UNIVERSITY OF THE WITWATERSRAND

FACULTY OF HEALTH SCIENCES

A RETROSPECTIVE STUDY ON THE OUTCOMES OF PERIPARTUM HYSTERECTOMIES FOR PUERPERAL SEPSIS AT CHRIS HANI BARAGWANATH ACADEMIC HOSPITAL

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Declaration

I, Esther Olusola, declare that this research report is my own work. It is 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 this University or any other University.

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Dedication

I dedicate this Master of Medicine to my late parents, Edward and Victoria Olusola and to my siblings Deborah and Victor Olusola. Your love and support through this journey has been invaluable.

Acknowledgements

I would like to express my gratitude and appreciation to my supervisor Dr P Naidoo for her patience and guidance throughout this process. I would also like to express my gratitude to Dr A Chikandiwa for his advice and statistical support.

A retrospective study on the outcomes of postpartum hysterectomies for puerperal sepsis at Chris Hani Baragwanath Academic Hospital.

Clinical article

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Abbreviations:

BMI: Body Mass Index

GCS: Glasgow Coma Scale

HIV: Human Immunodeficiency Virus

MODS: Multiple Organ Dysfunction Score

qSOFA: quick Sequential Organ Failure Assessment

RPR: Rapid Plasma Reagin

sBP: Systolic Blood Pressure

SOFA: Sequential Organ Failure Assessment

STAH: Subtotal abdominal hysterectomy

TAH: Total Abdominal Hysterectomy

Introduction

It is well known that sepsis during pregnancy and in the puerperal phase is one of the leading causes of maternal morbidity and mortality worldwide and accounts for 11% of maternal deaths in developing countries.[1,2,3,4,5] The definition of puerperal sepsis includes two or more of the following: fever, abnormal vaginal discharge, pelvic pain, offensive discharge or a delay in involution of the uterus.[6] Source control is defined as actions performed to eliminate the source of infection.[7] Hysterectomy, as a measure of source control is performed when uterine sepsis is the source of puerperal sepsis.

There are a number of risk factors that have been identified in maternal sepsis. The source of infection or sepsis can be divided into obstetric and non-obstetric causes. Obstetric related infections in the antepartum period have been noted to be septic abortions and chorioamnionitis in comparison to endometritis and wound infections in the postpartum period.[8] The non-obstetric sources of infection in both the antepartum and postpartum period were found to be urinary tract and respiratory tract infections.[9] Other potential risk factors for puerperal sepsis include chorioamnionitis, caesarean sections, post-partum hemorrhage, pre-term deliveries and patients with co-morbid disease such as diabetes and eclampsia.[10] Caesarean sections were noted to be a contributory factor to the development of puerperal sepsis with an increase in the sepsis mortality rate.[10]

The rationale behind conducting this study was to ascertain more information regarding the outcomes of women who had a hysterectomy for puerperal sepsis. Puerperal sepsis rates are rising and with the growing incidence of antibiotic resistance more information is required in order to treat patients appropriately. The

scoring systems (MODS, SOFA, qSOFA) are used to assess end organ dysfunction in Intensive Care Units and to determine their progress or worsening of condition.

The aim of this study was to describe the organisms cultured, their antibiogram, surgical characteristics and organ dysfunction scoring systems in women who had a hysterectomy as a measure of source control in the treatment of puerperal sepsis.

Materials and methods

This was a retrospective cross-sectional study. The medical records of all women who between 01 January and 31 December 2019 underwent a hysterectomy for puerperal sepsis and whose histology samples reflected endometritis at the Chris Hani Baragwanath Academic Hospital situated in Soweto, Johannesburg, were included. Women that had miscarriage, or a pregnancy at ≤ 24 weeks' gestation were excluded. Data pertaining to demographics, microbiology samples and sites, and histological reports were extracted and subjected to analysis. Duration of caesarean sections were identified through theatre notes and categorized accordingly. Organ dysfunction scores are not routinely calculated in this institution therefore these were calculated by the researcher. The post-operative scores were calculated 48 hours after hysterectomy. This was a retrospective record review therefore individual patient consent was not obtained.

Description of analysis

The data was analyzed by a statistician with Stata 15.0® software (StataCorp, 4905 Lakeway Drive, College Station, Texas 77845 USA). Difference between proportions was assessed using the Fischer's Exact Test. Frequencies and percentages were used to describe categorical data. Normally distributed data was presented as mean

whilst non-parametric data was summarized with medians and inter-quartile range (IQR). The Shapiro-Wilk test was used to test for normality of continuous variables. The differences between admission, pre-hysterectomy and post-hysterectomy values were evaluated using ANOVA (analysis of variance) for repeated measures test. A p-value of < 0.05 was considered statistically significant.

Ethics

Ethical clearance was obtained from the Human Research Ethics Committee (Medical), prior to commencement of this study (M200979). Permission was also obtained from the medical advisory committee of Chris Hani Baragwanath Academic Hospital and authorization for access to database obtained from the National Health Laboratory Service.

Results

In 2019, there were 18458 deliveries, of which 45.5% were delivered by caesarean section. During this period 33 (0.17%) hysterectomies were performed for puerperal sepsis. Table 1 shows the demographics and clinical characteristics of these women. There were seven (21%) women who were HIV seropositive. The median gestational age at the time of delivery was 38 weeks (range 34-40). The median body mass index was 28kg/m^2. Eight women (24%) had hypertensive related disorders.

Table 2 describes the mode of delivery characteristics. There were 29 (88%) women who had a Caesarean section and four (12%) that had a normal vaginal delivery. The surgical duration of Caesarean section was 30 to 60 minutes in 50% of women. The most prevalent indications for Caesarean sections in these women were fetal distress (n=14, 48%). The description of “other” which accounts for 34% of the women in the study included antepartum haemorrhage (uterine rupture and placenta previa), eclampsia, cephalopelvic disproportion and elective caesarean sections.

The surgical characteristics of the women who had puerperal sepsis are reflected in Table 3. There were 29 (88%) women who had a total abdominal hysterectomy in comparison to four (12%) who had a subtotal hysterectomy. Two of those women recovered uneventfully and were discharged home. One had ongoing sepsis and required cervical stump removal, and eventually recovered. The fourth woman who had a subtotal hysterectomy demised due to ongoing sepsis with *A Baumannii* bacteremia. Post-mortem results on this woman revealed she had a necrotic cervix. Fifteen (n=33, 45%), women had two exploratory laparotomies, eight (n=33, 24%) had one exploratory laparotomy and four (n=33,12%) had three laparotomies. Eleven women who had a total abdominal hysterectomy required a subsequent

exploratory laparotomy in comparison to two women who had a subtotal hysterectomy and required a subsequent laparotomy.

Common organisms identified in each culture site (intra-abdominal fluid, blood, urine and sputum) are represented in Table 4. *A. baumannii* was the only organism cultured in all four culture sites. Refer to Table 4 for further details. In the women with higher Multiple Organ Dysfunction Score (MODS), Sequential Organ Failure Assessment (SOFA) and quick Sequential Organ Failure Assessment (qSOFA) score the following organisms were cultured: *A. baumannii*, Staph. epidermidis, E. coli and Klebsiella species. In the HIV seropositive patients *A. baumannii*, *E. faecalis* and *Coagulase negative staphylococcus* were the organisms commonly cultured. In the HIV seronegative patients *A. baumannii, E. coli and Klebsiella spp* were the organisms commonly cultured. Of the two women who demised one, who was HIV seronegative, cultured *A. Baumannii* in blood and *E. coli* in urine.

The antibiogram of the organisms described are illustrated in Table 5. *A. baumannii* (n=16), the most common organism, was sensitive to ceftazidime and colistin in 44% of women, resistant to tazobactam in 69%, gentamycin in 56% and ceftazidime in 17% of women. Two organisms (*E. coli* and *Prevotella oralis)* were sensitive to Augmentin. *Prevotella oralis* was the only organism sensitive to metronidazole. *E. coli* was the only organism sensitive to gentamycin. Four organisms, *E. faecalis*, *Staph. ludgenensis*, *Staph. aureus* and *Strep. anginosus*, were sensitive to ampicillin.

Table 6 compares the different scoring systems. Table 6A compares the admission and post hysterectomy MODS and SOFA score. Table 6B illustrates the ranges of the various scoring variables at admission, pre-hysterectomy and post hysterectomy

218 with the p-values comparing the three parameters. More women had higher scores
219 post hysterectomy using the MODS system rather than the SOFA system. In the two
220 women that demised, one of them had an improvement in the qSOFA score, whilst in
221 the second woman all three scoring systems had worsened.

222 Table 7 reflects the findings noted at each laparotomy. Eight women had one
223 laparotomy, fifteen women had two laparotomies and four women had three
224 laparotomies. At the primary laparotomy, in four women (n=13, 31%) peritoneal pus
225 was localized to the pelvis. Four quadrant sepsis was described in three (n=3, 23%)
226 women and pus was described in the myometrium in one (n=1, 8%). There was one
227 woman in which the uterine scar was bleeding. Eight percent of women who had a
228 second and third laparotomy had peritoneal pus localized to the pelvis. Serous fluid
229 collection was found in 13 (n=21, 62%) women at the time of the primary laparotomy
230 and 38% in the second laparotomy. In the first laparotomy the uterine scar was noted
231 to be healthy in five (n=22, 23%) women and necrotic in 11 (n=11, 50%). In the first
232 laparotomy the uterus was described as healthy in eight (n=25, 32%), necrotic in
233 three (n=25, 12%) and atonic in ten (n=25, 40%). The description of findings of
234 localized pus in the pelvis and necrotic uterine scar were noted in two women
235 respectively who had a third laparotomy. Other findings included pus in the
236 myometrium in one woman and bleeding from the uterine scar in another.

237 Table 8 describes the location of other sources of sepsis. Respiratory tract infection
238 was found in four (12%) of the women, bacteremia was found in three women (9%)
239 and two women who had urosepsis (6%). Two women (6%) demised from other
240 complications. In one of these women the cause of death was identified as acute
241 respiratory distress syndrome secondary due to ongoing sepsis. In this woman the

cervix was still in situ and noted to be necrotic at post-mortem. The second woman that demised post total abdominal hysterectomy, had ongoing sepsis complicated by disseminated intravascular coagulopathy with the anterior abdominal wall being the site of infection. 94% of women in this study survived and were subsequently discharged home.

Table 9 compares the surgical intra-abdominal findings to the histopathologists' findings in terms of pus and uterine necrosis. Intra-abdominal pus was documented by the surgeon in 44% of women versus 53% by the histopathologist, p value 0.001. Uterine necrosis was described by the surgeon in 30% of women in comparison to 72% by the histopathologist, p value 0.004.

Table 10 reflects the histological findings of the uterus. Puerperal sepsis was reported in the majority (85%) of women. The endometrium was described as inflamed in 6% and myometrial ischemia in 3% of women. There was no histological evidence of sepsis reported in one (3%) woman. There was no report on one of the histology samples due to a laboratory related issue.

Discussion

Our study describes 33 women that underwent hysterectomy for puerperal sepsis. These women constituted 0.17% of the women who delivered at CHBAH during this study period. This highlights the number of young women rendered infertile secondary to a hysterectomy, with an increased risk in psychological complications.[11]

The background incidence of hypertension in pregnant women in Soweto is 11%. The finding of a 15% incidence of hypertension in our study may highlight the susceptibility of hypertensive women to hysterectomy for puerperal sepsis. It is not possible to ascertain whether this is due to the disease process or an increased frequency of iatrogenic interventions. This is a unique finding not previously described.

Total abdominal hysterectomy is a method of source control in the management of severe uterine sepsis. However, variations in technique, surgical experience and consistency of approach are not standardized but rather individualized on a patient-to-patient basis.[11,12] In our study, twenty-nine women (88%) had a total abdominal hysterectomy, while four (12%) had a subtotal hysterectomy. There is no literature that describes a TAH as superior to a STAH in the management of puerperal sepsis. The only evidence regarding TAH and STAH was in post and peripartum haemorrhage.[12] The mortality rate in this study was 6% which may suggest that early source control has better outcomes, however this study was not designed to assess the time to source control.

It is widely known that the common organisms of puerperal sepsis are *E. coli, Group B streptococcus, Klebsiella pneumonia* and *Staphylococcus species*.[13] In our study we found that ESKAPE organisms, namely *Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *A. baumannii*, *Pseudomonas aeruginosa* and *Enterobacter spp*. were the most common organisms that were cultured. With *A. baumannii* being the most frequently cultured followed by *E. coli* and *Klebsiella*. These same organisms were the most cultured in a study conducted in the Western Cape, South Africa.[12] There is a paucity of evidence arising from South Africa, which

indicates the types of organisms that is most often cultured. This study adds to the body of knowledge on the subject. All three of these organisms were found to be resistant to Augmentin, ampicillin and gentamycin, which are commonly used in our hospital facility to treat puerperal sepsis and chorioamnionitis. *E. coli* was the only ESKAPE organism to have some sensitivity to Augmentin. The organisms commonly cultured in Table 4 shows that our current prophylactic and treatment regimens are ineffective as most of these organisms are resistant to these. This finding substantiates the need to use targeted antibiotic therapy in the management of puerperal sepsis and highlights the importance of antimicrobial stewardship as more organisms are becoming resistant to broad-spectrum antibiotics.

The organisms that were cultured in the women that demised were *E. coli* and *A. Baumannii*. The study was not designed to ascertain whether these organisms contributed to the demise of this woman, however colonization with XDR *A. Baumannii* may have contributed to her demise as there was no adequate antibiotic cover that could be provided. Due to the increasing incidence of A. Baumannii, we may need an alternative broad spectrum antibiotic cover.[14]

The most prevalent organisms in women who had the highest SOFA and MODS scores were *A. Baumannii, Enterococcus faecalis* and *Coagulase negative staphylococcus*. There is no current literature to support the finding that high MODS, SOFA and qSOFA scores in the presence of common cultured organisms in puerperal sepsis.

It has been suggested that the use of the SOFA or obstetric modified SOFA score is a more thorough assessment of end organ dysfunction in septic pregnant woman as they take into account the physiological changes of pregnancy.[15] When comparing

the scoring systems, most women had higher score values which may be attributed to delays in definitive surgical management. The significant difference between the admission and post hysterectomy scores may be attributed to prolonged intubation and sedation. Women who were post hysterectomy had relatively higher scores using the MODS score than the SOFA score with respect to their admission. This difference may be explained by the use of different scoring criteria in each of the systems. The MODS score identified more renal impairment in the pre-hysterectomy women than in the post hysterectomy women. Though it must be stated that this study was not designed or powered to demonstrate this difference. This is a unique finding as there is no current literature that compares the MODS and SOFA score in women with puerperal sepsis. Further studies will need to be performed to ascertain which of the two scoring systems adds more clinical value to patient care.

The source of sepsis was independent of HIV seropositivity. The background rate of HIV seropositivity is 21% in Soweto, which is higher than observed in our study. This is an interesting finding and may be attributed to antiretroviral medication and possibly postpartum prophylactic antibiotic use may reduce puerperal sepsis leading to hysterectomy. There was no histopathological difference noted between HIV seropositive and seronegative women.

The findings of bacteremia, respiratory tract and urinary tract infection highlights the importance of concurrent investigations to improve detection as foci of infection may occur in more than one site.

One of the unique findings of this study was that most surgeons underestimated necrosis and the appearance of pus in comparison to the histological and microbiological findings and it was statistically significant. There is a paucity of literature regarding the surgeon's ability to identify necrosis, which highlights the need for an appropriate scoring system to objectively identify women who require a hysterectomy.

Study Strengths

This study was conducted in a single center and is reflective of a low to middle income South African population. The benefits of a single center eliminates the heterogeneity of protocols and challenges of different institutions. The histological comparison to intra-operative surgical findings illustrates the efficient documentation due to a uniform approach of documentation in this institution. Another strength is the availability of laboratory microscopy, sensitivity, culture to aid in the analysis of the antibiogram.

Study limitations

The main limitation is the sample size, which is attributed to the rarity of hysterectomies for sepsis. Further limitations include the retrospective nature of the study, the absence of other factors that may contribute to sepsis (e.g., surgical experience, delays in hospital presentation and timing of laparotomy as a measure of source control). Majority of the samples obtained were from the postpartum period. Other factors such as prolonged labour, meconium stained liquor, number of vaginal examinations and the length of rupture of membranes which may contribute to the

development of puerperal sepsis were not considered in this study. Whilst it is known that early source control contributes to better outcomes these were not evaluated in this study.

In summary timeous and appropriate hysterectomies as a measure of source control is required in uterine sepsis. Puerperal sepsis may result in multiple end organs being affected motivating for the use of multi-organ assessment models. This study creates awareness about the rising antibiotic resistance in this population and mandates a review of our prophylactic and treatment antibiotic regimen used in the population of South Africa.

Author contributions: E. Olusola designed the study, performed data acquisition, analyzed and interpreted the data that was acquired, wrote and revised the article. P Naidoo contributed to the study design, analysis and editing process. A. Chikandiwa contributed to the analysis and interpretation of the data.

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Conflict of interest: The authors have no conflict of interest.

Appendix A: Tables

Table 1 A description of demographic characteristics

Variable		Median (IQR) No (%) n=33
Age in years		28 (22- 34)
Parity		1 (0- 2)
Gravidity		2 (1- 4)
Gestational Age at delivery in weeks		38 (34- 40)
Race	Black	27 (82)
	Coloured	6 (18)
BMI (kg/m^2)		28 (26- 31)
RPR		2 (6)
HIV sero-positive		7 (21)
Co-morbidities	Hypertensive	5 (15)
	Pre-eclampsia	3 (9)
	Cardiac	2 (6)
	Diabetes	1 (3)

BMI= Body Mass Index, RPR= Rapid Plasma Reagin, HIV seropositivity = Human Immunodeficiency Virus

Table 2 Illustrates the mode of delivery characteristics

Table 2 A: Indications for Caesarean section

Indication	**No (%) n=29**
Fetal distress	14 (48)
Poor progress	2 (7)
Previous caesarean section in labor	4 (10)
Other	10 (34)

There were some women who had more than 1 indication for caesarean section

Table 2 B: Duration of caesarean section

Operative times	**No (%) n=29**
0-30 min	4 (14)
30-60 min	15 (52)
>60 min	4 (14)

Table 3 Surgical Characteristics of women that had puerperal sepsis

Surgical procedure	Surgical characteristic	No (%)
Hysterectomy type n=33	Subtotal hysterectomy	4 (12)
	Total hysterectomy	29 (88)
Number of exploratory laparotomies n=33	1	8 (24)
	2	15 (45)
	3	4 (12)
	Unknown	6 (4)

Table 4 Organisms identified in various sites

Organism	Sample site Frequency			
	Intra-abdominal fluid (n=42)	**Blood (n=8)**	**Urine (n=7)**	**Sputum (n=2)**
Acinetobacter baumannii	11 (26)	3 (38)	1 (14)	1 (50)
Coagulase negative staphylococcus		2 (25)		
Staphylococcus hemolyticus		1 (13)	1 (14)	
Escherichia coli	8 (19)		2 (29)	
Enterobacter cloacae			1 (14)	
Klebsiella species	6 (14)			1 (50)
Enterococcus faecalis	6 (14)			
Enterococcus faecium	3 (7)	1 (13)		
Staphylococcus aureus	2 (5)			
Prevotella oralis	1 (2)			
Proteus mirabilis	1 (2)			
Staphylococcus lugdenensis	1 (2)			
Staphylococcus epidermidis	1 (2)	1 (13)		
Streptococcus anginosus	1 (2)			
Candida albicans	1 (2)		2 (29)	

Table 5: Overall profile of antimicrobial drug susceptibility testing results for micro-organisms identified in blood, urine and intra-abdominal fluid cultures

Micro-organism	Name of organism	Drug	Sensitive No of samples[1] (%)	Resistant No of samples[2] (%)
Gram negative n=25	*Acinetobacter baumannii n=16*	Ampicillin		1 (6)
		Augmentin		1 (6)
		Ceftazidime	7 (44)	4 (25)
		Ceftriaxone		1 (6)
		Ciprofloxacin	1 (6)	
		Clindamycin		1 (6)
		Cloxacillin		1 (6)
		Colistin	7 (44)	
		Gentamycin		9 (56)
		Tazobactam		11 (69)
		Vancomycin		1 (6)
	Escherichia coli n=10	Ampicillin		6 (60)
		Augmentin	8 (80)	2 (20)
		Ceftazidime		1 (10)
		Ceftriaxone	2 (20)	2 (20)
		Gentamycin	1 (10)	
		Tazobactam	1 (10)	
	Klebsiella n=7	Ampicillin		4 (57)
		Augmentin		3 (43)
		Amikacin	2 (29)	
		Ertapenem	4 (57)	
		Imipenem	3 (43)	
		Tobramycin	1 (14)	

[1] Sample expressed as a percentage of the organism in question and not its gram or fungal status
[2] Sample expressed as a percentage of the organism in question and not its gram or fungal status

		Gentamycin		2 (29)
		Tazobactam		2 (29)
		Ceftriaxone	1 (14)	2 (29)
		Ceftazidime		2 (29)
	Prevotella oralis n=1	Metronidazole	1 (100)	
		Augmentin	1 (100)	
	Proteus mirabilis n=1	Ampicillin		1 (100)
		Augmentin		1 (100)
		Ceftazidime	1 (100)	
		Gentamycin		1 (100)
	Enterobacter cloacae n=1	Ampicillin		1 (100)
		Cotrimoxazole	1 (100)	
		Amikacin	1 (100)	
		Cefepime	1 (100)	
		Nitrofurantoin	1 (100)	
Gram positive n=19	*Enterococcus faecium n=4*	Ampicillin		2 (50)
		Vancomycin	2 (50)	
	Enterococcus faecalis n=7	Ampicillin	7 (100)	
	Staphylococcus lugdenensis n=1	Ampicillin	1 (100)	
		Cloxacillin	1 (100)	
	Staphylococcus aureus n=2	Ampicillin	1 (50)	
		Cloxacillin	2 (100)	
	Coagulase Negative Staphylococcus n=2	Vancomycin	2 (100)	
	Staphylococcus epidermidis n=2	Vancomycin	2 (100)	
	Staphylococcus hemolyticus n=2	Vancomycin	2 (100)	
	Streptococcus anginosus n=1	Ampicillin	1 (100)	
Fungus n=2	*Candida albicans n=2*	Fluconazole	2 (100)	

Table 6A: Comparison of scoring systems

Variable	MODS										P-value
	Admission n=33					Post hysterectomy n=33					
	0	1	2	3	4	0	1	2	3	4	
Respiration (PaO_2/FiO_2) n=22	15	2	2	0	0	6	5	6	1	0	**0.03**
Renal (Serum creatinine) n=29	20	5	2	2	0	29	0	0	0	0	**0.02**
Hepatic (Serum Bilirubin) n=27	18	2	0	0	0	19	2	2	0	0	0.65
Cardiovascular n=27	22	0	1	0	0	19	0	0	5	0	**0.05**
Coagulation (Platelet count) n=29	24	5	0	0	0	23	2	2	0	2	0.16
Neurological (GCS) n=25	23	1	0	0	1	17	0	6	0	2	**0.02**

Variable	SOFA Score										P-value
	Admission n=33					Post hysterectomy n=33					
	0	1	2	3	4	0	1	2	3	4	
Respiration (PaO_2/FiO_2) n=22	9	7	3	1	0	4	4	4	7	0	**0.06**
Coagulation (Platelets) n=29	23	4	2	0	0	21	3	2	3	0	0.41
Liver (Bilirubin) n=27	18	1	1	0	0	19	2	0	2	0	0.61
Cardiovascular (Hypotension) n=27	23	1	0	0	0	19	0	5	0	0	**0.05**
CNS (GCS) n=25	23	1	0	0	1	17	0	6	0	2	**0.02**
Renal (Creatinine) n=29	21	4	1	3	0	20	2	4	1	2	0.29

Reference:

1. SOFA score[16]

SOFA score	0	1	2	3	4
Respiration					
PaO_2/FIO_2 (mmHg)	> 400	301–400	201–300	101–200	≤ 100
(kPa)	> 5.3)	(4.1–5.3)	(2.8–4.0)	(1.4–2.7)	≤ 1.3)
Coagulation					
Platelets ($x10^3/mm^3$)	> 150	101–150	51–100	21–50	≤ 20
Liver					
Bilirubin (mg/dl)	< 1.2	1.2–1.9	2.0–5.9	6.0–11.9	≥ 12.0
(μmol/l)	< 20)	(20–32)	(33–101)	(102–204)	≥ 204)
Cardiovascular					
Hypotension	No hypotension	MAP < 70 mmHg	Dopamine ≤ 5 or dobutamine (any dose)*	Dopamine > 5	Dopamine > 15
Central nervous system					
Glasgow coma score	15	13–14	10–12	6–9	< 6
Renal					
Creatinine (mg/dl)	< 1.2	1.2–1.9	2.0–3.4	3.5–4.9	> 5.0
(μmol/l)	< 110)	(110–170)	(171–299)	(300–440)	> 440)
or urine output				< 500 ml/day	< 200 ml/day

* adrenergic agents administered for at least 1 h (doses given are in μg/kg/min)

2. qSOFA[1]

Table 3 Quick sepsis-related organ failure assessment score (qSOFA)[a]

Assessment	qSOFA score
Tachypnea: (≥22 breaths/min)	1
Hypotension: (SBP ≤100 mmHg)	1
Altered mentation: (GCS <15)	1

SBP: systolic blood pressure; GCS: Glasgow Coma Scale.
[a]Adapted from Singer et al.[22]

3. MODS[16]

The Multiple Organ Dysfunction Score (MODS)

Organ System	Score points				
	0	1	2	3	4
Respiratory (PaO_2/FiO_2)	> 300	226-300	151-225	76-150	≤ 75
Renal (Serum Creatinine) (μmol/l)	≤ 100	101-200	201-350	351-500	> 500
Hepatic (Serum Bilirubin) (μmol/l)	≤ 20	21-60	61-120	121-240	> 240
Cardiovascular (PAR) (HRxCVP/MAD)	≤ 10.0	10.1-15.0	15.1-20.0	20.1-30.0	> 30
Hematologic (Platelet count) (ml x 10^3)	> 120	81-120	51-80	21-50	≤ 20
Neurologic (Glasgow Coma Scale)	15	13-14	10-12	7-9	≤ 6

The pressure adjusted heart rate (PAR) is calculated as the product of heart rate (HR) multiplied by the ratio of the central venous pressure (CVP) to the mean arterial pressure (MAD).The Glasgow Coma Scale is preferably calculated by the patients nurse, and is scored conservatively (for a patient receiving sedation or muscle relaxants, normal function is assumed, unless there is evidence of intrinsically altered mentation).
(From: Marshall JC, Cook DJ, Christou NV, Bernard GR, Sprung CL, Sibbald WJ. Multiple organ dysfunction score: a reliable descriptor of a complex clinical outcome. Crit Care Med 1995;23(10):1638-52)

Variable	Admission n=33			Pre- Hysterectomy n=33			Post Hysterectomy n=33			P-value
	0	1	Unknown	0	1	Unknown	0	1	Unknown	
Respiration >22 n=26	16	8	2	11	12	4	21	1	4	0.005
sBP <100mmHg n=26	3	21	2	17	4	5	18	2	6	0.0001
Altered GCS n=26	24	1	1	22	2	2	16	7	3	0.06

Table 6 B: Comparison of MODS and SOFA score

Variable	MODS Median (range) n=33				SOFA Median (range) n=33			
	Admission	**Pre-hysterectomy**	**Post-hysterectomy**	**P value[c]**	**Admission**	**Pre-hysterectomy**	**Post-hysterectomy**	**P-value [d]**
Respiration n=22	394 (187-747)	368 (187-600)	255 (103-474)	0.001	402 (187-747)	368 (187-600)	255 (103-474)	0.001
Coagulation n=27	237 (87-570)	311 (98-526)	266 (19-624)	0.001	237 (87-570)	311 (98-526)	266 (19-624)	0.001
Liver bilirubin n=27	5 (2-34)	6 (3-92)	6 (3-85)	0.007	5 (2-34)	6 (3-92)	6 (3-85)	0.007

[c] P-value for Wilk's Lambda statistic obtained from the multivariate analysis of variance (manova).
[d] P-value for Wilk's Lambda statistic obtained from the multivariate analysis of variance (manova).

Cardiovascular (MAP) /Hypotension n=27	91 (57-172)	86 (48-116)	90 (76-118)	0.001	91 (57-172)	86 (48-116)	90 (76-118)	0.001
CNS-GCS n=25	15 (2-15)	15 (10-15)	15 (2-15)	0.01	15 (2-15)	15 (10-15)	15 (2-15)	0.01
Renal-creatinine n=29	76 (22-399)	73 (43-7320	71 (38-819)	0.001	76 (22-399)	73 (43-732)	71 (38-819	0.001

Reference:

1. **SOFA score[16]**

SOFA score	0	1	2	3	4
Respiration					
PaO_2/FIO_2 (mmHg) (kPa)	> 400 > 5.3)	301–400 (4.1–5.3)	201–300 (2.8–4.0)	101–200 (1.4–2.7)	≤ 100 ≤ 1.3)
Coagulation					
Platelets ($x10^3/mm^3$)	> 150	101–150	51–100	21–50	≤ 20
Liver					
Bilirubin (mg/dl) (μmol/l)	< 1.2 < 20)	1.2–1.9 (20–32)	2.0–5.9 (33–101)	6.0–11.9 (102–204)	≥ 12.0 ≥ 204)
Cardiovascular					
Hypotension	No hypotension	MAP < 70 mmHg	Dopamine ≤ 5 or dobutamine (any dose)*	Dopamine > 5	Dopamine > 15
Central nervous system					
Glasgow coma score	15	13–14	10–12	6–9	< 6
Renal					
Creatinine (mg/dl) (μmol/l) or urine output	< 1.2 < 110)	1.2–1.9 (110–170)	2.0–3.4 (171–299)	3.5–4.9 (300–440) < 500 ml/day	> 5.0 > 440) < 200 ml/day

* adrenergic agents administered for at least 1 h (doses given are in μg/kg/min)

2. **qSOFA[1]**

Table 3 Quick sepsis-related organ failure assessment score (qSOFA)[a]

Assessment	qSOFA score
Tachypnea: (≥22 breaths/min)	1
Hypotension: (SBP ≤100 mmHg)	1
Altered mentation: (GCS <15)	1

SBP: systolic blood pressure; GCS: Glasgow Coma Scale.
[a]Adapted from Singer et al.[22]

3. MODS[16]

The Multiple Organ Dysfunction Score (MODS)

Organ System	Score points				
	0	1	2	3	4
Respiratory (PaO_2/FiO_2)	> 300	226-300	151-225	76-150	≤ 75
Renal (Serum Creatinine) (μmol/l)	≤ 100	101-200	201-350	351-500	> 500
Hepatic (Serum Bilirubin) (μmol/l)	≤ 20	21-60	61-120	121-240	> 240
Cardiovascular (PAR) (HRxCVP/MAD)	≤ 10.0	10.1-15.0	15.1-20.0	20.1-30.0	> 30
Hematologic (Platelet count) (ml x 10^3)	> 120	81-120	51-80	21-50	≤ 20
Neurologic (Glasgow Coma Scale)	15	13-14	10-12	7-9	≤ 6

The pressure adjusted heart rate (PAR) is calculated as the product of heart rate (HR) multiplied by the ratio of the central venous pressure (CVP) to the mean arterial pressure (MAD).The Glasgow Coma Scale is preferably calculated by the patients nurse, and is scored conservatively (for a patient receiving sedation or muscle relaxants, normal function is assumed, unless there is evidence of intrinsically altered mentation).
(From: Marshall JC, Cook DJ, Christou NV, Bernard GR, Sprung CL, Sibbald WJ. Multiple organ dysfunction score: a reliable descriptor of a complex clinical outcome. Crit Care Med 1995;23(10):1638-52)

Table 7 Intra-operative findings of exploratory laparotomies

Finding		1st Laparotomy No (%)	2nd Laparotomy No (%)	
		%	**%**	**P-value[5]**
Peritoneal pus n=13	Localized to pelvis	4 (31)	1 (8)	0.67
	Four quadrant sepsis	3 (23)	0 (0)	
	Other[6]	1 (8)	1 (8)	
Serous collection n=21		13 (62)	8 (38)	0.52
Uterine scar n=22	Healthy	5 (23)	1 (5)	0.99
	Necrotic	11 (50)	3 (14)	
	Other[7]	1 (5)	0 (0)	
Uterus n=25	Healthy	8 (32)	1 (4)	0.26
	Necrotic	3 (12)	2 (8)	
	Atonic	10 (40)	1 (4)	

NB: Only 2 patients had a 3rd laparotomy, due to the small numbers these have been excluded from the Fischer's exact test

[5] P-value from Fischers exact test
[6] Other: Pus in the myometrium
[7] Other: bleeding

Table 8 Description of other sources of sepsis

Other source of sepsis	No (%) n=33
Bacteremia	3 (9)
Respiratory tract infection	4 (12)

Table 9 Comparison intra-operative findings to the histological and microbiological findings

Variable	Intra-operative findings n=27		Histological findings n=32		P value[8]
	n	%	n	%	
Presence of pus	12	44	17	53	0.001
Assessment of the uterus- necrosis	8	30	23	72	0.004

[8] P-value obtained from Fischers Exact test

Table 10 Histological findings of the uterus to ascertain the presence or absence of sepsis

Histological finding	No (%) n=33
Inflamed endometrium	2 (6)
Myometrial ischaemia	1 (3)
Puerperal sepsis reported	28 (85)
No puerperal sepsis reported	1 (3)
Unknown[9]	1 (3)

[9] Unknown: Specimen submitted but not reported on due to a laboratory related issue

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Appendix A: Approved Research Protocol

UNIVERSITY OF THE WITWATERSRAND

FACULTY OF HEALTH SCIENCES

A RETROSPECTIVE STUDY ON THE OUTCOMES OF PERIPARTUM HYSTERECTOMIES FOR PUERPERAL SEPSIS AT CHRIS HANI BARAGWANATH ACADEMIC HOSPITAL

PROTOCOL

CANDIDATE: DR ESTHER OLUSOLA

SUPERVISOR: DR POOVANGELA NAIDOO

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Introduction

Chris Hani Baragwanath Academic Hospital is the third largest hospital in the world. It is one of the teaching hospitals for the University of the Witwatersrand medical school. Each year approximately 20000 deliveries occur in their facility of which 45.5% are by caesarean section. The World Health Organization and other research institutions, have highlighted that sepsis during pregnancy and in the puerperal phase is one of the leading causes of maternal morbidity and mortality world wide (1). In the developed countries, sepsis related deaths account for 5% of maternal deaths, while in the developing countries 11% (1). Sepsis is defined as a life-threatening organ dysfunction caused by a dysregulation in the hosts response to infection. Septic shock is defined as sepsis with persistent hypotension that requires the use of vasopressors in order to maintain a mean arterial pressure (MAP) of more than or equal to 65, as well as a serum lactate level of more than 2 (1).

The World Health Organization defines maternal peripartum infection as any bacterial infection of the genital tract and its surrounding tissues at any time from the onset of labour or rupture of membranes until the 42nd day postpartum. It must include two or more of the following signs and symptoms: fever, abnormal vaginal discharge, pelvic pain, offensive discharge or a delay in involution of the uterus (2). The aforementioned definition has been modified to include procedures and conditions in relation to childbirth (2).

The main objective in the treatment of infection is to obtain source control. In the majority of cases a hysterectomy is required. In our institution, the current

criteria to perform a hysterectomy for puerperal sepsis are signs and symptoms of sepsis and the presence of a necrotic cervix, and/or pus draining from cervix and/ or two or more organ dysfunctions if the patient is unresponsive to antibiotic therapy.

Abbreviations

GCS- Glasgow Coma Scale

ICU- Intensive Care Unit

MODS- Multiple Organ Dysfunction Score

PTD- Preterm Delivery

PROM- Prelabour Rupture of Membranes

PPROM- Preterm Prelabour Rupture of membranes

SOFA- Sequential Organ Failure Assessment

qSOFA- Quick Sequential Organ Failure Assessment

UTI- Urinary Tract Infection

LITERATURE REVIEW

The rate of puerperal sepsis worldwide has increased with the majority of cases found to be in developing countries. According to the *Saving Mothers Report* 2014-2016 non pregnancy related infections are the leading cause of maternal mortality in South Africa (3). The fifth most common cause of all South African maternal deaths is pregnancy related sepsis (3). Puerperal sepsis is defined as an infection of the genital tract that occurs from the onset of the rupture of membranes up until the 42nd day post-delivery of which the following features should be present: fever, pelvic pain, offensive discharge or a delay in involution of the uterus. This definition however limited infection to the puerperium which excluded extragenital infections that contributed to sepsis such as the urinary tract or the breasts. Therefore, a new definition has been proposed “maternal peripartum infection” which builds on the previous definition but takes into consideration infections related to childbirth procedures and conditions (4).

Scoring systems

There are a number of scoring systems used to assess the severity of sepsis. The Sequential Organ Failure Assessment (SOFA) score is a system used to assess the severity of organ dysfunction. It uses 6 parameters namely respiration, coagulation, bilirubin level, hypotension, Glasgow coma scale and level of creatinine or the amount of urine output in order to assess the severity of organ dysfunction (1). The SOFA score when measured serially it can be used to identify patients who are at a higher risk of death (1). It is mainly used in an Intensive Care Unit (ICU) and therefore the quick SOFA (qSOFA) assessment was developed for its simplicity as no laboratory results are

required. An additional advantage of using the qSOFA scoring system enables clinicians to recognize sepsis earlier. It is scored out of 3, in comparison to 24 in the SOFA scoring system. The presence of 2 or 3 qSOFA points is indicative of an increased risk of death or possibly prolonged ICU admission (1). The three parameters used in the qSOFA system are tachypnoea, respiratory rate of 22 or more breaths per minute, hypotension with a systolic blood pressure of 100mmHg or less and an altered level of consciousness. A third scoring system to consider is the Multiple Organ Dysfunction Score (MODS), which uses the same parameters as the SOFA score however it has minor differences in the cut-off ranges and does not take into account diuresis when reassessing the creatinine levels in the renal system nor the ventilatory support in the respiratory system. The MODS and the SOFA score have both been noted to be reliable in predicting the outcome of critically ill patients (5). [Appendix 1]

Mortality rates

According to the Saving Mothers 2014-2016 report there has been a 12.5% reduction in maternal deaths (3). The institutional maternal mortality ratio was three times higher in caesarean section deliveries in comparison to vaginal deliveries (6). The number of women who died from pregnancy related sepsis accounted for 5.4% of the overall maternal deaths (6). Of the maternal deaths during this triennial report 46.7 % of woman had puerperal sepsis after normal vaginal delivery in comparison to 42.2% who had puerperal sepsis after a caesarean section (6). Delays in accessing healthcare is one of the major contributing patient factors (6). It was also noted that a lack of knowledge and skills was thought to be a contributory factor to the maternal deaths, as

clinicians underestimated or inadequately treated pregnancy related sepsis (6). Women aged 45 years and older had the highest number of maternal deaths due to pregnancy related sepsis (6).

A retrospective study conducted in Cape Town revealed that the mortality rate for pregnancy related sepsis was 5.2% (6). In comparison to the United States of America, two studies in Africa revealed that 19% of cases were found to have sepsis related deaths as oppose to 12%. Studies conducted in the United Kingdom have also noticed an increase in the puerperal sepsis related mortality from 0.85 per 100 000 maternity cases to 1.13 over a 4 year period (7). Another 4 year study that was conducted in Uganda revealed that puerperal sepsis accounted for 30.9% of maternal deaths in their hospital (8).

Risk factors

A number of risk factors that have been identified in maternal sepsis. Patient risk factors include asymptomatic bacteriuria, sexually transmitted diseases, maternal age of 35 years old and older, presence of co-morbidities as well as obesity (1). The source of infection or sepsis can be divided into obstetric and non-obstetric causes. In the antepartum period, septic abortions and chorioamnionitis were the most common sources of obstetric related infection in comparison to endometritis and wound infection in the postpartum period (9). The non-obstetric sources of infection in both the antepartum and postpartum period were urinary tract and respiratory tract infections (4). Appendicitis was the third most common cause of non-obstetric related sepsis in the antenatal period and gastrointestinal infections in the postpartum period

(4). A study conducted in New Zealand revealed that 30% of cases had no identifiable source of infection (4).

Other factors have been stipulated as potential risk factors for puerperal sepsis namely chorioamnionitis, caesarean sections, post-partum hemorrhage, pre-term deliveries and patients with co-morbid disease such as diabetes and eclampsia (10). A study conducted in the United States of America noted that there were less sepsis related deaths due to chorioamnionitis, the proposed theory behind this finding was due to chorioamnionitis being a clinical diagnosis and therefore diagnosed and managed earlier.

Caesarean sections were found to be a major contributing factor to the development of puerperal sepsis with a three-fold increase in the sepsis mortality rate (10). The increased rate of puerperal sepsis has been noticed to have increased with the increased rate of caesarean sections performed. In high income countries, the rate of caesarean sections have increased from 14.3% to 42.7% (11). In low income countries the rate of caesarean sections have increased from 2% to 19% (12). A study conducted in Boston found that there was a 7.4% rate of puerperal sepsis post caesarean section in comparison to a 5.4% rate post normal vaginal delivery (13). Similarly in the Netherlands, a nationwide cohort study was conducted and revealed that 42.9% of woman who developed puerperal sepsis had a caesarean section as the mode of delivery (13). In comparison, a study conducted in Pakistan reported that of the woman who presented with puerperal sepsis, only 10.8% of them had undergone a caesarean section (14). They noted that the mode of

delivery does not affect the rate of sepsis provided that adequate aseptic techniques are adhered to, and that the circumstances that lead to a patient undergoing a caesarean section likely increased the risk of sepsis (14).

With regards to preterm delivery there was a 2.4-2.7 fold risk of sepsis in comparison to a term delivery (7). It should be noted that other risk factors were identified such as race- with black African women were at higher risk due to poor access to health care in comparison to other racial groups, poor socio-economic status, and maternal age of less than 25 that also contribute to the increased incidence of puerperal sepsis (10). Factors that predispose women in low-socioeconomic regions to sepsis are anaemia, poor nutrition and prolonged labour which is most prevalent in primigravida women. A study conducted in Nigeria noted that of the patients that presented with sepsis, 69.2% were anaemic, 65.7% had a prolonged labour of more than 12 hours and 31.5% of these patients had premature rupture of membranes (13).

Organisms identified in puerperal sepsis

The most common organism that has been identified to be responsible for puerperal sepsis is Group A Streptococcus. Other organisms identified include Group B streptococcus, Listeria monocytogenes, Escherichia coli (E. coli) and Staphylococcus aureus, Gram-negative and anaerobic organisms (8, 4). The main source of infection was isolated from the genital tract followed by the urinary tract (7,15). One study showed that E. coli was the predominant pathogen found in all 3 stages of pregnancy, accounting for 37% of all the maternal sepsis cases. However, in the intrapartum period Group B Streptococcus was the predominant pathogen identified. Group B

streptococcus was isolated in 43% of cases in the intrapartum period in comparison to only 22% of cases where E. coli was isolated during this same period (7). One study conducted in the Western Cape isolated Acinetobacter baumanni in 22% of their cases of puerperal sepsis (16).

Antibiotic usage

The first line treatment of pregnancy related sepsis should always be broad and based on institutional guidelines until a source is known and targeted therapy can be used (1). This places emphasis on knowing the organisms that commonly cause infection in a specific institution. Targeted antibiotic therapy is imperative to avoid resistance of organisms to antibiotics.

A study conducted over an 8-year period revealed that 58% of E. coli isolated from cultures were resistant to amoxicillin, 15% to amoxicillin/clavulanic acid, 2.1% to piperacillin-tazobactam 2.1% and 1% to gentamycin. With regards to Group B streptococcus 11% of isolates were resistant to clindamycin, the remainder of the isolates were all susceptible to vancomycin and penicillin (7). Pathogen identification is important for clinicians to treat their patients with the appropriate antibiotic. In New Zealand, the current broad-spectrum antibiotics of choice for both chorioamnionitis and endometritis is ampicillin, gentamycin and either metronidazole or clindamycin. For urinary tract infections ampicillin and gentamycin are used (4). In the literature reviewed majority of the evidence aimed to reduce the risk of developing sepsis and for further guidelines to be made regarding the use of prophylactic antibiotics. In the study conducted in Uganda, access to antibiotics is often limited therefore putting their patients in a disadvantaged position where prophylactic and

possibly targeted therapy antibiotics could decrease the rate of postpartum hysterectomies (8).

The current first line of antibiotic treatment for our institution is ampicillin, gentamycin and metronidazole. If there has been no clinical improvement after 72 – 96 hours, the patients are upscaled to second line treatment: clindamycin and ceftriaxone.

Morbidity

Significant morbidity was found to be associated with maternal sepsis which was related to patients needing further specialized care (7). The minimum duration of stay in hospital for severely septic patients was 5 days. In this study severe sepsis was defined as patients who had other acute co-morbidities and required intensive care management (17). A study conducted in the Netherlands showed that 56% of women with sepsis were admitted to the intensive care unit (15). In patients that had undergone peripartum hysterectomies, if their markers of severity were increased post procedure there was an increased risk of maternal death (18).

It was mentioned that hysterectomies were performed in order to treat sepsis however few evidence was documented as to the outcome of the patients post hysterectomy (19). A study conducted in the Eastern Cape reported that over a two-year period 63 hysterectomies were performed of which 27% of them were due to puerperal sepsis. The patients who had a relook laparotomy accounted for 15.9% of the study group and the overall mortality rate was 19%, however, it was unclear as to what the main cause of death was (20). Majority of the literature stated that the haemorrhage secondary to uterine atony and

placenta previa spectrum disorders were the leading cause for peripartum or postpartum hysterectomies (21,22). A retrospective study conducted in Lagos, Nigeria showed that even though peripartum hysterectomies were primarily performed for uterine rupture (53.5% of cases), placenta previa spectrum disorders and puerperal sepsis (1.7%) early intervention decreased the overall morbidity and mortality of their patients (18).

Complications

The post-operative complications of peripartum and postpartum hysterectomies that were identified were: intra-operative and or post-operative haemorrhage, wound sepsis, relook laparotomy, bladder injuries, vesico-vaginal fistulas, blood transfusions, deep vein thrombosis, unilateral or bilateral salpingo-oophrectomies and death (20,21). Only two South African studies mentioned the emotional complications of peripartum and postpartum hysterectomies in the women involved, the main concern for future desired fertility, socio cultural beliefs and amenorrhea (16,20).

One study that was conducted in the Western Cape had further information regarding their hysterectomies for puerperal sepsis, the histopathology results for the specimens taken confirmed sepsis in 88.8% of their patients (16).

Cumulatively, the aforementioned results support the need for further research and investigation as to the causative organism and treatment of puerperal sepsis in our population. This will then potentially enable our institution to adequately treat our patients more conservatively and possibly reduce the overall morbidity and mortality rate of puerperal sepsis.

STUDY AIM

To describe the patient demographics, surgical characteristics and organ dysfunction scoring systems in women who had a hysterectomy as a measure of source control in the treatment of puerperal sepsis.

RESEARCH OBJECTIVES

1. To describe the following
    - The number of women who had hysterectomies for puerperal sepsis
    - The most common organism/organisms identified
    - The antibiogram of the above organisms
2. To describe the differences between the MODS, SOFA and qSOFA score in women who had hysterectomies.
3. To describe the findings of relook laparotomies with respect to the following
    - Pus
    - Serous collection
    - State of uterine scar
    - Description of the uterus
    - Other sources of sepsis
4. Compare histological and microbiological findings with the surgeons description of the following
    - Presence of pus
    - Subjective assessment of the uterus
5. Description of the histological findings of the uterus to ascertain the presence or absence of sepsis.

METHODOLOGY

Study setting

This will be a retrospective review of hospital records of patients at the Chris Hani Baragwanath Hospital situated in Soweto, Johannesburg, that were found to have puerperal sepsis. This hospital is one of the academic hospitals under the University of Witwatersrand used in the training of various medical staff.

Patients are either referred to our institution from the local clinic or are self-referred. On arrival they are assessed by the nursing staff and then assessed by the junior medical officers and subsequently the registrars according to our institutions guidelines and depending on the severity of their condition, they are either admitted to our infectious disease ward or to our maternity high care unit.

Study population

The study population comprises of all patients that delivered either by normal vaginal delivery or by caesarean section and required a relook laparotomy up until 6 weeks post-delivery at Chris Hani Baragwanath Hospital between 01 January 2019 and 31 December 2019 for puerperal sepsis.

Study design

The study design will be a cross sectional retrospective study requiring analysis of medical records of the patients who underwent a relook laparotomy and subsequently a hysterectomy for puerperal sepsis.

Sample size

The sample size of approximately 50-100 patients will be used to conduct this research.

Inclusion criteria

1. The records of all women who had puerperal sepsis and a hysterectomy
2. All women whose histology reflected endometritis

Exclusion criteria

1. All hysterectomies in women who had a miscarriage (any pregnancy in which the gestational age was less than or equal to 24 weeks gestation)

Data Collection

All registers in theatre will be surveyed for women who had a laparotomy and/or hysterectomy for puerperal sepsis. The data from medical records of women who had a hysterectomy for puerperal sepsis will be obtained from the records department. The histology reports of all women who had a hysterectomy will be reviewed and the data pertaining to all women who had endometritis will be included. Specimen analysis using the National Health Laboratories System to obtain blood, culture and histology results.

DATA ANALYSIS

The data will be analyzed with the aid of a statistician. Descriptive statistics using tables and diagrams to compare the various outcomes. The use of parametric or non parametric tests will be determined by distribution of data obtained.

ETHICS

This study will begin once approval for this research has been obtained from the Human Research and Ethics committee at the University of the Witwatersrand. Each patient in this study will be allocated a study number in order to protect their identities.

PROJECT TIMELINE

Once approval has been obtained from the faculty and ethics committee, the aim is to begin data collection between September and October 2020 and hopefully complete the research project by April 2021.

	Feb	Mar	Apr	May	Jun	Jul	Aug	Sept	Oct	Nov	Dec	Jan	Feb	Mar	Apr
Literature review	**X**														
Preparing Protocol		**X**	**X**	**X**											
Protocol assessment					**X**										
Ethics application							**X**	**X**							
Data collection									**X**	**X**					
Data Analysis											**X**	**X**			
Write up-Thesis													**X**	**X**	

Write up- Paper															**X**

FUNDING

This research project will be funded by the researcher. Anticipated costs will include paper, pen and mobile data to look up the results.

LIMITATIONS

The foreseeable limitations include that this is a retrospective study therefore finding enough files and information required may be challenging.

Appendix 1:

1. SOFA score (5)

SOFA score	0	1	2	3	4
Respiration					
PaO_2/FIO_2 (mmHg) (kPa)	> 400 (> 5.3)	301–400 (4.1–5.3)	201–300 (2.8–4.0)	101–200 (1.4–2.7)	≤ 100 (≤ 1.3)
Coagulation					
Platelets ($x10^3/mm^3$)	> 150	101–150	51–100	21–50	≤ 20
Liver					
Bilirubin (mg/dl) (μmol/l)	< 1.2 (< 20)	1.2–1.9 (20–32)	2.0–5.9 (33–101)	6.0–11.9 (102–204)	≥ 12.0 (≥ 204)
Cardiovascular					
Hypotension	No hypotension	MAP < 70 mmHg	Dopamine ≤ 5 or dobutamine (any dose)*	Dopamine > 5	Dopamine > 15
Central nervous system					
Glasgow coma score	15	13–14	10–12	6–9	< 6
Renal					
Creatinine (mg/dl) (μmol/l) or urine output	< 1.2 (< 110)	1.2–1.9 (110–170)	2.0–3.4 (171–299)	3.5–4.9 (300–440) < 500 ml/day	> 5.0 (> 440) < 200 ml/day

* adrenergic agents administered for at least 1 h (doses given are in μg/kg/min)

2. qSOFA (1)

Table 3 Quick sepsis-related organ failure assessment score (qSOFA)[a]

Assessment	qSOFA score
Tachypnea: (≥22 breaths/min)	1
Hypotension: (SBP ≤100 mmHg)	1
Altered mentation: (GCS <15)	1

SBP: systolic blood pressure; GCS: Glasgow Coma Scale.
[a]Adapted from Singer et al.[22]

3. MODS (3)

The Multiple Organ Dysfunction Score (MODS)

Organ System	Score points				
	0	1	2	3	4
Respiratory (PaO_2/FiO_2)	> 300	226-300	151-225	76-150	≤ 75
Renal (Serum Creatinine) (µmol/l)	≤ 100	101-200	201-350	351-500	> 500
Hepatic (Serum Bilirubin) (µmol/l)	≤ 20	21-60	61-120	121-240	> 240
Cardiovascular (PAR) (HRxCVP/MAD)	≤ 10.0	10.1-15.0	15.1-20.0	20.1-30.0	> 30
Hematologic (Platelet count) (ml x 10^3)	> 120	81-120	51-80	21-50	≤ 20
Neurologic (Glasgow Coma Scale)	15	13-14	10-12	7-9	≤ 6

The pressure adjusted heart rate (PAR) is calculated as the product of heart rate (HR) multiplied by the ratio of the central venous pressure (CVP) to the mean arterial pressure (MAD).The Glasgow Coma Scale is preferably calculated by the patients nurse, and is scored conservatively (for a patient receiving sedation or muscle relaxants, normal function is assumed, unless there is evidence of intrinsically altered mentation).
(From: Marshall JC, Cook DJ, Christou NV, Bernard GR, Sprung CL, Sibbald WJ. Multiple organ dysfunction score: a reliable descriptor of a complex clinical outcome. Crit Care Med 1995;23(10):1638-52)

Appendix B: Data Collection Sheet

Study Number		
Age		
Parity		
Gravity		
Gestational age at delivery		
Weight		
Race	African	1
	Caucasian	2
	Coloured	3
	Indian	4

Co-morbidity	
Chronic hypertension	1
Pre-eclampsia	2
Cardiac disease	3
Diabetes Mellitus	4
HIV/AIDS	5
Epilepsy	6
Asthma	7
Other	8

Antenatal	Booking gestation				
	Booking bloods	Rh	Pos- 1		
			Neg-2		
		RPR	Pos- 1		
			Neg-2		
		RVD	Pos- 1	If reactive: CD4 count	
			Neg-2	ARV	Y- 1
					N-2
	Number of ANC visits				
	Prenatal infections	Y- 1		Urinary tract	1
		N-2		Respiratory tract	2
				Central nervous system	3
				Other	4

Ultrasound				
	Early	Y- 1	Gestational age	
		N-2		
	Late	Y- 1	Gestational age	
		N-2		

Delivery				
Gestation at delivery				
Caeserean section	1	Duration	0-30min	1
			30-60min	2
			>60min	3
		Indication	Fetal distress	1
			Poor progress	2
			HELLP Syndrome	3
			Prev c/s in labour	4
			Other	5
NVD	2			
Assisted Delivery	3	Forceps	1	
		Vacuum	2	
		Episiotomy	3	

Labour complications					
Prolonged rupture of membranes	1	Y-1	If prolonged	Antibiotic use	Y-1
		N-2			N-2
Multiple per vaginal examinations	2	Y-1	If yes	0-5	1
		N-2		5-10pv	2
				>10	3
Prophylactic Antibiotics	3	Y-1	If yes	Azithromycin	1
		N-2		Ampicillin	2
				Metronidazole	3
				Gentamycin	4
Meconium stained liquor	4	Y-1	If yes	Grade 1 (Aparticulate)	1
		N-2		Grade 2	2
				Grade 3 (Particulate)	3
Post-partum haemorrhage	3	Y-1	If yes	Atonic uterus	1
		N-2		Retained products	2
				Tears/lacerations	3
				Uterine rupture	4

Investigations		
Blood Pressure	Systolic:	Diastolic:
Heart Rate		
Respiratory rate		
Temperature- Value:	Pyrexial	1
	Apyrexial	2
	Not documented	3
Oxygen Saturation		
Bloods	White Cell count	
	Haemoglobin	
	Platelet	
	C-reactive protein	
	Procalcitonin	
	BD Glucan	
Ultrasound	NAD	1
	Free fluid seen	2
Chest X-ray	NAD	1
	Infiltrates	2
	Pleural effusion	3

qSOFA Score			
-	Patient Value	0	1
Tachypnea (breaths/min)		≤21	≥22
Hypotension (mmHg)		≥101	≤100
Altered mentation		15	<15

SOFA Score						
	Patient value	0	1	2	3	4
Respiration PaO2/FiO2 (mmHg)		>400	301-400	201-300	101-200	≤100
Coagulation (Platelets) ($x10^3/mm^3$)		>150	101-150	51-100	21-50	≤20
Liver (Bilirubin) (µmol/l)		<20	20-32	33-101	102-204	≥204
Cardiovascular (hypotension)		No hypotension	MAP<70 mmHg	Dopamine ≤5	Dopamine >5	Dopamine >15
Central nervous system (GCS)		15	13–14	10 –12	6– 9	<6
Renal (Creatinine)(µmol/l)		<110	110-170	171-299	300-440	>440

Organ System	0	1	2	3	4
Respiratory (PaO2/Fi02)	>300	226-300	151-225	76-150	≤75
Renal (Serum creatinine µmol/l)	≤100	101-200	201-350	351-500	>500
Hepatic (serum bilirubin µmol/l)	≤20	21-60	61-120	121-240	>240
Cardiovascular (MAP)	≤65	60-64	55-59	50-54	<50
Haematologic (Platelet count ml x 10^3)	>120	81-120	51-80	21-50	≤20
Neurological (Glasgow Coma Scale)	15	13-14	10_-12	7_-9	≤6

Scoring systems	Admission	Pre-Hysterectomy (before surgery)	48hrs Post Hysterectomy
SOFA score			
qSOFA			
MODS			

Indication for surgery						
Clinical suspicion/sonar	1					
Necrotic cervix	2	Y-1				
		N-2				
Pus draining from cervix	3	Y-1				
		N-2				
Organ dysfunction	4	Y-1	Renal	1	Urea	
		N-2			Creatinine	
			Haematological	2	HB	
					Platelets	
			Liver function	3	Albumin	
					LDH	
					INR	
					PTT	
					TB	
			CNS	4	GCS	

Culture	Blood	1	1- Positive	Gram positive	1- Positive
			2- Negative		2- Negative
				Gram negative	1- Positive
					2- Negative
				Parasites	1- Positive
					2- Negative
				Anaerobes	1- Positive
					2- Negative
	Urine	2	1- Positive	Gram positive	1- Positive
			2- Negative		2- Negative
				Gram negative	1- Positive
					2- Negative
				Parasites	1- Positive
					2- Negative
				Anaerobes	1- Positive
					2- Negative
	Sputum	3	1- Positive	Gram positive	1- Positive
			2- Negative		2- Negative
				Gram negative	1- Positive
					2- Negative
				Parasites	1- Positive
					2- Negative
				Anaerobes	1- Positive
					2- Negative
				GXP	1- Positive
					2- Negative
	Fluid	4	1- Positive	Gram positive	1- Positive
			2- Negative		2- Negative
				Gram negative	1- Positive
					2- Negative
				Parasites	1- Positive
					2- Negative
				Anaerobes	1- Positive
					2- Negative
				GXP	1- Positive
					2- Negative

Organisms cultured	Ampicillin	Gentamycin	Augmentin	Vancomycin	Clindamycin	Ceftriaxone	Tazobactam	Cloxacillin	Ceftazidime
Group A Streptococcus									
Group B Streptococcus									
Escherichia coli									
Staphylococcus aureus									
Acintobacter baumanni									
Enterococcus faecalis									
Other:									

Surgical intervention		**Intraoperative findings**								
1st Laparotomy	1									
		Pus	1	1- Positive	If positive	Localized to pelvis	1			
				2- Negative		4 Quadrant pus	2			
						Other	3			
		Serous fluid	2	1- Positive						
				2- Negative						
		State of uterine scar	3	Healthy	1					
				Necrotic	2		Scar excised	Y-1		
				Other	3			N-2		
		State of uterus	4	Healthy (Pink and blanching)	1					
				Atonic	2					
				Necrotic	3		Hysterectomy performed	Y-1	TAH	1
								N-2	STAH	2
							Washout	Y-1		
								N-2		
Relook Laparotomy	2	Pus	1	1- Positive	If positive	Localized to pelvis	1			
				2- Negative		4 Quadrant pus	2			
						Other	3			
		Serous fluid	2	1- Positive						
				2- Negative						
		State of uterine scar	3	Healthy	1					
				Necrotic	2		Scar excised	Y-1		
				Other	3			N-2		
		State of uterus	4	Healthy (Pink and blanching)	1					
				Atonic	2					
				Necrotic	3		Hysterectomy performed	Y-1	TAH	1
								N-2	STAH	2
							Washout	Y-1		
								N-2		

Outcome Post Hysterectomy						
Source controlled	1	Y-1	If no	Other sources identified	Septicaemia	1
		N-2			Respiratory	2
Improved SOFA score	2	Y-1			CNS	3
		N-2			Urinary	4
Worsened SOFA score	3	Y-1				
		N-2				
Discharged home	4	Y-1				
		N-2				
Demised	5	Y-1		Autopsy results		
		N-2				
Histology results of uterus						
Features suggestive of endometritis						
Necrosis Other:						

Evidence of sepsis comparison		
	Surgeons description	Microbiology
Pus	Y-1	Y-1
	N-2	N-2
Necrotic Uterus	Y-1	Y-1
	N-2	N-2

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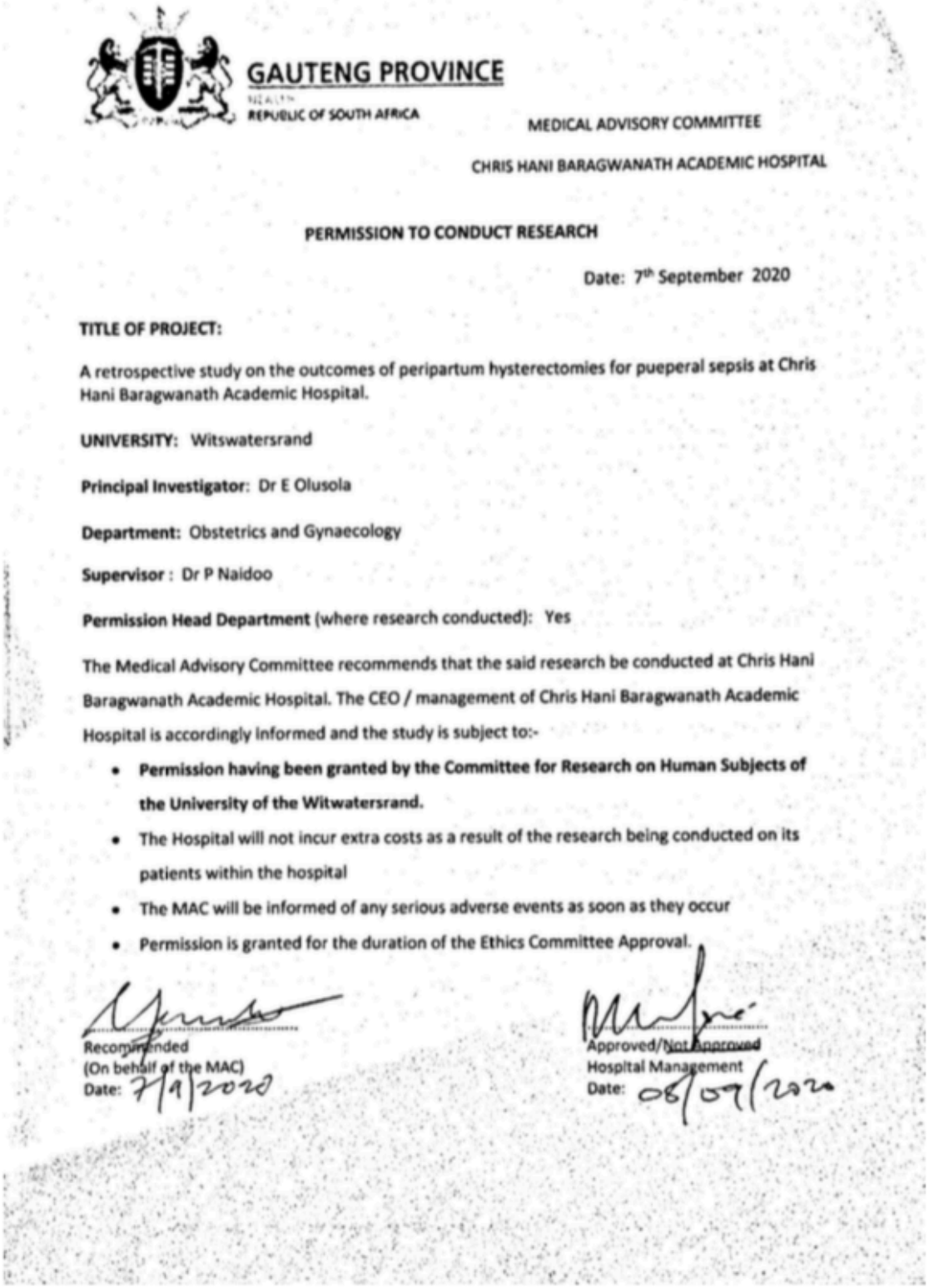
Appendix C: Permission letters to conduct research study



GAUTENG PROVINCE
HEALTH
REPUBLIC OF SOUTH AFRICA

MEDICAL ADVISORY COMMITTEE

CHRIS HANI BARAGWANATH ACADEMIC HOSPITAL

PERMISSION TO CONDUCT RESEARCH

Date: 7th September 2020

TITLE OF PROJECT:

A retrospective study on the outcomes of peripartum hysterectomies for pueperal sepsis at Chris Hani Baragwanath Academic Hospital.

UNIVERSITY: Witswatersrand

Principal Investigator: Dr E Olusola

Department: Obstetrics and Gynaecology

Supervisor : Dr P Naidoo

Permission Head Department (where research conducted): Yes

The Medical Advisory Committee recommends that the said research be conducted at Chris Hani Baragwanath Academic Hospital. The CEO / management of Chris Hani Baragwanath Academic Hospital is accordingly informed and the study is subject to:-

- **Permission having been granted by the Committee for Research on Human Subjects of the University of the Witwatersrand.**
- The Hospital will not incur extra costs as a result of the research being conducted on its patients within the hospital
- The MAC will be informed of any serious adverse events as soon as they occur
- Permission is granted for the duration of the Ethics Committee Approval.

Recommended
(On behalf of the MAC)
Date: 7/9/2020

Approved/~~Not Approved~~
Hospital Management
Date: 08/09/2020

NATIONAL HEALTH LABORATORY SERVICE
UNIVERSITY OF THE WITWATERSRAND – JOHANNESBURG

UNIVERSITY OF THE WITWATERSRAND JOHANNESBURG

SCHOOL OF PATHOLOGY
Division of Anatomical Pathology

NATIONAL HEALTH LABORATORY SERVICE

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Faculty of Health Sciences
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Dr Y Perner MBBCh (Witwatersrand) FCPath (SA); MMed (Witwatersrand)

Human Research Ethics Committee (Medical)
University of the Witwatersrand
Johannesburg
20000

November 11, 2020

Re: Consent for access to NHLS database

This letter serves to confirm that the Department of Anatomical Pathology at the University of the Witwatersrand and NHLS is happy to assist Dr Esther Olusola with her study entitled "A retrospective study on the outcomes of peripartum hysterectomies for puerperal sepsis at Chris Hani Baragwanath Hospital".

Publication of such work is encouraged and in the event that the information used comprises the diagnosis only then joint authorship from a member of staff in the Department of Anatomical Pathology would not be expected. However, should additional information be extracted from the report for purposes of further interpretation such as morphological details and immunohistochemical profiles, it would be expected that this would be done in conjunction with a member of staff in the Department of Anatomical Pathology and that joint authorship would follow in resulting publications. Dr Olusola will be in contact with the Department of Anatomical Pathology in respect of this. Dr Lungile Ngobese will collaborate with her on this project.

Dr Olusola will ensure that she registers on the NHLS AARMS system.

Assuring you of the Department of Anatomical Pathology's co-operation in this and future research projects.

With best wishes.

Yours sincerely,

Dr Yvonne Perner
Head: Department of Anatomical Pathology

Appendix D: Ethics certificate

UNIVERSITY OF THE WITWATERSRAND JOHANNESBURG

R49 Dr E Olusola

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
CLEARANCE CERTIFICATE NO. M200979

NAME: (Principal Investigator)	Dr E Olusola
DEPARTMENT:	School of Clinical Medicine Department of Obstetrics and Gynaecology Medical School University
PROJECT TITLE:	A retrospective study on the outcomes of peripartum hysterectomies for puerperal sepsis at Chris Hani Baragwanath Academic Hospital
DATE CONSIDERED:	2 October 2020
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Dr P Naidoo
APPROVED BY:	Dr CB Penny, Chairperson, HREC (Medical)
DATE OF APPROVAL:	4 December 2020

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

DECLARATION OF INVESTIGATORS

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

I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated from the research protocol as approved, I/we undertake to submit details to the Committee. I agree to submit a yearly progress report. When a funder requires annual re-certification, the application date will be one year after the date when the study was initially reviewed. In this case, the study was initially reviewed in **September** and therefore reports and re-certification will be due in the month of **September** each year. Unreported changes to the study may invalidate the clearance given by the HREC (Medical).

Signature of Principal Investigator Date

Appendix E: Guidelines for International Journal of Gynaecology and Obstetrics

5.1. Clinical articles

For information on clinical trials, please also see section **5.1.1. Clinical trials** below.

Observational studies in epidemiology (cohort, case-control, and cross-sectional studies) should follow the STROBE statement and checklist.

Clinical Articles should discuss original research, and must include the following elements:

- **Title**

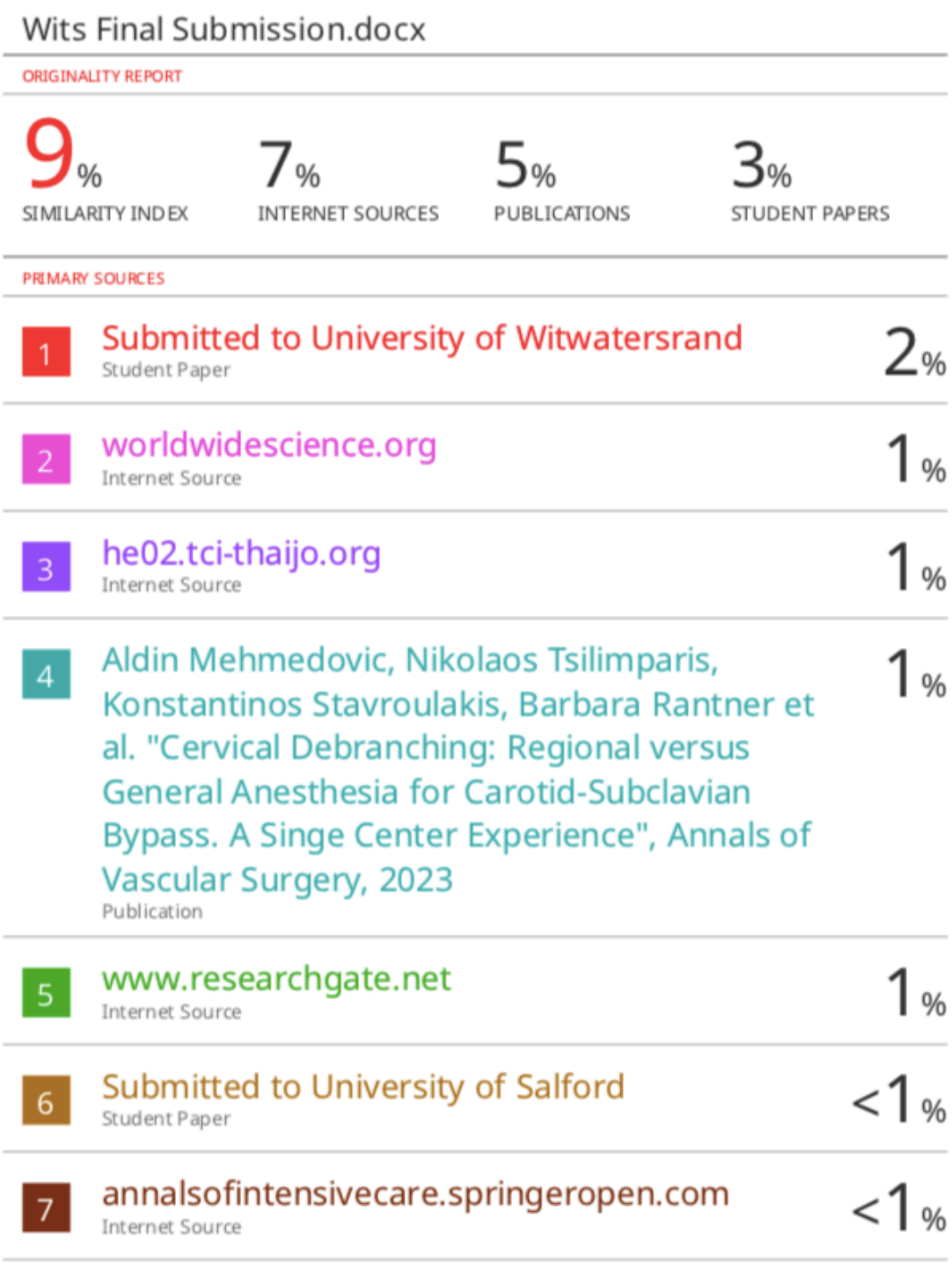
  The title of the manuscript should include the subtitle 'Randomized controlled trial' or 'Clinical trial'.

- **Authors**
  - Primary research studies carried out in **low-/middle-income countries** must have at least one local co-author.
- **Author affiliations**
  - Please list department, institution, city, country only.
- **Corresponding author info**
  - Only one corresponding author should be listed. The corresponding author listed in the manuscript file must match the corresponding author listed in Editorial Manager.
  - Full postal address and email address should be listed.
- **Structured abstract**
  - Headings: Objective; Methods; Results; and Conclusion.
  - Guideline word count: Up to 250 words.
- **Keywords**
  - Guideline: Up to 8 keywords. At least 3 keywords must be included.

- **Synopsis**
  - Brief synopsis of up to 25 words describing the key findings of the study.
- **Main text**
  - Guideline word count: Up to 2500 words
  - Continuous line numbering used throughout
  - Citations: in-text references listed using Arabic numerals in square brackets (e.g. [1,2]), OR using superscript reference indicators (e.g. [1,2]). Do not use parentheses (curved brackets).
  - No footnotes
  - Main headings:
    - *Introduction*
      - Present the background to the study briefly, supported by a limited number of references. State the rationale for the study, and include the study objectives and hypothesis at the end of this section.

- *Materials and methods*
  - State the type of study at the beginning of this section (e.g., retrospective cohort study).
  - Describe concisely the study setting, dates (day, month and year), participants, methods and procedures, and statistical methods. Where appropriate, state the program used for statistical analysis (including model and version number), and the cut-off for statistical significance. This section should include sufficient detail to allow others to replicate the study.
  - For studies of patients, patient records, or volunteers, include a statement of **prospective** local Ethics Committee approval (including full name of Committee).
  - For studies with human participants, include a statement about informed consent. If consent was not needed/obtained, include an explanation. Authors must provide copies of the appropriate documentation if requested.
- *Results*
  - Include the outcome of the study and statistical significance, if appropriate.
  - Tables and figures should be cited here in order, to illustrate the outcomes and supplement the text.
- *Discussion*
  - Discuss the relevance of the results. Compare with previously published studies; discuss strengths and limitations of the study; address any proposals for future research where relevant.
- *Conclusions*
  - Discussion and Conclusions sections may be formatted as one section as preferred.
  - Briefly state the key findings of the study, and major implications for clinical practice/research where relevant.
- **Author contributions:** List each author's role in the design, planning, conduct, data analysis, and manuscript writing. Ensure that all authors meet the **ICMJE criteria for authorship** (anyone who does not fulfil all four criteria should be moved to an Acknowledgments section).
- **Funding:** All sources of funding received for the research, authorship, and/or publication of the article must be listed here. This should match any funding sources listed in Editorial Manager. If no funding was received for the research, state 'None'.
- **Conflict of interest:** List any relationships that may be deemed COIs, or state 'The authors have no conflicts of interest'.
- **References:** See **6.3. References** for reference style. Guideline: up to 25 references.
- **Figures and tables:** See Figures and Tables sections below for further information.

Appendix F: Turn It in Plagiarism Report



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