
- To compare pregnancy outcomes with surgical experience, i.e. cerclages done by consultants compared to those done by junior staff – registrars and medical officers (MOs).

3.2 SETTING

The study was conducted at the CHBAH's poor obstetric history clinic (POHC).

CHBAH is a tertiary referral centre for seven community health centres and one level 1 hospital, Jabulani hospital, in Soweto, Johannesburg. Four level 2 hospitals, i.e. Sebokeng, Leratong, Natalspruit and Klerksdorp Hospitals also form part of the

referral system. CHBAH is a teaching hospital and its staff composition includes consultants, registrars, MOs and interns.

The CHBAH obstetric unit does about 20 000 deliveries a year. The type of patients delivered are high risk obstetric patients with a wide spectrum of conditions and complications e.g. cardiac disease, hypertensive disorders, obstetric haemorrhage, and other medical and surgical disorders. The POHC is a consultant-driven clinic and its function is to manage patients with a history of poor pregnancy outcomes. This clinic runs once a week and approximately 20 to 30 patients are seen per week.

The following are indications for referral to the clinic (as adapted from the clinic protocol):

- Two or more spontaneous second trimester miscarriages
- One spontaneous second trimester miscarriage plus one preterm labour (before 37 completed weeks)
- Three or more consecutive first trimester miscarriages
- Unexplained stillbirths or intrauterine deaths
- Recurrent pre-eclampsia
- Any autoimmune diseases e.g. systemic lupus erythematosus (SLE)

Cervical cerclage is indicated in patients with suspected cervical insufficiency based on either history or ultrasound measurement of cervical length. The history suggestive of cervical insufficiency is that of painless cervical dilatation, in the absence of uterine contractions and any other identifiable pathology, and subsequent delivery before 24 weeks[1]. Transvaginal ultrasound findings are that of a cervical length of less than 25mm before 23 weeks gestation. Cervical cerclages are inserted around 14 weeks gestation and removed at 37 weeks of gestation. A rescue cerclage is done until 23 weeks of gestation and is usually performed when there is evidence of cervical dilatation, with or without bulging foetal membranes, in the absence of uterine contractions, vaginal bleeding or rupture of membranes.

An abdominal cerclage is indicated if previous cervical cerclages failed more than two times, the patient then requires a caesarean section for delivery. At caesarean section the cerclage may be removed if no other pregnancies are planned, or left in situ if future pregnancies are desired.

Method of cervical cerclage

The method of cerclage advocated by the CHBAH POHC protocol is a modified Shirodkar, described as a high transvaginal cerclage, involving a purse string suture placed above the level of the cardinal ligaments, following bladder mobilization.

3.3 STUDY POPULATION

3.3.1 The study population was patients who were seen at the POHC and had a cervical cerclage during the study period.

3.3.2 Inclusion criteria were:

- Age 18 years and older
- Both history- and ultrasound-indicated cerclage
- Singleton pregnancy

3.3.3 Exclusion criteria were:

- Patients with multiple pregnancies
- Pregnancies with confirmed congenital abnormalities

3.4 DATA COLLECTION

Data were extracted from the patients' hospital records using a standardized data extraction tool, Appendix A. Patient records are kept in a dedicated records room in the department of Obstetrics and Gynaecology at CHBAH. Patients were identified using theatre, antenatal clinic and foetal medicine department registers. The National Health Laboratory Services (NHLS) database was used to check for any outstanding blood results.

All collected data were entered onto a Research electronic database (REDCap)[25] and exported to Microsoft excel. Statistical analysis was done using Stata 13.0 software. Analysis of categorical data was expressed as percentages and proportions. Means and standard deviations (SD) were used to summarize continuous data. Both Student's t-test and Chi-squared tests were used for further analysis and a P value of less than 0.05 was accepted for statistical significance.

3.5 ETHICS

Ethical clearance was obtained from University of the Witwatersrand human research ethics committee (HREC), clearance no M150745 (Appendix B). Medical records were used anonymously for research purposes, and no patient identifiers, i.e. names, identification numbers or dates of birth, were used. Patients were assigned study numbers and only hospital numbers were captured in the data collection tools. Data were made available to the researcher and the supervisor only.

The study was self-funded by the researcher.

CHAPTER FOUR – RESULTS

4.1 Patient demographics

A total of 153 patients had a cerclage inserted during the two-year period (January 2013 to December 2014). Eleven patient records could not be found and this resulted in 142 records included in the study (142/153= 92.8%). The patient demographics are presented in Table 1. The mean age of the study participants was 29.9±4 years, and the median parity and gravidity were 1 (interquartile range (IQR) 1, 2) and 4 (IQR 2, 8), respectively. Overall, 66% (95/142) of participants booked for antenatal care in the first trimester, at a mean gestational age of 11.4±4.2 weeks.

4.2 Obstetric history

A history of two or fewer spontaneous second trimester miscarriages were found in 72% (102/142) of patients, and 28% (40/142) had three or more previous spontaneous second trimester miscarriages. A total of 42/142 (30%) had a history of previous preterm delivery. A history of an intrauterine fetal death (IUFD) was found in 5% (8/142) of participants – six occurred during the second trimester and two in the third trimester.

4.3 Investigations

HIV infection was diagnosed in 23 (16%) patients, and the median CD4 count was 398 cells/mm^3 (IQR 218, 602). All but one patient were on antiretroviral treatment (ART) in the form of an efavirenz-based fixed dose combination. The patient who was not on ART was lost to follow up. Viral loads were only done in eight patients and the results of five were less than 20 copies/ml, i.e. undetectable. The other three viral load results were 307 000, 65 900, 20 000 copies/ml, respectively. None of the participants had other chronic medical conditions.

Screening for antiphospholipid syndrome (APLS) was performed in 48% (68/142) of the patients. Positive results were found in 11/142 (7.7 %) patients and treatment in the form of enoxaparin 40mg daily and aspirin 75mg was instituted. Aspirin and enoxaparin were stopped at 34 and 36 weeks gestation, respectively. The commonest reasons for screening for APLS were: (1) history of three or more consecutive first trimester miscarriages, (2) more than one IUFD, and (3) severe early onset pre-eclampsia.

Screening blood tests done for APLS were anticardiolipin antibodies (IgG and IgM), beta 2 glycoprotein-1 antibodies (IgG and IgM), lupus anticoagulant.

4.4 Details of cervical cerclage

The details of cervical cerclage are presented in Table 2. The mean gestational age at insertion of cerclage was 16±5.8 weeks. The commonest method of insertion was a modified Shirodkar at 59% (84/142). Registrars, both junior and senior, performed the majority of cerclages, 76/142 (53%). Consultants performed 38.7 % (55/142) of the cerclages and MOs 7.8 % (11/142). MOs who performed the cervical cerclages were seniors. Three abdominal cerclages were done in patients with previously failed cervical cerclages, i.e. more than two previous cerclages. Post cerclage insertion, a total of 120/142 (84.5 %) patients received indomethacin suppositories for tocolysis, and the rest did not receive the drug due to unavailability. Two doses of 12 mg betamethasone, 12 hours apart, were administered intramuscularly for foetal lung maturity, at a mean gestational age of 27±5 weeks. Overall, 84% (121/142) of the patients received betamethasone; 10 of whom were found to have pre-viable pregnancies of less than 26 weeks gestation.

The median gestational age at removal of cerclages was 34.3±4.2 weeks. The most frequent reason reported for removal of cerclage before 34 weeks was preterm labour in 16% (23) of patients. Other reasons were prelabour rupture of membranes and antepartum haemorrhage.

Table 1: Patient demographics and obstetric history, n=142

Demographics		**n (%)**	
Maternal age (years), mean (SD)	<35	120 (85)	29.9 (4)
	≥35	22 (15)	
Parity, median (n,%)	0	59 (41.5)	
	1	48 (33.8)	
	>2	35 (24.6)	1 (1,2)
Gravidity, median (n,%)	1	1 (0.7)	
	2	4 (2.8)	
	3	35 (24.6)	
	>4	102 (71.8)	4 (2,8)
Gestational age at booking (weeks), mean (SD)	<12	95 (66.9)	
	13-18	36 (25.3)	
	>1	11 (7.7)	11.4 (4)
Obstetric history			
Previous T2 miscarriages	<2	102 (72)	
	>3	40 (28.1)	
Previous preterm delivery		42 (30)	
Previous cerclage insertion		41 (29)	
Previous progesterone use		4 (2)	
Previous cervical surgery (dilatation\cone biopsy)		3 (2.1)	
Screening and treatment			
APLS screening performed		68 (47.8)	
Enoxaparin use		16 (11.6)	
Aspirin use		38 (26.7)	

T2=second trimester; APLS= antiphospholipid syndrome

Delivery after 34 weeks gestation occurred in 67.6 % (n=96) of patients and the mean gestational age of delivery was 35.3±4.8 weeks. In total, 29 (20%) patients delivered between 39 and 41 weeks. The mean birth weight was 2414±73.2 grams.

Table 2: Details of cerclage (n=142)

		n (%)
Gestational age at insertion (weeks), mean (SD)		16.3 (2.4)
Gestational age at removal (weeks)	≤26	21 (14.7)
	27 to 33	23 (16.2)
	34 to 37	89 (62.6)
	≥38	9 (6.3)
Gestational age at delivery (weeks)	<28	25 (17.6)
	≥28 to 34	21 (16.9)
	≥34 to 38	26 (18.3)
	≥38	70 (49.2)
Surgical experience:	Registrar	76 (53.5)
	Consultant	55 (38.7)
	Medical officer	11 (7.7)
Surgical method:	Modified Shirodkar	84 (59.1)
	McDonalds	55 (38.7)
	Abdominal cerclage	3 (2.1)

When comparing the level of experience of the surgeon, i.e. consultant, registrar or MO, and gestational age at delivery, there was no statistically significant association found, p=0.263. There was also no significant association between gestational age of insertion of the cerclage and gestation at delivery (p=0.498).

4.5 Obstetric outcomes

Infant birth weights are presented in Table 3. Post cerclage insertion, 13/142 (9.1%) patients presented with spontaneous second trimester miscarriages. IUFDs were found in 1.5% (2/129) of the patients at delivery. A total of 124 live babies were delivered; five (4%) were admitted to the neonatal intensive care unit (NICU) for extreme low birth weight (LBW) complications and all subsequently died.

Table 3: Birth weight, n=142

Birth weights	n	%
<800g	7	4.9
>=800g & <1000g	7	4.9
>=100g & <1500g	12	8.4
>=1500g & <2500g	31	21.8
>=2500g	85	59.8
Total	142	100.0

There was no statistically significant association between gestational age at delivery and history of spontaneous second trimester miscarriages (p=0.498). The mode of delivery was a caesarean section in 38% (n=55) of the patients and 85% (n=47) were emergencies. The most common indications for a caesarean section were fetal distress, antepartum haemorrhage and poor progress of labour – Figure 1.

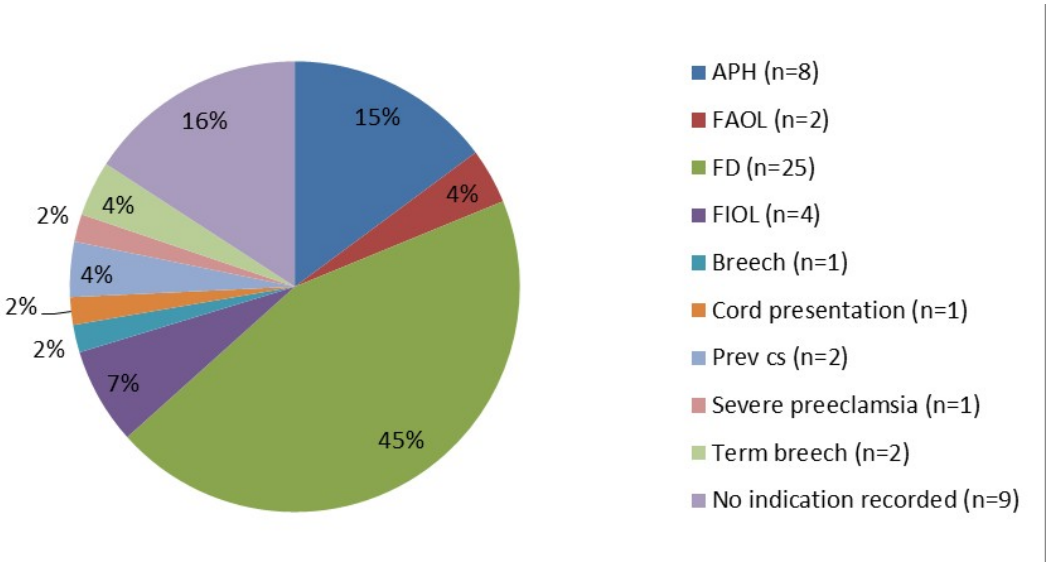

Figure1: Indications of caesarean section (n=55)

APH=antepartum haemorrhage; FAOL= failed augmentation of labour; FD= fetal distress; FIOL= failed induction of labour; CS= caesarean section; Prev=previous

CHAPTER FIVE – DISCUSSION

In this study, a history of two or fewer spontaneous second trimester miscarriages were found in 72% of patients who had a cerclage inserted. The mean gestational age at insertion of cerclage and removal was 16±5.8 and 34.3±4.2 weeks, respectively. Just over a half, 53%, of the cerclages were done by junior staff, owing to the fact that CHBAH is a training institution. Delivery after 34 weeks gestation occurred in 67.6 % (n=96) of patients and the mean gestational age at delivery was 35.3±4.8 weeks. Furthermore, delivery after 38 weeks was found in half of the patients. No significant association was found between the surgeon's experience and pregnancy outcomes, the main outcome was gestational age at delivery. More than half of the women had one or more live children born at term from their previous obstetric history.

The mean gestational age at cerclage insertion was 16 weeks, similar to findings of a study by Alabi J et al that showed a mean gestational age of 15.7 weeks at the time of cerclage insertion.[19] There is no consensus in the literature about the timing of cervical cerclage insertion. Shennan et al in their review recommended placement of a history-indicated cerclage from 12 to 14 weeks gestation.[1] The ACOG recommends placement of prophylactic cerclages at 13 to 14 weeks gestation.[16] A literature search for an association between surgical experience and pregnancy outcomes in patients with cerclage did not reveal any results. No randomised controlled trial has been conducted to directly assess the method of cerclage insertion and pregnancy outcomes. However, no difference in delivery rate before 33 weeks of gestation was found in a secondary analysis of four randomised control trials of women with a short cervix in those who had Shirodkar suture compared to McDonalds suture.[1]

Some women were found to have children before the history of recurrent second trimester miscarriages, and others had viable pregnancies in between the miscarriages. Term birth rates are as high as 60 to 70% in women with a prior second trimester spontaneous loss, and the majority of them are without any interventions.[15] Only a third of the patients in the study reported a history of three or more spontaneous second trimester miscarriages. This finding suggests that the majority of patients might have been overtreated. The Medical Research Council (MRC)\RCOG's randomised control trial on history-indicated cerclage, in 1292 women at risk of preterm birth, demonstrated a significant overall reduction in births at less than 33 weeks gestation for women with three or more previous spontaneous second trimester miscarriages (15% vs 32%, $p<0.05$).[15] Shennan et al, in their study, recommended that history-indicated cerclage should not be routinely offered to women with two or fewer spontaneous second trimester losses. [1]

In this study, 30% of deliveries occurred spontaneously before 34 weeks of gestation. This indicates that the cerclages failed. The outcome of this study is probably influenced by patient selection – more than two thirds of patients had two or more previous spontaneous

second trimester miscarriages. The evidence from a large RCT conducted by the MRC and the RCOG demonstrated no effect of a cervical cerclage in patients with a history of two or fewer previous spontaneous second trimester miscarriages – 12% versus 14% delivered before 33 weeks gestation in the cerclage group versus the control group, respectively.[1]

Half of patients in this study were found to have delivered after 38 weeks and a further 20% delivered between 39 to 41 weeks. This finding suggests that patient selection and criteria for cerclage were not stringent as patients with true cervical insufficiency are more likely to deliver before 38 weeks gestation. Evidence from a retrospective cohort study found a 14 day mean interval between removal of cerclage and spontaneous labour.[19] The mean gestation at removal was 36.7 weeks and this finding is similar to the study by Alabi-Isama L .[19]

There was an 11% positive finding in the patients that were screened for APLS. In this subset of patients, there was a mixed history of first and second trimester miscarriages. The typical history of spontaneous second trimester miscarriages was not properly documented in this group of patients. In retrospect, this finding gave the impression that these women did not require cervical cerclage as APLS was confirmed and managed appropriately. However, patients with dual pathologies, i.e. cervical insufficiency and APLS, could not be excluded. Of the women who were started on aspirin, there was no clear indication in the clinical records. The Dutch study APRIL, to assess the role of aspirin in preventing recurrent spontaneous second trimester miscarriages/preterm births showed no benefit.[21]

In this study, 96% of all viable pregnancies received betamethasone and 84% had indomethacin suppositories administered post cerclage insertion. The adjuvant therapy of betamethasone for lung maturity and indomethacin for perioperative tocolysis might have had effects on perinatal outcomes. A literature search for an association between the use of indomethacin and perinatal outcomes in patients with cervical insufficiency revealed insufficient evidence. There were no randomised controlled trials found directly assessing the effectiveness of indomethacin in patients with CI. In a retrospective cohort involving 101 women who had an ultrasound-indicated cerclage, there was no significant difference in the rate of preterm births before 35 weeks of gestation in women who received indomethacin compared to the control group (39% vs 34%, p=0.164).[17]

Five babies were admitted to the NICU for complications of extreme LBW, mostly respiratory problems, and all died. Overall, 95% of babies did not require NICU admission. These findings could be associated with administration of betamethasone as discussed above, and also the fact that the majority of deliveries occurred after 34 weeks gestation.

5.2 Strengths

Although the sample size was small, detailed data were extracted from the patient records thereby allowing plausible conclusions from examination of results. Overall, 92.8 % of patient records were retrieved.

5.3 Limitations

The study was retrospective and data in some hospital records were incomplete due to poor recording of clinical notes. There was no clear and detailed history about the nature of miscarriages in some records. The sample size was small and the study was conducted in only one centre. Also, poor filling of records due to lack of space made it difficult to retrieve records. There were also different surgeons involved leading to surgical technique heterogeneity.

5.4 Conclusion

In this study, more than half of the women had one or more live children born at term prior to the spontaneous second trimester miscarriages, suggesting that cervical incompetence might be an acquired condition. The majority of patients might have been over-treated owing to the fact that only a third of patients had a history of three or more spontaneous preterm deliveries. There was no significant association found between surgeons' experience and pregnancy outcomes. Delivery after 38 weeks was found in half of patients and this may have been because of less stringent patient selection and criteria for cerclage insertion. Larger studies are needed to evaluate patient selection and criteria for cervical cerclage in our population.

5.5 Recommendations

There is a need for stricter criteria for patient groups that may benefit from cervical cerclage and this includes the recommended criteria of a history of three or more spontaneous second trimester miscarriages. Indications for cerclage should also be reviewed and patients should be individualised and offered serial sonographic cervical length surveillance if significant historic risk factors are present.

CHAPTER SIX – REFERENCES

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CHAPTER SEVEN – APPENDICES

Appendix I: Data collection sheet

File number:_____ Date of data collection: _____

Study number: _____

Background information

Age:____years Parity:____ Gravidity: ____

Booking bloods:

Rhesus: □Positive □Negative RPR: □Positive □Negative □not done

Trepanema Pallidum antibodies: □Positive □Negative □not done

HIV: □ Positive □ Negative If positive CD4 count:____ On Antiretrovirals: □Yes □No

Booking Haemoglobin: _____g\dL

Gestational age at booking:_____weeks

Details on previous viable pregnancies:

Year	Mode of delivery	Birth weight	Gestation at delivery	Complications

Details of miscarriages:

	Year	Duration of pregnancy	Evacuation of the uterus
1st trimester miscarriage – spontaneous			
1st trimester – missed abortion			
2nd trimester miscarriage – spontaneous PTL			
2nd trimester – IUFD			
3rd trimester – spontaneous PTL			
3rd trimester –IUFD			
Other			

Comments:

_____

_____

_____

_____

_____

History of previous cerclage: Yes/No

If yes, how many times? Comments about pregnancy outcomes:

_____

_____

_____

_____

History of previous progesterone use: Yes/No

If yes, how many times? Comments about pregnancy outcomes:

_____

_____

Comorbidities: □Diabetes Mellitus □Hypertension □Asthma □Epilepsy □Other, specify_____

Chronic medication, specify:

_____

Anti-Phospholipid screening (Anti-Nuclear Antibodies, Lupus Anti-coagulant, Beta 2 glycoprotein): Done YES\No Positive\Negative

Previous cervical surgery: Yes \No

If yes, comments:

Details on index cervical cerclage

Indication of cerclage: □History □ Cervical length on ultrasound: 1st trimester \ 2nd trimester

Gestation of cervical length measurement:_____Weeks

Cervical length at insertion:_____mm

Gestational age at insertion:_____weeks

Surgical method used: □Modified Shirodkar □Mcdonalds □Abdominal cerclage

Surgeon: □Registrar □Consultant □Medical officer

Surgical complications: □Bleeding from cervix □Iatrogenic rupture of membranes □Infections □None □Other, specify:

_____

Antenatal care

Post insertion ultrasound: Done Yes\No

Cerclage correctly placed at the internal cervical os: Yes\No

Number of antenatal clinic visits: ____

Celestone given: Yes\No specify gestation:____weeks

Vaginal Cyclogest given: Yes\No Duration:_____weeks

Prophylaxis used: □Low dose aspirin □Clexane □None

Ultrasound follow-up: □ Normal growth □IUGR □other:
specify_____

Antenatal complications, specify:
_____

Details on Delivery

Gestation at removal of cerclage:_____weeks

Reason for removal: □Elective □Emergency

Gestation at delivery:_____weeks

Delivery: □Spontaneous >37 completed weeks □spontaneous Preterm labour <37 weeks □Induction of Labour, indication:
_____

Mode of delivery: □ Normal vaginal delivery □ Emergency caesarean section
□ Elective caesarean section

Indication of caesarean section:

_____

Neonatal outcomes

□Alive □Fresh stillbirth □Intrauterine fetal death □Information not available

Birth weight:_____grams

NICU admission: Yes\No

Reason for admission:

_____

Outcome on NICU discharge: □ Alive □ Died □Information not available

Appendix II: ethics approval letter from the University of the Witwatersrand Ethics Committee

R14/49 Dr Gift Dingiswayo

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M150745

NAME: (Principal Investigator)	Dr Gift Dingiswayo
DEPARTMENT:	Obstetrics and Gynaecology Chris Hani Baragwanath Academic Hospital
PROJECT TITLE:	A Retrospective Review of Pregnancy Outcomes in Patients who had a Cervical Cerclage at Chris Hani Baragwanath Academic Hospital between January 2013 and December 2014
DATE CONSIDERED:	31/07/2015
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Dr CN Mnyani
APPROVED BY:	Professor A Dhai, Co-Chairperson, HREC (Medical)
DATE OF APPROVAL:	15/12/2015

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 Secretary in Room 10004, 10th floor, Senate House, University.
I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to resubmit the application to the Committee. **I agree to submit a yearly progress report**.

Principal Investigator Signature Date

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES