MATERNAL MORTALITY DUE TO SEPSIS AFTER CAESAREAN SECTION AT CHRIS HANI BARAGWANATH ACADEMIC HOSPITAL FROM 1997 TO 2014

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

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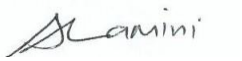
DECLARATION

I, Zandile Barbara Dlamini, declare that this research report is my own work.

It is being submitted to the Faculty of Health Sciences 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 other degree or examination at this or any other University.

14th day of July 2017

Signed 

DEDICATION

I dedicate this research report to my loving and supportive husband, Dr Sifiso Bulunga for his enormous support and encouragement and to my three children Lisa, Asivile, and Zelwande, to my parents for telling me that “hard work pays”.

ABSTRACT

Background

Pregnancy related sepsis is one of the leading direct causes of preventable maternal morbidity and mortality. Evidence shows that caesarean section increases the risk of developing sepsis threefold compared to vaginal deliveries. Maternal death from sepsis after caesarean section can be prevented by proper monitoring of patients from the antenatal period, during labour and delivery and by early recognition and aggressive treatment of puerperal sepsis. This study was conducted to determine the frequency of maternal death from sepsis after caesarean section at Chris Hani Baragwanath Academic Hospital, and to identify associated factors including the role of HIV infection.

Methods

This was a retrospective descriptive study of maternal death due to sepsis after caesarean section at Chris Hani Baragwanath Academic Hospital from January 1997 to December 2014. Maternal death records of women who died of sepsis after caesarean section were obtained from the maternal death data base in the Department of Obstetrics and Gynaecology at the hospital.

Results

There were 108 299 caesarean sections performed during the study period, and 24 women died from sepsis after caesarean section from 1997 to 2014. These deaths made up 3.6% of the 661 maternal deaths at the hospital in this period. Three women presented as referrals, and 21 had their operations done at Chris Hani Baragwanath. The frequency of maternal death from sepsis after caesarean section at the hospital was 0.02% or 19.4/100 000 caesarean sections. The mean age of the women was 28.8 years, with three (12.5%) less than 20 years of age. Twenty women (83.3%) had emergency caesareans. The most common indication for caesarean section was

Prolonged labour (50%). Sixteen (66.7%) women were HIV-infected. Twenty women (83.3%) required surgical intervention for puerperal sepsis after caesarean section.

Conclusion

On average, one to two women die each year at Chris Hani Baragwanath Academic Hospital from puerperal sepsis associated with caesarean section. This study showed that sepsis after caesarean section was more commonly observed with emergency than with elective procedures, and that prolonged labour was the most frequently associated obstetric indication. HIV infected women were more susceptible to death from sepsis after caesarean section, compared with HIV uninfected women. Obstetricians and midwives need to be skilled in the prevention, identification and treatment of life-threatening sepsis after caesarean section.

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LIST OF ABBREVIATIONS

ACOG	American College of Obstetricians and Gynecologists
ANC	Antenatal care
ART	Antiretroviral therapy
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ARDS	Acute respiratory distress syndrome
Bpm	Beats per minute
BP	Blood pressure
CDC	Centre for Disease Control and Prevention
CHBAH	Chris Hani Baragwanath Academic Hospital
CMACE	Centre For Maternal and Child Enquiries Report
CPD	Cephalo pelvic disproportion
CRP	C- Reactive protein
DBP	Diastolic blood pressure
DIC	Disseminated intravascular coagulopathy
FBC	Full blood count
FD	Fetal distress
GAS	Group A Streptococcus
HB	Haemoglobin
ICU	Intensive care unit
IV	Intravenous Infusion
IQR	Interquartile range
MDG	Millennium Development Goals

MMR	Maternal Mortality Ratio
RCOG	Royal College of Obstetricians and Gynaecologists
RPOC	Retained Products of Conception
MAP	Mean arterial pressure
Rpm	Respirations per minute
NICE	National Institute for Health and Care Excellence
NF	Necrotizing fasciitis
UK	United Kingdom
UTI	Urinary tract infection
PPH	Postpartum haemorrhage
PROM	Premature rupture of membranes
PMTCT	Prevention of mother-to-child transmission
SSA	Sub-Saharan Africa
SD	Standard deviation
SSI	Surgical Site Infection
SMR	Saving Mothers Report

DEFINITIONS

Puerperal sepsis is defined as a temperature rise above 38^0c maintained over 24 hours or recurring during the period from the end of the first day to the tenth day after childbirth.

Sepsis is defined as the presence of infection, together with systemic manifestation of infection (systemic inflammatory response syndrome).

Severe sepsis is sepsis complicated by organ dysfunction and/or tissue hypoperfusion.

Maternal death is defined as the death of a woman while pregnant or within 42 days of the termination of pregnancy irrespective of the duration and site of the pregnancy, from any cause related to or aggravated by the pregnancy or its management but not from accidental or incidental causes.

Direct obstetric deaths are maternal deaths resulting from obstetric complications of the pregnancy state (pregnancy, labour or puerperium), from interventions, omissions or incorrect treatment, or from a chain of events resulting from any of the above.

Indirect obstetric deaths are maternal deaths resulting from previously existing diseases, or diseases that developed during pregnancy, not due to direct obstetric causes, but aggravated by the physiological effects of pregnancy.

Maternal mortality ratio (MMR) is the number of maternal deaths per 100 000 live births.

CHAPTER 1: LITERATURE REVIEW

1.1 Introduction

Puerperal sepsis is one of the leading causes of preventable maternal mortality and morbidity in both developing and developed countries (1). It is also one of the most common complications of delivering by caesarean section. Caesarean delivery increases the risk for puerperal sepsis by 5- 20 fold compared to vaginal delivery (2).

The maternal mortality ratio (MMR) due to sepsis increased in the United Kingdom (UK) from 0.65 per 100 000 live births in 2000 to 1.13 in the years 2006 – 2008, but recent data show a decline to 0.50 per 100 000 in 2010 – 2012. Despite these improvements, there is still a significant risk of maternal demise due to the increased severity of cases seen with puerperal sepsis after caesarean section, often requiring intensive care unit admissions (1).

1.2 Maternal Mortality

Global maternal mortality is unacceptably high. Around the world, about 800 women die on a daily basis from preventable pregnancy or childbirth related complications; 293 000 women died in 2013 worldwide from pregnancy complications and childbirth and 99% of these maternal deaths occurred in developing countries (3).

Maternal mortality is a global health problem. Due to its importance it is often used as a yardstick for general socio economic status of a country and can also be used to estimate the adequacy of obstetric care (4).

Maternal mortality has been a cause for concern for health authorities worldwide leading to the formulation of numerous policies to help reduce it. In 1987, the World Health Organisation

(WHO) launched the Safe Motherhood Initiative, which focused on family planning, antenatal care, clean and safe delivery, obstetric and basic maternity care, and women and equity – all aimed at reducing maternal mortality by half by the year 2000 (5).

There was no significant reduction in global maternal mortality ratios with this initiative, thus resulting in the establishment of the Millennium Development Goals (MDGs) (5). Number 5 of these goals called for the reduction of maternal mortality by 75% between 1990- 2015. There followed a notable decline in worldwide maternal mortality ratio from 385 per 100 000 in 1990 to 216 per 100 000 in 2015. While few countries were able to achieve the said target there was an overall 44% decline in global maternal mortality. This improvement differed from region to region. Sub Saharan Africa is still the leader in maternal mortality ratio, with 546 per 100 000 compared to the global 216 per 100 000 global MMR. This may be due to the fact that Sub Saharan Africa has been most affected by the HIV pandemic. This high rate of infection combined with high levels of poverty and a sizeable number of births occurring outside the health care system have resulted in little improvement of the MMR (4).

In South Africa, the MMR has shown a recent downward trend following a sharp increase from 230 per 100 000 in 1990, to 440 per 100 000 in 2005, then a decline to 410 in 2008, 300 in 2010, and 154 in 2011 – 2013 as reported in the most recent Saving Mothers Report of the Department of Health (6, 7). According to MDG number 5, South Africa should have achieved an MMR of 38 per 100 000 in 2015 (6, 7). By 2013, there was no indication that this goal would be achieved. This could be explained by the fact that there was no reliable assessment of maternal mortality in South Africa in 1990, with under reporting of cases and poor record keeping and no tool for assessing maternal deaths (4-6). Possibly, however, the greatest contribution to the failure in

achieving MDG Goal 5 was the HIV epidemic that most affected mortality rates in the late 1990s and early 2000s (8).

Global causes of maternal mortality reveal that obstetric haemorrhage is the leading cause of death followed by hypertensive disorders and pregnancy-related sepsis. The frequency of these conditions varies from region to region, with haemorrhage accounting for 36.9% of direct maternal deaths in southern Africa and 16.3% in developed regions, while hypertension-related maternal mortality was high in Latin America and the Caribbean, accounting for 22.1% of regional maternal deaths. In addition, deaths resulting from sepsis were more frequent in developing countries and southern Asia (7, 8).

Sub-Saharan Africa showed the highest frequency of indirect causes of maternal death, most likely related to the high prevalence of HIV. This may also explain the increase of maternal death due to sepsis as it highlights the impact of the underlying immunosuppression (7). In South Africa, the five leading causes of maternal deaths from 2005 – 2007 were non-pregnancy related sepsis (43.7%), hypertensive disorders of pregnancy (15.7%), obstetric haemorrhage (12.4%), medical conditions (6%) and pregnancy-related sepsis, which accounted for only 5.6% of all maternal deaths (8) . This is in comparison to the most recent Saving Mothers report from 2011- 2013, where the rate of maternal death due to non-pregnancy related sepsis had reduced by 9% but pregnancy-related sepsis had risen to 9.5% of all maternal deaths. This figure is made up of septic miscarriages (4.3%) and puerperal sepsis (5.2%) (6, 7).

There has been a remarkable reduction in mortality due to non-pregnancy related infections. As these deaths are mainly related to HIV infection, the successful roll-out of antiretroviral

treatment and the improvement of HIV testing and treatment after 2010 has had a large impact on maternal deaths in South Africa (8, 9).

1.3 Caesarean section

Caesarean section is the most commonly performed surgical procedure globally and has a rapidly increasing rate in developing countries (10). For many women, and their obstetricians, it has become a preferred method of delivery compared to vaginal birth. Increasingly, the procedure is being done on maternal request with no medical indication, partly due to the convenience of planning the delivery compared to an unscheduled vaginal birth (11, 12). Increased caesarean section rates in both developed and developing countries are also explained by fear of litigation, increased use of electronic fetal monitoring, and repeated caesarean sections (12). Delivery by caesarean section, however, carries a greater risk of adverse outcomes compared with vaginal birth (12). Liu et al, found that women who had undergone caesarean section had a higher incidence of readmission for complications compared with vaginal birth (13)

Indications for caesarean section have evolved over time from being performed to save the child of a dying mother to a lifesaving procedure for both mother and child. Although the procedure offers a lifesaving role in modern obstetrics, it remains a surgical intervention and is therefore not without risk (14). This is true of caesarean sections in South Africa where there is an increase of maternal mortality related to the procedure as stated in the Saving Mothers report (6). The most common causes of maternal mortality as a result of undergoing the procedure is bleeding at caesarean section, as well as sepsis, the latter partly because of delay in doing the procedure in an emergency setting when the woman has been in labour for many hours (6,15).

The rising rates of the procedure are an issue of global concern. Caesarean section is associated with bowel injury, anaesthesia-related problems, and future potentially-fatal complications, such as difficult repeat caesarean section or morbidly adherent placenta (16, 17). The ideal caesarean section rate as suggested by the WHO in 1985 was 10 – 15% at national levels. Recently studies done by the WHO have confirmed that a rate higher than 10-15% is not associated with reductions in perinatal and maternal mortality (14). Worldwide rates per country for caesarean section range from 1-40% with an increasing trend over the past 30 years. Recent caesarean section rates quoted include 29.1% in the United States, 21.5% in England and 54.9 % in China (12). The rising trend is also seen in developing countries, for example in an Ethiopian study, which found an increase from 2.3% in 1995-1996 to 24% in 2010 (16).

In South Africa the latest national caesarean section rate according to the Health Systems Trust is 24.7%. The figures vary widely from province to province, ranging from 17% in Limpopo to 29% in the Western Cape (18). The most common indications for caesarean section are failure to progress in labour and fetal distress (18). Social inequalities in the country have resulted in different patterns of indications for the procedure between the public and private health sector. In private practice, which caters for middle and high socio economic groups, 74.5% of caesarean sections are done electively (19). They are planned for the patient and service provider's convenience. In the public sector the procedure is mostly done as an emergency which then increases the risk of complications such as sepsis. A caesarean section done after prolonged labour is more likely to complicate with postpartum haemorrhage, sepsis and maternal death (20).

It is important to bear in mind that maternal morbidity and mortality after
Caesarean section is not always directly attributable to the procedure. The intrinsic risk of caesarean sections may not be easy to separate from the medical and obstetric indications that

lead to the procedure being performed (21). The risks of caesarean section are also associated with patient characteristics, surgical and anesthetic skill and quality of care from support staff, for example nursing. This complicates attempts to define a mortality risk: benefit ratio for the procedure (16, 21).

1.4 Sepsis

Sepsis is defined as the presence of infection together with systemic manifestations of infection (systemic inflammatory response syndrome). Severe sepsis includes sepsis induced organ dysfunction or tissue hypo perfusion (22, 23). Sepsis, irrespective of source or cause, is the most prevalent cause of mortality and morbidity worldwide. It is the leading cause of death in intensive care units in the United States (24).

Normal physiological changes of pregnancy obscure the signs and symptoms of sepsis in the pregnant population, therefore a high index of suspicion is required when dealing with pregnant patients (25). In normal pregnancy there is an increased heart rate, reduced blood pressure and decreased peripheral vascular resistance, all of which mimic clinical signs of sepsis. Pregnancy itself causes a mildly immunocompromised state which reduces the maternal ability to cope with sepsis. (26). These challenges result in failure to diagnose sepsis promptly, leading to complications and failure to initiate appropriate treatment efficiently. Other systems like the respiratory, renal, gastro intestinal and blood may also manifest impairment in the presence of sepsis that could be classified as a normal physiological change in pregnancy. The coagulation changes in pregnancy lead to a more rapid progress to disseminated coagulopathy than in the non-pregnant state (26).

Puerperal sepsis is infection of the genital tract occurring at any time between the rupture of membranes, labour and delivery until the 42nd day post-partum (22, 27, 28). Puerperal sepsis may be life threatening and has potential to cause life altering morbidity. It is responsible for up to 15% of admissions to adult intensive care units (28, 29).

In developed countries puerperal sepsis accounts for 2.1% of maternal deaths overall, while in Africa it causes about 9.7% of all maternal deaths, more than the 5.2% reported in the Saving Mothers report of 2011-13 (4, 27). In developing countries there are difficulties in obtaining accurate data on maternal mortality due to sepsis, because a considerable number of births still occur outside the health care system. Even when complications set in after the birth, the hospital is not the first line of seeking help, as people may consult traditional healers and may not access the health care system (30). A Ugandan study by Ngozi et al recently reported an exceptionally high incidence of maternal death due to sepsis. Their study found puerperal sepsis as the cause of maternal mortality in 30% of women. This is contrary to the global pattern of haemorrhage as the leading cause of maternal death. While they did not consider the mode of delivery, they removed miscarriage-associated deaths, leaving only viable births responsible for these high figures (31).

Puerperal sepsis has historically been linked to caesarean deliveries as many patients who underwent the procedure did not survive due to sepsis related complications (32, 33). In modern obstetrics, death occurs three times more frequently in women who deliver by caesarean section as compared to normal vaginal birth (33). Acosta et al in a Scottish population-based study found that severe maternal sepsis was more common following caesarean delivery as compared to vaginal delivery. These results remained after controlling for all other possible risk factors in their statistical analysis (34). In a French study, Deneux-Tharaux et al found that 80% of women who died from puerperal sepsis had delivered by caesarean section (35). However, in Brazil,

Esteves-Pereira could not find an association between sepsis related mortality and caesarean section, even though infection is a well-known complication of any surgery (36).

In South Africa, maternal death from caesarean section related sepsis shows a stable or downward trend, as reported in the most recent Saving Mothers reports. In 2008-2010 caesarean section sepsis was responsible for 115(44.6%) of all pregnancy related sepsis death while it was 99 (38.9%) in 2011-2013 (6, 7).

The predictors of progression from sepsis to severe sepsis and eventually mortality are not clearly understood, but there are some known predictors of poor outcome such as age more than 35 years, obesity, nutritional status, HIV infection, immunosuppression and late health seeking behaviour (3, 36, and 37). A retrospective cohort study by Acosta et al considered risk factors associated with maternal sepsis severity. They identified four groups of women, who had: 1) no sepsis in pregnancy and puerperium; 2) uncomplicated sepsis; 3) severe sepsis; and 4) septic shock. Delivery by caesarean section showed a relatively high incidence of severe sepsis and septic shock, as did diabetes mellitus as a comorbid condition, and inadequate attendance at antenatal clinic. While this study addressed factors that contribute to progression of sepsis, it did not address the progression from septic shock to mortality (29).

The prevention of the progression from uncomplicated sepsis to severe sepsis, shock and eventually death has improved with the introduction of antibiotics, washing of hands by medical staff, and safer medical practices (23). This provides a platform to consider sepsis as a preventable cause of maternal mortality. Looking at the possible risk factors for sepsis prior to delivery and attending to them can help curb the incidence.

1.5 Presentation of Puerperal Sepsis.

1.5.1 Endometritis

Puerperal endometritis refers to the infection of the decidua. It is usually a polymicrobial infection caused by bacteria ascending from the lower genital tract, mainly the bacterially colonised vagina (2). Some colonies are commensal in the lower genital tract and yet pathogenic when introduced to the upper genital tract (33). The incidence of puerperal endometritis is affected mostly by the mode of delivery as it is most prevalent after caesarean section, compared to vaginal delivery, with incidences of 5-15% and 1-3% respectively (33). The chance of developing endometritis after caesarean section is increased when the procedure is done at an advanced cervical dilatation or where membranes have ruptured compared to the procedure done with a closed cervix (24, 25). The incidence of developing endometritis has been found to be 28.6% following emergency caesarean section and 9.2% after elective caesarean section (24). With emergency caesarean section, the woman goes into labour, and has repeated vaginal examinations which increase the chance of ascending infection, while elective procedure patients do not even go into labour and no vaginal examinations are performed(40, 41). Colle et al similarly reported in their study that women who delivered by caesarean section after the onset of labour had an increased risk of developing severe genital tract sepsis compared to those who had procedures done before labour onset and those who delivered by spontaneous vaginal birth (37). HIV infection is also related to the development of endometritis. A Ugandan study found that endometritis was the major cause of post caesarean morbidity and mortality in HIV-infected women following emergency caesarean section, and this was predisposed to by long intervals from onset of labour and procedure (7-12 hours) (42).

1.5.2 Surgical Site Infection (SSI).

Wound infection is a common complication of caesarean section delivery. Some degree of wound infection occurs in 2-16% of women who deliver by caesarean section (37). The severity can range from being an uncomplicated superficial wound infection to deep and severe infection that extends to the abdominal cavity. The mechanism of wound infection is via direct contamination by skin commensals such as *Staphylococcus aureus*, or mixed aerobic/anaerobic bacteria. It is difficult to estimate the overall rate or extent of the problem of surgical site infection (SSI) due to the short duration of hospital stay post operatively (42). A study by Johnson and Buchmann, performed at Chris Hani Baragwanath Academic Hospital, reported a low incidence of 1.5% of women readmitted with puerperal sepsis, with 11% having mild wound infection that did not require admission. Their study considered risk factors for infection, including HIV, but none were identified as significant contributors. Only the first two weeks after delivery, not the whole puerperium, was covered in the study (44).

Risk factors for SSI are obesity, poor personal hygiene, malnutrition and under nutrition. The increased risk of sepsis with obesity is related to adipose tissue taking time to heal, together with reduced oxygen supply, making a good breeding space for micro-organisms. Dhar et al have shown that comorbid conditions like diabetes and anaemia increase the risk of surgical site infections (38). Wloch et al had similar findings in obese and diabetic women. Rates of obesity and metabolic related conditions such as diabetes mellitus are increasing worldwide, and women of childbearing age are significantly affected. Obese and diabetic women undergoing caesarean section will therefore be at risk. Another risk factor for SSI is long duration of surgery (45).

Reduction of SSI can be achieved by pre-operative skin preparation such as preoperative shaving and antiseptic showering; however, there is insufficient data to prove that these measures are

effective. Some of these practices have already been abandoned by institutions as they failed to show significant benefit on sepsis prevention (46, 47). Tanner et al in a 2011 review of randomised control trials on pre-operative hair removal versus no removal showed no statistical difference between shaving, creams and clipping. In a resource constrained setting the exercise can be wasteful and therefore indirectly harmful to the health care system. Antibiotic prophylaxis is one proven effective method of SSI (and endometritis) prevention that is now standard practice at all caesarean sections (47).

1.5.3 Urinary Tract Infection

Urinary tract infection is one of the most common causes of puerperal sepsis. Diagnosis is usually made on clinical evaluation including laboratory analysis of urine showing more than 10^5 colony- forming units /ml. In caesarean sections, the most common risk factor for acquiring this infection is indwelling urinary catheter which is usually inserted prior to the procedure (25). Catheter associated urinary tract infection account for 40% of all nosocomial infections, with catheterisation carrying an addition risk of infection of 5-10% with each day of indwelling catheterization (40). Pandey et al reported a 29.3% rate of UTI in patients with indwelling catheter after caesarean section compared to 4% in the non-catheterised group (48). It has been a routine practice to insert an indwelling catheter prior to caesarean section procedures. The reason for this practice is to reflect the bladder out of the surgical field to prevent bladder injury, urinary output monitoring during surgery and bladder management after regional analgesia. This practice has discouraged ambulation after surgery, increased the need for antibiotics, increased the risk of thrombotic events and increased discomfort for the patient. Benefits of this practice have proved to be outweighed by the risks associated with it. Urinary catheters should be removed as soon as possible after surgery, and almost immediately if general anaesthesia has been used (48).

1.5.4 Retained Products of Conception.

Retained products of conception (RPOC) refer to placental and fetal tissue that remains in the uterus after delivery or miscarriage. RPOC can result in septic miscarriage which is one of the leading causes of maternal mortality in developing countries (49). It is associated with unsafe termination of pregnancy usually done outside the formal health sector. Sepsis due to RPOC is also seen after term birth, even following caesarean section. It may present as post-partum haemorrhage or endometritis with varying grades of severity including septic shock and severe acidosis (49, 50).

The diagnosis of RPOC can be challenging but clinical examination and ultrasonography, including colour Doppler, can increase the pick-up rate. The most common risk for RPOC in full term pregnancy is incomplete delivery of the placenta and membranes, manual delivery of a retained placenta where placenta comes out piece-meal, morbidly adherent placenta, and a succenturiate lobe of the placenta which can be missed during delivery of the placenta (49, 50). The clinical presentation of RPOC varies depending on interval of diagnosis from delivery. Primary postpartum haemorrhage may be seen soon after delivery, while sepsis, offensive vaginal discharge, secondary post-partum haemorrhage and pain may begin several days later. In cases of severe sepsis with organ failure, metabolic acidosis and shock, speculum examination is critical as it can help the clinician decide on further management such as hysterectomy if the cervix appears necrotic (49).

1.5.5 Necrotising Fasciitis (NF)

NF is a soft tissue infection usually caused by toxin producing bacteria and characterised by widespread fascia necrosis. There is intense local pain, fever and severe systemic sepsis that can rapidly deteriorate to death. The infection usually spares the skin and underlying muscle and affects the fascia and adipose tissue (51, 52). Risk factors for developing NF include diabetes and immuno-suppression. It can spread beyond the anterior wall into the chest wall, external genitalia and extremities. Survivors of NF often suffer debilitating morbidity and disfigurement (51, 52). This complication is rare after caesarean section. The mode of transmission is through ascending organisms colonising the vagina, one of which is *Streptococcus pyogenes,* associated with deep NF (52).

1.5.6 Pelvic Abscess

Pelvic abscess formation is rare following caesarean section; it may arise as a complication of delayed treatment of endometritis (53). It is usually located in the broad ligament, anterior to the uterus or in the pouch of Douglas. Patients may present in a critical state with signs of septic shock. Clinical and ultrasonographic examination are the key to diagnosis as the abscess can be felt as a fluctuant mass on bimanual pelvic examination and is visible on ultrasonography. Percutaneous, ultrasound guided, trans abdominal drainage is a useful alternative to exploratory laparotomy (52).

1.5.7 Septic Thrombophlebitis

Septic pelvic thrombophlebitis is the inflammation of pelvic or ovarian veins. It is more common after caesarean delivery compared with vaginal birth (1-2% vs. 0.05% respectively) (24). The condition may be related to the hypercoagulable state of pregnancy, with the risk of thrombotic

disease further increased due to surgery. Prolonged duration of surgery can also accelerate the cascade of septic thrombophlebitis (53, 54).

1.6 Risk Factors for Puerperal Sepsis

1.6.1 Limited Antenatal Care

The link between poor antenatal care and sepsis after caesarean section may not be clear but it is known that health education given to women during pregnancy helps to impart knowledge on what to expect in their pregnancy. Early booking and attendance of antenatal clinic (ANC) is essential for screening and detection of problems that may pose a threat to the parturient such as anaemia, malnutrition, infections or chronic conditions, including diabetes and hypertension. Infections such as HIV/AIDS and Group B Streptococcus (the latter not screened for in South Africa) can, if detected early, be treated to prevent serious maternal and neonatal sepsis. Antenatal health education plays an important role in helping women to identify features of puerperal sepsis and to encourage them to seek medical intervention early (55). In a Nigerian study, Ujah et al studied factors that contributed to maternal mortality. They found that unbooked women had a 20 times higher rate of maternal mortality compared to women who attended antenatal classes (30). Similar results were shown in a Ugandan study by Ngozi et al who found that lack of antenatal care increased the risk of maternal death. Mothers who did not attend antenatal classes had a higher likelihood of poor obstetric and perinatal outcome (31). These findings may have been confounded by socio-economic status. Disadvantaged women may not make use of available maternity services due lack of resources. In an overview of the evidence, Carroli et al looked at the effectiveness of antenatal care in preventing maternal mortality and serious morbidity; they found that attending ANC can help to screen for diseases including anaemia, hypertension, diabetes and infections such as HIV and syphilis. However, it was found

to be difficult to screen antenatally for puerperal sepsis since usually it settles in during labour or delivery (55). They agreed with other literature on the importance of health education to help identify problems early. This emphasises the fact that education given during ANC is important in the prevention and early recognition of sepsis.

Poor attendance at ANC is also related to quality of care and lack of access. In a rural South African study, Amnesty International looked at barriers to antenatal care and identified three reasons preventing women from attending antenatal care and in turn contributing to high rates of maternal mortality. The reasons included: 1) lack of privacy (patient's confidentiality and informed consent at health facilities around implementation of HIV testing during antenatal care) 2) lack of information and knowledge about sexual and reproductive health and rights including lack of training on the part of health care workers; and 3) persistent problems relating to the availability and costs of transport (56).

1.6.2 Poor socioeconomic status

Poor hygiene practices and poor living conditions play a major role in development of wound sepsis after caesarean section. In South Africa, migration and urbanization has resulted in the development of informal settlements with poor provision of water and sanitation (57).

As detailed in the Millennium Development Goals (MDGs), environmental sustainability is essential for good health of the general population. All the MDGs are inter-dependent and influence health (57). Late presentation to hospital due to poverty and lack of resources has for centuries been directly linked to maternal mortality (58). Poor general condition, for example, anaemia, dehydration and poor personal hygiene prior to admission were cited by Sekirime and Lule in a Ugandan study as major contributing factors for postpartum sepsis (42). Shamshad et

al in a Pakistani based study found that there were greater chances of sepsis in poor women suffering from chronic ill health and malnutrition compared to socially elite groups (23). Some cultural beliefs may prevent women from seeking medical help even in life threatening situations resulting in late presentation or presentation with multi-organ failure due to sepsis. Use of toxic herbal remedies can sometimes result in, or aggravate multi-organ failure. Sepsis after caesarean section is closely related the triad of poverty, illiteracy and social constraints (23, 30).

1.6.3 Prolonged labour

Labour is considered to be prolonged when its duration exceeds 24 hours. This term is used interchangeably with obstructed labour where, regardless of strong contractions, the presenting part fails to descend. Prolonged labour is cited as a major risk factor for puerperal sepsis (59). Prolonged labour is usually associated with long periods of fasting, resulting in maternal exhaustion and dehydration. Tissue necrosis and fistula formation (in extreme cases) are complications of prolonged labour which will further provide favourable conditions for puerperal sepsis. Prolonged labour, together with prolonged second stage, followed by caesarean section may result in extensive iatrogenic injuries, haemorrhage and puerperal sepsis (58). A Nigerian study was performed looking at caesarean sections performed where the fetal head was impacted (59). This study showed a greater risk of genital tract sepsis and extensive vaginal lacerations when delivery of the baby required pressure via the vagina to disimpact the fetal head (59). Prolonged labour is also a known risk for chorioamnionitis which is further increased when membranes are ruptured, allowing a pathway for micro-organisms to ascend into the uterus (60).

1.6.4 Emergency caesarean section

Emergency caesarean section is a major risk factor for puerperal sepsis (18). The most common indications for emergency caesarean section are prolonged labour and cephalopelvic disproportion, both well known risk factors for sepsis (61). Caesarean sections performed for these indications are also more likely to be performed during advanced cervical dilatation with fetal head impaction (59). In caesarean sections performed for prolonged second stage, manoeuvres may be required to facilitate delivery. These manipulations can result in tears to the uterus, cervix and vagina. Extensive trauma to the genital tract can result in tissue necrosis, fistula formation and may complicate with sepsis (60). Chama et al found in a Nigerian study that sepsis was the leading complication for emergency caesarean section; 75% of the women who had emergency caesarean section developed a form of sepsis, either wound, genital tract or urinary tract infection post operatively (14).

1.6.5 Preterm Labour

The incidence of puerperal sepsis is three times higher after preterm than term birth. Patients may be delivered by caesarean section for other associated indications, but they will be more prone to sepsis postpartum (60). A randomised controlled trial done by Alfirevic et al compared vaginal birth with elective caesarean section for preterm birth. They found major postpartum complications associated with caesarean section in caesarean preterm delivery compared with vaginal birth. These complications included haemorrhage, due to poor lower uterine segment formation, and puerperal sepsis due to ascending infection. Other complications seen in these women included wound dehiscence and endotoxic shock (33). These findings confirm that

preterm delivery carries a risk of developing puerperal sepsis. Infections are a major causative factor in premature labour therefore these women enter the puerperium with a pre-existing infection which complicates with a major puerperal infection (61).

1.6.7 HIV infection

During pregnancy the normal immune response includes a decline of the CD4 cell count and increase in CD8 cells, changes which are also features of HIV infection. Combined with HIV infection, this may result in a rapid decline of immune status of an already compromised HIV infected pregnant woman resulting in increased susceptibility to opportunistic infections such as tuberculosis and pneumonia (62). HIV infection has had a remarkable impact on MMRs over the past 20 years. Sub-Saharan Africa has been the hardest hit by the epidemic (63). A prospective study by Sewankambo et al in Uganda reported MMRs of 1687 and 310 per 100 000 births in HIV infected and non-infected mothers respectively. Not all of these deaths were sepsis related but the findings emphasise the vulnerability of HIV infected mothers from a wide spectrum of diseases to which non-infected mothers are not exposed (64). HIV is also the major contributor to indirect maternal death in South Africa. According to the Saving Mothers report from 2011-2013, non-pregnancy related infections, mainly HIV related, were responsible for 35% of maternal deaths. Among the women who died from pregnancy-related sepsis associated with viable pregnancies, 67% were HIV infected (6).

Caesarean delivery has been shown to be an effective way of preventing vertical transmission of HIV. The European Mode of Delivery collaboration showed a 50% reduction in transmission with caesarean delivery (65). A committee opinion of the American College of Obstetricians and Gynaecologists (ACOG) recommends caesarean delivery of all HIV infected mothers (66). These opinions were formulated without considering the possible impact of the procedure on

immunocompromised women in poorly-resourced regions. In developing countries, caesarean sections in state facilities are only offered for medical indications. Caesarean section is not performed for prevention of mother to child transmission because of the detrimental consequences which are an even greater risk in the presence of HIV infection.

The contribution of HIV to maternal mortality is undoubtedly substantial, and this was shown by Stanton and Ronsmans in their meta-analysis of studies where they found that HIV infected women had eight times the risk of pregnancy related death compared to non- infected women (67). The meta-analysis could not provide data to explain the high mortality among the HIV infected population. The answer is, however, likely to be the increased risk of non-pregnancy related infections and pregnancy-related sepsis in HIV infected women (67).

1.6.8 Obesity

The prevalence of obesity continues to increase worldwide, and particularly affects women of reproductive age (63). Obese women are at greater risk of having diabetes in pregnancy, macrosomic babies, caesarean delivery, a difficult surgical procedure, and poor wound healing, all factors associated with an increased risk of puerperal sepsis. Obese women, as discussed earlier, frequently suffer surgical site complications such as wound infection, dehiscence, haematoma or seroma. The reasons for poor wound healing in patients with a high BMI may not be easily understood but cited reasons include poor blood supply to adipose tissue resulting reduced oxygenation and poor delivery of antibiotics (53, 63). It is also possible that antibiotic doses are insufficient for the patient's weight. Also, skin folds, often close to the surgical site, harbor micro-organisms that thrive in moist conditions and contribute to the development of sepsis after caesarean section (38). Tonidandel et al in their retrospective cohort study looking at anaesthetic and obstetric outcomes in morbidly obese parturients found that women with a high

BMI were more prone to delivery by caesarean section, with a longer hospital stay after delivery by caesarean section compared with women with a lower BMI (70).

1.6.9 Maternal age

The risk of maternal death is relatively high among mothers younger than 15 years and older than 40 years (36). Teenage pregnancy is a significant problem in low and middle income countries. The incidence of births by teenage mothers is 2% in China, 18% in Latin America and the Caribbean and more than 50% in sub-Saharan Africa. The risk of maternal death is four times higher in adolescents younger than 16 years than among women in their twenties (71). They are more prone to pregnancy complications such as cephalo-pelvic disproportion (CPD) and prolonged labour, which may in the very young, be due to an underdeveloped pelvis. Caesarean section in such circumstances carries a high risk of subsequent sepsis. Due to associated low socioeconomic status and dependence on others for help and financial needs, there may be delay in seeking help, sometimes resulting in serious and life threatening situations (24, 62).

In advanced maternal age, increased morbidity and mortality are related to increased prevalence and severity of chronic medical conditions such as diabetes and obesity resulting in delayed wound healing. The bodies of older women do not recover as quickly as younger women, further increasing the risk of developing sepsis (54, 64).

1.7 Microbial aetiology

Pathogenic microorganisms are responsible for causing puerperal sepsis. These organisms may be endogenous, exogenous and nosocomial. Endogenous organisms are found in the woman's genital tract and lower gastrointestinal tract, where they are part of the normal flora e.g. *E. coli*. Exogenous organisms come from community-acquired external contamination, and nosocomial

infections are hospital acquired. Common pathogens responsible for puerperal sepsis are beta-haemolytic group A *streptococcus, E. coli, S. aureus* and methicillin resistant *S. aureus* (22, 24)

1.7.1 Beta-haemolytic group A *streptococcus* (GAS)

GAS is the most commonly cultured pathogen in puerperal sepsis. It is also responsible for a variety of infections including impetigo, throat infections, scarlet fever and rheumatic fever. GAS is not a normal vaginal commensal, however, it is found in 30% of women as the causative organism of sepsis following vaginal delivery (24,37). The most lethal form in obstetric patients is postpartum invasive GAS causing necrotizing fasciitis and fulminant toxic shock syndrome. GAS was found to be the primary cause of death for 13 of the 29 maternal deaths in the UK during 2006-2008 as stated in their confidential enquiries into maternal death. (37, 68)

1.7.2 Escherichia coli

E. coli is a commensal of the lower gastrointestinal system. It is the most common causative organism of urinary tract infection (UTI) in pregnancy. A study by Kankuri et al found that *E.coli* was one of the most common pathogens causing sepsis after caesarean section, while Acosta et al found that *E.coli* was responsible for most cases of severe puerperal sepsis (25, 27).

1.73 Staphylococcus aureus

S. aureus is normally found on the skin as a commensal microorganism. Infection after caesarean section is usually due to a disturbance of skin architecture and its point of entry is usually the surgical site (45). Bacteraemia due to *S. aureus* is commonly seen following caesarean section (28).

1.7.4 Methicillin-resistant *Staphylococcus aureus* (MRSA)

MRSA causes a nosocomial infection that follows hospital admission. Worldwide, the infection rate among postpartum mothers by this micro-organism is said to be 2.1%.Treating the infection poses a challenge because of multiple drug resistance (66).

1.7.5 Enterococcus fecalis

E. fecalis is commonly found in the gastrointestinal tract of human. It is also known as Group D *streptococcus.* While it is well known as a harmless commensal of the gastro-intestinal tract, it has become one of the most common hospital acquired infections cultured in surgical wounds with increasing antibiotic resistance (67).

1.7.6 Other organisms

Other pathogens identified are *Strep. pneumoniae, Morganella morganii, Klebsiella* species, *Clostridium septicum, Listeria monocytogenes* and gram negative bacilli (46, 68).

Poly-microbial infections are found in most fatal cases of puerperal sepsis (25). HIV infected patients are more prone to fatal outcomes when infected by these pathogens due to immune depletion (64).

1.8 Prevention of puerperal sepsis

Prevention of disease or health problems can either be primary, secondary, or tertiary. Primary prevention implies avoiding the emergence of disease, secondary entails halting the disease process prior to clinically recognizable disease and tertiary means prevention of complications caused by the disease. Primary and secondary prevention will be discussed below.

1.8.1 Primary prevention

Early booking for ANC helps in early recognition of risk factors for sepsis and preventing problems before they arise. Medical conditions that increase the risk of sepsis such as HIV/AIDS, diabetes and anaemia can be optimized before delivery. Women can be given health education about good nutrition and personal hygiene (55). Education using community forums on teenage pregnancy, advanced maternal age and use of contraception in these age groups has useful potential, both to prevent at-risk pregnancies and to encourage appropriate self-care in these groups (31, 71). Health worker education on importance of hand washing and prevention of cross infection is essential (22, 72).

1.8.2 Secondary Prevention of sepsis

This level of intervention provides actual procedures that are used to reduce surgical site infection. These interventions can be done pre operatively, intra operatively and post operatively.

In the pre-operative phase, measures are taken to decolonise the skin of micro-organisms that may cause surgical site infection. Patients can take antiseptic showers or baths before surgical procedures in non-emergency situations, or use antiseptic skin preparations before the procedure (68). *S. aureus* is one major skin commensal that is cultured in most surgical wound exudates. The use of antiseptic solutions has been practised worldwide to prevent surgical site infection. In the operating room, surgical site cleaning and strict aseptic technique is used during preparation of the patient for surgery (68, 69).

A Cochrane systematic review by Hadiati et al. (2012) compared different measures of pre-operative skin preparation for prevention of surgical site infection after caesarean section (74).

Randomised, and quasi-randomised, trials evaluating skin preparations prior to an elective or emergency caesarean section were included. Five trials were selected (n=1462), with two trials comparing incisional drapes with no drapes in women who received the same skin preparation and three trials comparing different skin antiseptic preparations. Solutions used were iodine and chlorhexidine. The review's conclusion was that there was insufficient evidence to determine the most effective type of skin preparation before caesarean section to prevent surgical site infection (74).

Hair removal has a long tradition in reducing skin contamination before surgery. However, there has been much debate that shaving, hair clipping and creams increases the incidence of SSI. Using razors can cause skin abrasion that encourages the multiplication of micro-organisms. Some studies suggest that if hair removal is required it should be done close to the time of surgery (74, 75).

The use of prophylactic antibiotics is one of the applied measures to prevent infectious complications following caesarean section. The main purpose of using prophylactic antibiotics is to reduce the load of colonizing pathogens introduced to the patient during the operation, thus enabling the patient's immune system to overcome the infection. The use of prophylactic antibiotics before caesarean delivery reduces the risk of infection by about 50% (75). Even with the use of antibiotics, roughly 10% of caesarean deliveries are followed by sepsis. In their Cochrane meta-analysis of randomised trials, Smaill and Grivell showed significant reductions in febrile morbidity, wound infection, urinary tract infection and endometritis with the use of prophylactic antibiotics compared to no prophylactic antibiotics given before caesarean delivery. The benefits of using prophylactic antibiotics outweighed the risks. These benefits were reduced

hospital stay, less pain related to wound infection and reduced incidence of maternal mortality from sepsis (76).

Timing of antibiotic administration has traditionally been after clamping of the cord. This was recommended to prevent masking of neonatal sepsis, to prevent colonization of the newborn with antibiotic resistant organisms, and rarely to prevent fetal compromise due to maternal anaphylaxis. While these considerations are reasonable, there is clear evidence on the benefit of giving antibiotics prior to performing the skin incision (75). The ACOG guidelines currently recommend that antibiotic prophylaxis must be given within 60 minutes of the start of the procedure. This helps to increase antibiotic concentration in blood and tissue (77).

1.9 Diagnosis of puerperal sepsis

1.9.1 Diagnostic criterion

This is infection of the genital tract occurring at any time between rupture of the membranes and labour until the 42nd day postpartum in which two or more of the following are present: pelvic pain, fever: temperature less than 35.8°C or 38.5^{o}C or higher on any occasion, abnormal vaginal discharge or presence of pus; alternatively, as a temperature rise above 38°C maintained over 24 hours or recurring during the period from the end of the first day to the tenth day after childbirth or abortion. (22, 78)

1.9.2 Classification of severity

Severe sepsis is associated with organ dysfunction, hypotension or hypoperfusion. Associated features include arterial hypoxaemia, raised lactate, acute oliguria or deranged renal function, coagulation abnormalities and hyperglycaemia in the absence of diabetes (78).

Septic shock is a state where there is sepsis and refractory arterial hypotension despite adequate fluid resuscitation. It is a clinical diagnosis that depends on the recognition of subtle signs that indicate developing tissue hypoxia and organ dysfunction (78, 79).

In the diagnosis of septic shock, tachypnoea and tachycardia are early signs followed by hypotension and poor urine output. As shock progresses, the patient will be pale with cold peripheries and an altered level of consciousness (80).

1.10 Management of puerperal sepsis

In managing sepsis the initial goal, according to the Surviving Sepsis Campaign, is to optimise resuscitation in the first six hours of contact with the patient. Early detection of sepsis also helps to improve outcome, and this can be achieved by recording vital data such as temperature, heart rate, blood pressure, respirations and oxygen saturation. All microbiologic specimens (blood and other fluids) should ideally be taken before antibiotic initiation. Administration of antibiotics must be started within the first hour of sepsis recognition, taking into account allergies and drug safety for breastfeeding mothers. Supportive management is also equally important in preventing mortality. This may include ventilation, blood transfusion, glucose maintenance, thrombo-prophylaxis, inotropic support, dialysis, prevention of gastro intestinal ulcers and analgesia. Surgical intervention to remove the source of infection is important and may involve wound debridement, draining of abscesses, and/or hysterectomy (78, 80). A detailed review of treatment strategies is beyond the scope of this literature review.

CHAPTER 2: AIMS OF THE STUDY

2.1 Problem Statement

Puerperal sepsis is one of the five major causes of maternal mortality in South Africa. It is classified as a direct cause of maternal mortality and is an avoidable cause of maternal death. Caesarean section is known as one of the major risk factors. The procedure is routinely done under aseptic settings, but the risk of developing sepsis after caesarean section still far exceeds that of vaginal delivery. The question that often remains unanswered is whether these patients develop sepsis before or after the procedure. Does delivering by caesarean section *per se* increase the chance of developing sepsis or are other factors involved in the development of sepsis after caesarean section? Chris Hani Baragwanath Academic Hospital (CHBAH) has seen 661 maternal deaths over a period of 18 years. Some of these deaths were due to sepsis after caesarean section. There is limited information on the progression from sepsis after caesarean section to maternal death, and the database of maternal deaths at the hospital provides an opportunity to study this progression.

2.2 Objectives

- To determine the frequency of maternal death due to sepsis following caesarean delivery, at CHBAH from 1997-2014.
- To determine the prevalence of independent obstetric variables that may be associated with mortality from caesarean section sepsis e.g. duration of labour, prolonged rupture of membranes, pre-term labour and chorioamnionitis.
- To determine the prevalence of HIV infection in women who die from sepsis after caesarean section.

CHAPTER 3: METHODOLOGY

3.1 Study Setting

From 1997 to 2014, CHBAH was serving a population of about 1.4 to 1.8 million people in Greater Soweto, Orange Farm and Lenasia. These areas are located to the south-west of Johannesburg. The maternity unit was also a referral center for community health centers in Soweto, primary and secondary level hospitals in Gauteng and a regional hospital in the North-West Province. About 22000 deliveries are performed at the hospital per annum, a considerable portion of which are delivered by caesarean section. The maternity ward has about 20 delivery cubicles, a 7-bed high care area, and attached to the labour ward are two caesarean section theatres which operate 24 hours a day. All maternal deaths at CHBAH from 1997 have been routinely notified to the national confidential enquiries, and the original case notes have been kept in the hospital's Department of Obstetrics and Gynaecology, and entered on an electronic database. In the database, the primary cause of maternal death has been assigned in each case, using the classification of the National Committee for Confidential Enquiries into Maternal Deaths (6). For postnatal deaths, the mode of delivery is specified in the database.

3.2 Study Population

The study included all women who died from pregnancy-related sepsis after caesarean section at CHBAH from 1 January 1997 to 31 December 2014.

3.3 Study Design and Data Collection

This was a retrospective descriptive study of maternal death due to sepsis after caesarean section at CHBAH, using the electronic database to identify the maternal deaths. All entries on the database have a reference number that allows for retrieval of the original case notes. Using the

database, the original clinical records of women who died of sepsis after caesarean section were obtained from the Department of Obstetrics and Gynecology at the Hospital. Women who delivered by caesarean section from satellite hospitals and private hospitals and presented with sepsis were included in the study. If the original case notes for a woman could not be found, the record on the computerized database was used for data collection.

Data were collected into a data sheet (Appendix A), including baseline demographic, antenatal, intrapartum and intraoperative data. The HIV status, CD4 count and antiretroviral treatment were recorded. Prolonged labour was defined as labour (latent and active phase) exceeding 20 hours in a health care institution. The data were entered into a Microsoft Excel spreadsheet and then exported to STATA 13 statistical software (Statacorp, College Station, Texas, USA). Descriptive data management was used. Categorical variables were expressed as frequencies and percentages, while continuous (numerical) variables were expressed as means ±standard deviations (SDs), or medians with interquartile ranges (IQRs).

3.4 Ethics

Ethics approval was granted by the University of Witwatersrand Ethics Committee (HREC) (Appendix B), and permission to access clinical files was obtained from the Department of Obstetrics and Gynaecology and the Chief Executive Officer at CHBAH (Appendix C).

Chapter 4: RESULTS

4.1 Obstetric and demographic characteristics

There were 108 299 patients delivered by caesarean section from January 1997 to December 2014. Twenty-four women died from pregnancy-related infection. Twenty-one (87.5%) had a caesarean section done at CHBAH, two (8.3%) were referrals from satellite hospitals and one (4.2%) had a caesarean section done at a private hospital. The frequency of sepsis after caesarean section at CHBAH was 0.02% or 19.4 per 100 000 caesarean sections.

The mean age of the 24 women was 28.8 years, with a range of 16-46 years. Three women (12.5%) were teenagers. The median (IQR) parity for these women was 2 (1-2) and six (28.0%) women were in their first pregnancy. Fourteen files had antenatal cards, allowing calculation of gestational age. In the 24 files analysed only 12 women had both height and weight recorded. The median (IQR) body mass index (BMI) for the 12 women was 36.2 kg/m^3 (30.5 - 41.5 kg/m^3) (Table 4.1), with a range of 23.0-45.0 kg/m^3.

Table 4.1 Participant demographics and other characteristics

Characteristic	Frequency	Percent
Age in years (mean ± standard deviation) 28.8 ± 8.2		
15-19	3	12.5%
20-24	4	16.7%
25-29	7	29.2%
30-34	2	8.3%
35-39	6	25.0%
> 40	2	8.3%
Parity		
0	6	25.0%
1	8	33.3%
2	6	25.0%
3	3	12.5%
>4	1	4.2%
Gestational age in weeks (n=14)		
<37 weeks	6	42.9%
38-40weeks	8	57.1%
Body-mass index in kg/m3 (n=12)		
<25.00	1	8.3%
25.00-29.99	1	8.3%
30.00-34.99	4	33.3%
≥35.00	6	50.0%

Table 4.2 outlines risk factors related to sepsis after caesarean section. Fourteen (58.3%) women had antenatal cards on which antenatal care visits could be assessed. Seven (50%) of these had attended antenatal clinics less than 3 times. Twelve women (50 %) had prolonged labour (were in labour for more than 20 hours) and six (25.0%) women had more than four vaginal examinations in labour. Sixteen (66.7%) women were HIV infected, seven (29.2%) of whom were on triple-drug antiretroviral treatment. Fifteen (93.8%) had CD4 counts <200/mm^3 (Table 4.3).

Table 4.2: Risk Factors for sepsis in women who died from sepsis after caesarean section (n=24)

Characteristic	**Frequency (%)**
Limited antenatal care (<3 visits)	12 (50)
Preterm labour <37 completed wks.	6 (25)
Prolonged labour >20hrs	12 (50)
Vaginal examinations ≥5 in labour	6 (25)

Table 4.3 HIV Infection and treatment status

HIV Status	**N**	**(%)**
Not known	3	(12.5)
Positive	16	(66.7)
Negative	5	(20.8)
CD4 Count		
0-100	10	(62.6)
101-200	5	(31.3)
201-350	1	(6.1)
ART Status		
On treatment	7	(29.2)

Twenty (83.3%) women had emergency caesarean sections with two elective operations (8.3% and two unknown (8.3%). The most frequent indication for surgery was prolonged labour (n=12; 50%) (Table 4.4).

Table 4.4 Indications for caesarean section

Primary indication for C/S	N	(%)
Prolonged/obstructed labour	12	(50)
Fetal distress	8	(33.3)
Diabetes	3	(12.5)
Chorioamnionitis	1	(4.20)

4.2 Events during caesarean section

Thirteen (54.2%) women had transverse skin incisions, seven (29.1%) had sub umbilical midline incision and four (16.7%) had no record of the skin incision used. The median blood loss was 600 mL (IQR 500-800 mL). Three (12.5%) received blood transfusion during caesarean section. Three (12.5%) had peritoneal drains inserted after caesarean section. One (4.2%) underwent a subtotal hysterectomy after caesarean section due to postpartum haemorrhage, and she lost a total of 2700 mL of blood during the three- hour operation. One (4.2%) had a total abdominal hysterectomy for placenta praevia major. Another (4.2%) had a bladder injury intra-operatively during caesarean section. The mean duration of operation was 60 minutes (IQR 40-60 minutes). The median duration of immediate postnatal hospital stay was 2.5 days (IQR 2-4 days), with a maximum of 12 days.

4.3 Readmission with sepsis

Nineteen (79.2%) out of the 24 women were discharged home after their caesarean sections and readmitted with sepsis. Two (8.33) came as referrals from public satellite hospitals and one (4.2%) presented after having a caesarean section in a private hospital. Clinical vital data on

readmission is shown in Table 4.5. The median temperature was 38.5 degrees, and the median heart rate was 129/minute. One quarter of women had systolic blood pressures less than 83 mmHg.

Table 4.5 Clinical vital data on readmission

	Median (IQR)	**Range**
Temperature (degrees C)	38.5 (38.0-39.0)	35.0-40.0
Respiration rate	30.5 (26.0-38.0)	20.0-40.0
Heart rate per minute	129.5 (120.0-144.0)	96 -163
Systolic blood pressure (mmHg)	96.0 (83.0-110.0)	50.0-134.0
Diastolic blood pressure (mmHg)	55.0 (40.0-70.0)	22.0-80.0

4.4 Biochemical and microbiological results

The blood results presented are those from testing on readmission (n=23) or at the time that sepsis was detected while still in hospital (n=1). Fifteen (62.5%) women of the 24 women had anaemia. Twenty (83.3%) women had renal impairment either elevated creatinine or urea levels or both, of which one women was admitted for renal failure to medical wards and was undergoing dialysis when it was later discovered that she was postpartum and required a hysterectomy.

Ten (41.7%) women had positive blood culture results and fourteen (58.3%) patients had blood taken for blood cultures but results did not appear in the files. *S. aureus* was cultured in 80% of the women with results, where more than half of these (62.5%) were wound swab cultures and 37.5% were isolated from blood cultures. *Streptococcus pyogenes* was isolated in blood cultures

and *E. coli* was isolated from urine cultures and Gram-negative bacilli while *Acinetobacter baumanni* was only found in blood cultures.

Table 4.6 Results of blood investigations

Investigation	**Result**	**N**	**(%)**
Hb (g/dL)	≤ 10	15	(62.5)
	≥10.1	9	(37.5)
WCC ($x10^9$/L)	≤4.0	3	(12.5)
	4.1-11.9	12	(50)
	≥12	9	(37.5)
Platelets($x10^9$/L)	<50	0	
	50-100	2	(8.33)
	101	22	(91.2)
Urea(mmol/L)	≤ 7	4	(16.7)
	≥ 7.1	20	(83.3)
Creatinine (micromol/L)	≤ 60	6	(25)
	≥61-100	4	(16.7)
	≥ 101	14	(58.3)

Table 4.7: Causative organisms

Causative organism	**N**	**(%)**
Staphylococcus aureus	8	(80)
Streptococcus pyogenes	3	(30)
Klebsiella species	2	(20)
Acinetobacter baumanni	2	(20)
Gram-negative bacilli	2	(20)
Escherichia coli	2	(20)

4.5 Antibiotics administered

On readmission due to sepsis, 11 (45.8%) women received co-amoxiclav; metronidazole was received by nine (37.5%) women. Amikacin, tazobactam, and meropenem were each given to four (16.7%) women. Three (12.5%) women received ceftriaxone and two (8.2%) women received ampicillin, metronidazole and gentamicin as triple antibiotic therapy. Antibiotics were combined for broad-spectrum coverage (Table 4.8)

Table 4.8 Antibiotics or antimicrobials administered to women in the study (n=24)

Antibiotics	**N**	**(%)**
Co-Amoxiclav	11	(45.8)
Metronidazole	9	(37.5)
Cefazolin	4	(16.7)
Clindamycin	4	(16.7)
Gentamicin	4	(16.7)
Meropenem	4	(16.7)
Tazobactam	4	(16.7)
Amikacin	4	(16.7)
Ceftriaxone	3	(12.5)
Ampicillin	2	(8.30)
Vancomycin	1	(4.20)

4.7 Site of infection

Fifteen women (57.3%) had intra-abdominal sepsis with pus collections, 5 (21%) had surgical site infections, 4 (17%) had severe endometritis, manifested as a profuse, foul smelling vaginal discharge, in addition to systemic signs of infection as described above.

Source control

Twenty (83.3%) of the 24 women required surgical intervention. Five (20.8%) women had wound debridement for surgical site infection and 14 (58.3%) women had wound debridement

for surgical site infection as well as a hysterectomy for intra-abdominal sepsis. One (4.2%) woman had an evacuation of the uterus for retained products of conception.

Thirteen women (54.1%) were admitted to the hospital multidisciplinary intensive care unit (ICU) following surgical intervention for sepsis. Five (20.8%) women met local criteria for ICU admission, but could not be accommodated due to bed unavailability. These women were cared for in the labour ward high care area. Twenty women (83.3%) died less than 5 days after readmission with sepsis. The remaining four women died after 6, 8, 12 and 22 days respectively.

CHAPTER 5: DISCUSSION

5.1 Frequency of maternal death due to sepsis following caesarean section

The mortality rate (19.3/100 000 caesarean sections, or one death for every 5180 operations) is similar to the South African figure of 15.1/100 000 or 99 deaths for every 655686 operations for the three years covered in the 2011-2013 Saving Mothers report (6). It also compares with findings from a study done in West Africa by Colle et al., where the maternal death rate due to sepsis after caesarean section was 22.6/100 000 live birth. Based on previous work done at CHBAH, where the rate of readmission for caesarean section related sepsis was 1.5%, the case fatality rate for women readmitted is about 1.3% at the hospital (37). International data on caesarean section-related mortality are limited. In high-income countries, all-cause mortality from puerperal sepsis (including vaginal births) is low, with rates of 0.5 per 100 000 live births in the Netherlands and 0.4-0.85/100000 live births in the United Kingdom (5). In comparing these rates with those from this study, from South Africa as a whole and from West Africa, simple calculations (not shown here) suggest an approximately 20-fold higher rate of mortality from caesarean section sepsis in sub-Saharan Africa compared with Western Europe (4).

5.2 Prevalence of risk factors for puerperal sepsis

Analysis of age groups of women who died did not reveal any suggestive pattern of risk, and appeared not significantly different from the age groups of women giving birth at CHBAH. While the mean gestational age was 37.5 weeks, 42 % of those with complete files delivered preterm. While the numbers were small and prone to sampling error, preterm labour is a well-known risk for puerperal sepsis, possibly related to chorioamnionitis with our without pre-labour rupture of the membranes.

Prolonged or obstructed labour was the commonest indication (50%) for caesarean section in this study. The association of sepsis with caesarean section for prolonged labour is also well known and has been demonstrated in a Pakistan based study by Shamshad and in Nigeria by Chama (14, 25). Prolonged exposure of the uterine cavity to vaginal bacteria, often with ruptured membranes, provides a plausible reason for a higher rate of postoperative infection. The same considerations apply for emergency versus elective caesarean section, with 20 of 22 caesarean sections (in which this data was available) being emergency operations in this study. Similar findings have been reported by Wloch et in their study in risk factors for surgical site infection following caesarean section (45).

5.3 Patient weight

The median BMI in our study was 36.2 kg/m^2, and 83.3% of the women who died from sepsis after caesarean sections were obese. This finding was not unexpected and has been reported previously, for example in a study done in Saudi Arabia by Al-Jama where the mean BMI was 35.3 and obesity was linked to poor wound healing and wound sepsis (43). Surgical site infection is of particular concern in obese women undergoing abdominal surgery (70).

5.4 Readmission with sepsis, and clinical management

Twenty three patients (95.8%) had their vital data taken on re-admission with sepsis after caesarean section. A large proportion had abnormal vital signs such as pyrexia, tachypnoea, tachycardia and hypotension. Most had systemic inflammatory response syndrome on admission, with a large number already having evidence of severe sepsis (renal dysfunction, thrombocytopenia and hypotension). This is in line with the poor prognostic outcomes for severe sepsis as stated by Wanderer et al in their study of obstetric care admissions to ICU (79).

Wound sepsis was the primary reason for seeking medical attention, and 83% of the women had extensive sepsis that required surgery. A large variety of antibiotics was used, possibly reflecting different stages in the progression from sepsis to death. The use of antibiotics was in line with what is stated in publications of the Surviving Sepsis Campaign (78). Most of the women required ICU admission, although some could not be admitted due to unavailability of beds in the intensive care unit. It is possible that the unavailability of beds contributed to the deaths, but an audit of avoidable factors was not done in this study.

5.5 Microbiological findings.

The most frequent cultured organism in the study was *Staphylococcus aureus,* found in blood and wound swab specimens. *Streptococcus pyogenes* bacteraemia was also a frequent finding, in line with a study by Kankuri et al from Finland, where the most commonly cultured organisms were group A and group B streptococci (25). It was disappointing that not all of the culture results were obtained by the clinicians, even though records suggest that blood and pus swab specimens were taken for culture.

HIV infection was a dominant factor in our findings, with 16 women (66.7%) being HIV infected. This is not surprising, given HIV-related immunosuppression and lack of available antiretroviral treatment for most of the years in which the study covered. Up to about 2008, HIV was mostly untreated and highly stigmatised in South Africa. The South African Saving Mothers data from 2011-2013, when HIV treatment was available, found that the HIV seroprevalence in all puerperal sepsis was 67%. This is much higher than the approximately 30% seroprevalence in pregnant women during that period (6)

5.6 Limitations of the Study

The study has several limitations. With only 24 women included, estimates of prevalence of risk factors may have been affected by random error. It was also difficult to assess fully the possible predisposing factors for sepsis due to missing information in the patient files. Given social and economic determinants for sepsis and maternal deaths, it would have been useful to know the level of education, living conditions including water supply and sanitation, and internal immigrant status. Some women came as referrals from other hospitals without the medical records of those hospitals. These deficiencies are inherent in a retrospective study of this kind. The ideal study design to determine the influence of risk factors would have been a prospective cohort study planned from 1997, with control groups including women with caesarean section who did not develop sepsis, as well as women who developed sepsis but did not die. Such a design was clearly not feasible.

It is possible that there were actually more deaths from puerperal sepsis following caesarean section. Some women may have been admitted in other departments and not referred back to the maternity department as usually warranted within 42 days of delivery. Certain of these women may have been diagnosed provisionally in internal medicine wards with other forms of sepsis such as pneumonia, related to HIV infection. Some women who had caesarean sections at CHBAH may have died at home, or presented at other Johannesburg hospitals with sepsis. It however unlikely that these groups made up a large number, but it should be remembered that the study number is a minimum and the estimate for mortality from sepsis is a minimum estimate.

CONCLUSION

Puerperal sepsis is still a major cause of maternal mortality at CHBAH. Caesarean section is a major risk factor for puerperal sepsis. HIV seropositivity was observed in more than half of the women who died from sepsis after caesarean section. Prolonged labour was the most prominent risk factor. *Staphyloccus aureus* was the most prominent causative organism for puerperal sepsis found in wound and blood specimens.

For future studies it would be interesting to investigate pregnancy-related sepsis mortality with respect to HIV and its treatment. Another useful approach would be a prospective study on the risk factors and aetiology of caesarean sepsis, including women who suffer sepsis with readmission, severe sepsis and death.

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APPEDICES

Appendix A – Data Sheet

Data Sheet STUDY No

Age	…..years	
Booked	Y	N
Number of Visits		
Gestational Age	…../40	
Parity		
Gravidity		
Previous Caesarean Section	Y	N
Hypertensive Disease	Y	N
Diabetes	GDM	IDDM

Booking Data

Hb (Booking)	g/dl
HIV	+ / -
• CD4 Count	
• ART	
Weight	kg
Height	m
BMI	kg/m2

Antepartum

PPROM	<24 hours	>24 hours
Antibiotics	Y	N
Chorioamnionitis	Y	N

Indications for Caesarean Section

Elective Caesarean Section
Emergency Caesarean Section • Chorioamnionitis (1) • Failed Induction of Labour (2) • Fetal Distress (3) • Severe Preeclampsia (4) • Diabetes (5) • Poor Progress/CPD (6)

Intrapartum

PROM	**Y**	**N**
Number of PV Exams		
Antibiotics (Pre-op)	Y	N
Duration of labour	…./hours	
Partogram	Y	N

Peri-operative Data

ROM	Y	N
Labour	LPL	APL

Time of Surgery	08H00-20H00		20H00-08H00
Duration of Operation	…. Minutes		
Anaesthesia	General		Regional
Prophylactic Antibiotics	Y		N
Skin Incision	Low Transverse		Midline
Uterine Incision	Classical		Low Transverse
Peritoneal Closure	Y		N
Injuries	None	Bowel	Bladder
Hysterectomy	Subtotal		Total
Blood Loss	…. Ml		
Blood Transfusion	Y		N
Drains	Peritoneal		Subcutaneous

Post-operative Data

Admission	High Care	PNW	Intensive Care Unit
Post-operative Antibiotics	Y		N
Hospital Duration	….Days		

Readmission

BP …/….mmHg	Pulse …./min	Temp ….°C	GCS …/15	Resp Rate …./min
Haematology FBC • WCC • Hb • Platelets				
Renal Dysfunction U&E Na/K/CL/HCO3/U/Cr				
Liver • Conj • Unconj • Prot • Alb • AST • ALT				
CRP				
Metabolic Status (ABG) Ph/Be/Lact/Pco2/P02				
Endocrine (HGT)				
Blood Cultures (Organism and sensitivity)				

Days post-operative	…. Days	
Days admitted	…. Days	
Site of infection		
Antibiotics		
Transfusion	Y	N
Relook Laparotomy • Debridement • Hysterectomy		
ICU admission	Y	N

Appendix B – Ethics Clearance Certificate

R14/49 Dr Zandile Dlamini

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M150756

NAME: (Principal Investigator)	Dr Zandile Dlamini
DEPARTMENT:	Obstetrics and Gynaecology Chris Hani Baragwanath Academic Hospital
PROJECT TITLE:	Maternal Mortality Due to Sepsis after Caesarean Section at Chris Hani Baragwanath Academic (CHBAH) From 1997-2014
DATE CONSIDERED:	31/07/2015
DECISION:	Approved unconconditionally
CONDITIONS:	
SUPERVISOR:	Prof Eckhart Buchmann
APPROVED BY:	Professor P Cleaton-Jones, Chairperson, HREC (Medical)
DATE OF APPROVAL:	20/11/2015

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 Research Office Secretary in Room 10004, 10th floor, Senate House/2nd Floor, Phillip Tobias Building, Parktown, University of the Witwatersrand. I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to resubmit the application to the Committee. **I agree to submit a yearly progress report**.

Principal Investigator Signature Date

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

Appendix C - Permission to conduct research

GAUTENG PROVINCE

REPUBLIC OF SOUTH AFRICA

MEDICAL ADVISORY COMMITTEE
CHRIS HANI BARAGWANATH ACADEMIC HOSPITAL

PERMISSION TO CONDUCT RESEARCH

Date: 21 Aug 2015

TITLE OF PROJECT: Maternal mortality due to sepsis after caesarian section at Chris Hani Baragwanath Academic Hospital

UNIVERSITY: Witwatersrand

Principal Investigator: Z Dlamini

Department: Obstetrics

Supervisor (If relevant): E Buchmann

Permission Head Department (where research conducted): Yes

Date of start of proposed study: Aug 2015
Date of completion of data collection: Dec 2017

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

- Permission having been granted by the Human Research Ethics Committee 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: 21 August 2015

Approved/Not Approved
Hospital Management
Date: 01/11/15