UNIVERSITY OF ZIMBABWE

MASTERS OF MEDICINE IN OBSTETRICS AND GYNAECOLOGY DISSERTATION

RANDOMISED CONTROL TRIAL COMPARING TWO REGIMENS OF PROPHYLACTIC ANTIBIOTICS FOR WOMEN UNDERGOING CAESAREAN SECTION

BY

ASAPH ZIRUMA **REGISTRATION NUMBER: R0021124**

Supervisor: Dr F M Gidiri
Department of Obstetrics & Gynaecology
University of Zimbabwe

Dissertation in partial fulfillment of the requirements for the Masters of Medicine Degree in Obstetrics and Gynaecology

TABLE OF CONTENTS

Chapter 3

RESULTS

Demographic data:

Outcomes:

Chapter 4

FIGURES AND TABLES LIST

ACKNOWLEDGEMENTS

I am so grateful to Dr Gidiri for his professional assistance in designing and supervising this study.

I thank Dr Nhara for his assistance in carrying out this study.

I thank Mr G Mandozana for assistance in statistical analysis of the study findings

I thank my wife, Precious for her understanding and support during my constant absence from home.

I also extend my gratitude to the following people

- Staff at Mbuyanehanda and Harare Maternity Hospitals
- Mr Vuragu and Mr Chiluba (chief pharmacists at Parirenyatwa and Harare hospitals respectively) for availing drugs for the smooth running of this study

LIST OF ABBREVIATIONS

EDLIZ	Essential Drugs List and Standard Treatment Guidelines for Zimbabwe
MU	Mega-units (dose of benzyl penicillin)
RCT	Randomised Control Trial
g	grams (doses of drugs)
mg	milligrams (doses of drugs)
C/S	Caesarean Section
RR	Relative risk
CI	Confidence interval
OR	Odds ratio
aOR	Adjusted odds ratio
SSI	Surgical site infection
BPD	Bronchopulmonary dysplasia
HIV	Human Immunodeficiency Virus
tds	ter die sumendum (three times a day)
qid	quarter in die (four times a day)
cm	centimeters
O' level	Ordinary Level
IQR	Interquartile Range
CPD	Cephalopelvic disproportion
MSL	Meconium stained liquor
APH	Antepartum haemorrhage
PMTCT	Prevention of mother to child transmission of HIV
BP	Hypertensive disease
ART	Antiretroviral therapy
EVAC	Evacuation of the uterus
RPOCs	Retained products of conception
iv	Intravenously
po	Orally

ABSTRACT

Introduction

Infection is one of the major complications of surgery. Caesarean section is the single most important risk factor for postnatal infections [2]. Prophylactic antibiotics have become a standard of management for people undergoing surgery. According to the EDLIZ 2006, women undergoing caesarean section should be given a single dose of Benzyl penicillin 5MU iv and Chloramphenicol 1gram iv. However at Parirenyatwa and Harare hospitals, patients get antibiotics for an average of 7days. The prolonged course which is in practice increases the work load on the hospital staff which is already overwhelmed due to understaffing. It also increases costs to the patients, demands patient compliance and increases risks of antibiotics resistance. We did a study to see if the current practice can be justified. We compared current practice of prophylactic antibiotics to a proposed single dose regime of prophylactic antibiotics for women undergoing caesarean section. The current practice was standardized for the purpose of this study.

OBJECTIVES:

Main Objective

- To compare the effectiveness of "single dose ceftriaxone and metronidazole" with the current practice of week-long course of prophylactic antibiotics for caesarean section.

METHODOLOGY

A prospective Randomized Control Trial was done at Parirenyatwa and Harare hospitals from 2 February 2012 to 30 May 2012. Women undergoing caesarean sections were recruited following an inclusion and exclusion criteria. These were randomized into Arm 1 and Arm 2. Those in Arm 1 were given a single dose of Ceftriaxone and Metronidazole preoperatively and no more antibiotics postoperatively, except for treatment. Those in arm 2 were given a standardized week-long course of antibiotics representing the current practice. The patients were followed up for 6weeks.

The sample size of 260 patients was calculated, which meant 130 patients were needed for each arm. 280 patients were initially recruited but at the end, 232 were analysed after losing some patients during follow-up (see flow diagram).

RESULTS

Two hundred and thirty two patients were analyzed. 112 were in Arm 1 while 120 were in arm 2. These were compared for the incidence of hyperpyrexia, admission with puerperal sepsis, wound sepsis, prolonged hospital stay, laparotomy for pelvic abscess and mortality. Infective morbidity was defined by the presence of at least one of the above parameters. Infective morbidity occurred in 28 out of 232 (12%). 15 of these patients were in ARM 1 (Single dose group) while 13 were in ARM 2 (Week – long group). The difference was not statistically significant..

CONCLUSIONS

In this setting, the administration of single dose preoperative ceftriaxone 1g in combination with metronidazole 500mg, is clinically equivalent to the current practice of week-long course of antibiotics for the prevention of puerperal infections. We therefore recommend the single dose regimen due to lower costs and lesser burden to hospital staff who will administer reduced number of doses of antibiotics

CHAPTER 1

INTRODUCTION

One of the complications of major surgery is infection. This can be infection of the surgical wound or organs which are exposed to the infective organisms during or after the surgery. According to the Department of Surgical Education, Orlando Regional Medical Centre, surgical site infection accounts for 15% of nosocomial infections. The National Perinatal Epidermiology Unit in Oxford carried out a meta-analysis of the randomized controlled trials of the value of antibiotic prophylaxis for caesarean section. In the groups given placebo or no treatment the incidence of frank pus or positive bacterial culture was 9%. The incidence of febrile illness was 40% while that of endometritis was 26%. In this analysis, women who had received prophylactic antibiotics had infection rates that were one third of the untreated controls.

Surgical site infections are associated with prolonged hospital stays and increased costs to the patient and the health delivery system. Usually infection develops when endogenous flora are translocated to a normally sterile site. Seeding of the operative site from normal commensals can occur with infection coming from the skin and hollow viscus like the bowel, vagina and mouth. Factors influencing the development of surgical site infections include bacterial inoculum and virulence, host defenses, perioperative care, and intraoperative management.

Caesarean section is the single most important risk factor for postnatal infections [2]. It is associated with a 20 fold greater risk of infection compared with vaginal delivery. Infectious complications that occur after cesarean delivery are an important and substantial cause of maternal morbidity and are associated with a significant increase in hospital stay. These include fever, wound infection, endometritis, bacteremia, pelvic abscess, septic shock, necrotizing fasciitis, septic pelvic vein thrombophlebitis and urinary tract infection [2, 54, 55). However fever can occur after any operative procedure

and low-grade fever following a cesarean delivery may not necessarily be a marker of infection [56].

Factors associated with increased risk of infection after caesarean section include emergency caesarean section, labour and its duration, rupture of membranes and duration of rupture, socioeconomic status, vaginal examinations during labour, internal fetal monitoring, urinary tract infection anemia, blood loss, obesity, diabetes, general anesthesia, the skill of the surgeon and operative technique [2, 54, 55]. Labour and ruptured membranes are the most important factors. Bacterial vaginosis is associated with an increased incidence of endometritis [40].

The most important source of micro-organisms responsible for post caesarean section infection is the genital tract. Even in the presence of intact membranes, microbial invasion of the intrauterine cavity is common, especially with preterm labour [32]. Pathogens isolated include Escherichia coli and other aerobic gram negative rods, Group B streptococcus and other streptococcus species, Enterococcus faecalis, Staphylococcus aureus and coagulase negative staphylococci, anaerobes (including peptostreptococcus species and Bacteroides species), Gardnerella vaginalis and genital mycoplasmas. Wound infections caused by Staphylococcus aureus and coagulase negative staphylococci arise from contamination of the wound with the endogenous flora of the skin at the time of surgery [33].

General principles for the prevention of any surgical infection include good surgical techniques, skin antisepsis and antimicrobial prophylaxis. Timing of prophylactic antibiotics differ, but the first dose has to be given intraoperatively or not more than 1 hour before the surgeon makes an incision on the patient. A single dose is the standard and sometimes a second dose is given if indicated within 24hours of the operation. The choice of antibiotics is determined by the targeted organism. In some centres in the United States prophylactic antibiotics are given intravenously within 1 hour prior to the surgical procedure (Department of Surgical Education, Orlando Regional Medical centre). A single dose is usually given and if the procedure is prolonged, a few more

doses may be given depending on the surgeon's discretion and this should not be continued beyond 24 hours.

JUSTIFICATION FOR THE STUDY

There is overwhelming evidence in literature showing that single dose of antibiotics are effective in preventing post-surgical infections. Local guidelines recommend single dose of prophylactic antibiotics but antibiotics are given for one week to all patients in our hospitals. Our local guidelines are based on old evidence of a study done on our population [16]. Clinicians have drifted away from these guidelines over time to a practice of giving antibiotics for 1 week. This has increased the workload in our understaffed hospitals, increased the costs to our poor patients and under-resourced health system, increased burden for patient compliance and increased risks of antibiotics resistance. It was necessary to test if the current practice of prolonged course of antibiotics can be justified in our hospitals.

OBJECTIVES

Main Objective

- To compare the effectiveness of a proposed single dose prophylactic antibiotics with the conventional week long course of prophylactic antibiotics for caesarean section

Other Objectives

- To come up with guidelines of antibiotics prophylaxis for women having caesarean section.

- To establish the prevalence of Puerperal Infections in our setting.

OUTCOME MEASURES

- Pyrexia >38^{o}C
- Admission with puerperal sepsis
- Wound sepsis
- Maternal death
- Hospital stay
- Laparotomy for pelvic abscess

LITERATURE REVIEW

Why prophylactic antibiotics?

Puerperal infections are among the top 5 causes of maternal mortality in both the developing and developed world [1]. Women delivered by cesarean section classically have a 5 to 20-fold increased risk of developing puerperal infections [2]. The most common infections are surgical site infections and infection of the urinary tract. Pelvic abscesses, septic pelvic phlebitis, pneumonia and sepsis, although rare, are also increased. These infections are associated with considerable health and economic burdens [3]. Despite antibiotic prophylaxis, at least 10% of caesareans overall are complicated by infection, and over 15% by fever [4]. Fifteen to 80% of infections may actually occur after discharge from the hospital [5, 6].

Worldwide cesarean section rates are rising [7, 8]. The increase has been noted in both the primary and repeat caesarean sections. More and more patients are now requesting caesarean section with no obstetric indications [9]. WHO reported in 2005 that in Latin America, rates were as high as 35%. This trend of increased rates of caesarean sections is worldwide although generally rates are lower in developing compared to developed countries. It is imperative that new strategies to enhance the effectiveness of antibiotic prophylaxis in reducing post-cesarean infection must emerge [5, 10, 11].

There is overwhelming evidence that prophylactic antibiotics reduce surgical site infections [4, 5, 10, 12, 13]. In one metaanalysis [4] eighty-one randomized trials were included, comparing antibiotic prophylaxis or no treatment for both elective and non-elective cesarean section. Use of prophylactic antibiotics substantially reduced the incidence of episodes of fever, endometritis, wound infection, urinary tract infection and serious infection after cesarean section. A recent Cochrane Review looked at 86 studies involving over 13000 women [14]. In this review prophylactic antibiotics substantially reduced the incidence of febrile morbidity (average risk ratio (RR) 0.45; 95% confidence

interval (CI) 0.39 to 0.51, 50 studies, 8141 women), wound infection (average RR 0.39; 95% CI 0.32 to 0.48, 77 studies, 11,961 women), endometritis (RR 0.38; 95% CI 0.34 to 0.42, 79 studies, 12,142 women) and serious maternal infectious complications (RR 0.31; 95% CI 0.19 to 0.48, 31 studies, 5047 women). No conclusions can be made about other maternal adverse effects from these studies (RR 2.43; 95% CI 1.00 to 5.90, 13 studies, 2131 women). None of the 86 studies reported infant adverse outcomes and in particular there was no assessment of infant oral thrush. There was no systematic collection of data on bacterial drug resistance. The findings were similar whether the cesarean section was elective or non elective, and whether the antibiotic was given before or after umbilical cord clamping.

In a Zimbabwean study done in 1988, 232 patients undergoing elective lower segment caesarean section were randomly allocated to receive a pre-operative prophylactic dose of a combination of crystalline penicillin and chloramphenicol or a placebo [16]. The two groups were comparable in terms of patient characteristics and operation variables. The group receiving antibiotics had significantly fewer febrile and infectious morbid events and thus spent fewer days in hospital than the group receiving the placebo.

A meta-analysis looked at prophylactic antibiotics for nonlabouring patients who underwent caesarean section [18]. Use of antibiotics decreased the risk of all infectious outcomes reported. When the results of 4 studies were pooled, prophylactic antibiotic use was associated with a significant reduction in postoperative fever (RR 0.25; 95% CI 0.14-0.44). A similar reduction was noted for endometritis in 4 studies (RR 0.05; 95% CI 0.01-0.38). Two studies reported on wound infection and showed a trend toward a protective effect (RR 0.59; 95% CI 0.24-1.45).

Not all studies have shown a clear benefit of prophylactic antibiotics. A South African study showed little benefits of prophylactic antibiotics for cesarean section [17]. Wound infection occurred in 13.3% and 12.5% of women in the placebo and cefoxitin groups, respectively. Prophylactic antibiotics did not decrease febrile morbidity, wound infection, endometritis, urinary tract infection and pneumonia. Those who received cefoxitin stayed

on average a day less in hospital than those who received placebo (6.9 vs 7.8 days, risk difference 0.94 CI 1.57 - 0.31 days). Eleven women (4.6%) in the placebo group and eight (3.4%) in the cefoxitin group had microbiological evidence of wound infection. Staphylococcus aureus was the most common pathogen (43%) isolated. Similar proportions in both groups (6.3% placebo and 5.1% cefoxitin) required a course of therapeutic antibiotics.

Timing of prophylactic antibiotics

The most recent studies have demonstrated that antibiotics are most effective if administered before the initial incision as opposed to intraoperatively or postoperatively. While this is generally understood, there are fears about the possible effects of these antibiotics on the normal flora and subsequent development of the immune system in the unborn fetus exposed to preoperative antibiotics. Antibiotics commonly used for cesarean prophylaxis are rapidly transferred to the fetal compartment raising concerns that fetal exposure to antibiotics might also mask infection in the neonate and promote the selection of resistant organisms [11]. Pediatricians have historically performed invasive and costly sepsis work-ups on neonates who were exposed to antibiotics immediately prior to delivery [19]. As a result of this prophylactic antibiotics for caesarean section have generally been given intraoperatively, after cord clamping [4, 11]. However antibiotics have been given to pregnant women for therapeutic purposes where the benefits outweigh the possible harm.

One powerful metaanalysis looked at randomized controlled trials on this subject [20]. The purpose of this study was to summarize the available evidence on timing of perioperative antibiotics for cesarean delivery. They searched the literature for studies that compared prophylactic antibiotics for cesarean delivery that are given before the procedure versus at cord clamping. Preoperative administration significantly reduced the risk of postpartum endometritis (relative risk [RR], 0.47; 95% CI, 0.26-0.85; P = .012) and total infectious morbidity (RR, 0.50; 95% CI, 0.33-0.78; P = .002). There was a trend toward lower risk of wound infection (RR, 0.60; 95% CI, 0.30-1.21; P = 0.15).

Preoperative administration of antibiotics did not significantly affect suspected neonatal sepsis that requires a workup (RR, 1; 95% CI, 0.70-1.42), proven sepsis (RR, 0.93; 95% CI, 0.45-1.96), or neonatal intensive care unit admissions (RR, 1.07 95% CI, 0.51-2.24). Although antibiotic exposure did not appear to influence neonatal sepsis in any single trial or in the metaanalysis, none of these studies was sufficiently powered to determine a clinically significant difference in this outcome. As many as 4,800 cesareans would be needed to ascertain a 33% difference in neonatal sepsis with 80% power assuming a baseline incidence of about 5%. No differences in frequency of neonatal sepsis work-ups or proven sepsis were noted under the blinded conditions of these clinical trials. There was no significant heterogeneity between the randomized controlled trials.

Another metaanalysis done in France showed similar results [21]. The objective was to compare the effect of preoperative with antibiotics after umbilical cord clamping. Preoperative administration of antibiotics (n=456) rather than after cord clamping (n=563) provides a significant reduction in the incidence of endometritis (OR 0.59 [95% CI 0.35-0.98]) and of total maternal infectious morbidity (OR 0.51 [95% CI 0.32-0.82]). However this benefit was not observed regarding the incidence of wound infection (Peto OR 0.58 [95% CI 0.29-1.16]), neonatal infection (Peto OR 1.06 [95% CI 0.57-1.96]), neonatal sepsis workup (OR 1.02 [95% CI 0.67-1.54]), neonatal documented sepsis (Peto OR 0.93 [95% CI 0.43-2.02]) or neonatal intensive care unit admission (OR 0.97 [95% CI 0.61-1.56]). No significant heterogeneity was observed between the included studies.

An American study looked at the effects of a change in policy on the timing of prophylactic antibiotics for caesarean section [22]. The purpose of this study was to examine the effect of a change in policy regarding the timing of antibiotic administration on the rates of postcesarean delivery surgical-site infections (SSI) A policy change was instituted in which prophylactic antibiotics were given before skin incision rather than after cord clamp.The results showed that overally, rate of SSI fell from 6.4 to 2.5% (P = 0.002). After controlling for potential confounders, there was a decline in overall SSI with an adjusted odds ratio (aOR) of 0.33 (95% CI 0.14-0.76), a decrease in endometritis

(aOR 0.34; 95% CI 0.13-0.92), and a trend towards a decrease in cellulitis (aOR, 0.22; 95% CI 0.05-1.22).

The Committee on Obstetrics Practice in the USA gave an opinion on the timing of prophylactic antibiotics for cesarean section [23]. The Committee looked at multiple relevant randomized controlled trials and recommended that antimicrobial prophylaxis for all cesarean deliveries should be administered within 60 minutes of the start of the cesarean delivery unless the patient is already receiving therapeutic antibiotics.

Choice of antibiotics

Many factors come into play when making a choice of antibiotics to use for prophylaxis. Cost and availability of the antibiotic are among the most important considerations to be made before choosing the antibiotic. The efficacy of the antibiotic should also be supported by studies done on the population in which the drug is to be used.

In some centres, first generation cephalosporins are recommended over broader spectrum antibiotics, as they are equally effective and less costly than the latter [11, 24]. However, the broad-spectrum antibiotics that have been evaluated are mainly single-agent extended-spectrum penicillins, or 2^{nd} or 3^{rd} generation cephalosporins [24]. In one small trial, ampicillin was compared to ampicillin plus gentamycin. In this study ampicillin alone was associated with significantly higher risk of endometritis, febrile morbidity and longer hospitalization [25].

Accumulating evidence from randomized clinical trials suggest that extended-spectrum regimens using a regimen involving the use of both the standard narrow-spectrum antibiotic in addition to a second antibiotic of a different class e.g. azithromycin, gentamycin or metronidazole are significantly more effective in reducing post-cesarean infections (by 30–60%) and shortening hospital stay than narrow-spectrum agents alone [25, 26]. A cohort study confirmed a corresponding drop in rates of post-cesarean

endometritis with increasing use of azithromycin-based extended spectrum prophylaxis at one US center over a period of 14 years [27]. The incidence of wound infection also decreased from 3.2 to 1.3% over the same time period [28]. These findings are limited by the possibility that they are entirely due to other concurrent changes during the time periods. The association of extended-spectrum antibiotic prophylaxis with reduced rates of post-cesarean infection conforms to the principle that the selected prophylactic antibiotic regimen should have activity against microbial agents commonly involved in surgical site contamination and actual infections [5, 10, 11].

Post-cesarean infections are polymicrobial, involving aerobes, anaerobes and *Mycoplasmas*. The most frequent microbes isolated from endometrial cultures of women with post-cesarean endometritis include *Ureaplasmas/Mycoplasmas*, aerobic gram-negative rods, enterococci, *Gardnerella* and anaerobes [29-32]. The most common organisms isolated from wound infections also include Ureaplasma as well as staphylococci and enterococci [33-34]. Furthermore, when specifically identified, *Ureaplasma* (or *Mycoplasma*) is the most common organism isolated from the amniotic fluid and chorioamnion at cesarean delivery, and is associated with a 3 to 8-fold increased risk of post-cesarean endometritis or wound infection [35-39]. Bacterial vaginosis is also associated with as much as a 6-fold increased risk of post-cesarean endometritis [40]. These organisms may also vary from institution to institution. Narrow-spectrum regimens like cefazolin alone do not cover frequent isolates or risk factors such as *Ureaplasma* and anaerobic bacteria thereby modifying flora towards the increased presence of resistant organisms such as anaerobes [29, 41]. According to some literatue, azithromycin or metronidazole appropriately suppressed ureaplasma or anaerobes respectively and it was likely that the origin of the observed benefits extended to the suppression of other susceptible organisms. Azithromycin appeared to be a good option for a 2nd antibiotic for extended-spectrum regimens for cesarean delivery. It has a longer half-life of 68 hours, higher tissue concentration and lower potential for fetal transfer than the other antibiotics in published studies [42-43]. In addition, azithromycin had both aerobic and some anaerobic coverage. It effectively covered for Ureaplasma, and was the only choice associated with significantly reduced incidence in both endometritis and

wound infection [25, 44,45,26,27,28]. With evidence suggesting that more than 20% of preterm neonates may have *Ureaplasma* bacteremia [46] and suggestions that bronchopulmonary dysplasia (BPD) is associated with neonatal *Ureaplasma* infection [47] pre-incisional use of azithromycin-based extended spectrum prophylaxis may theoretically prevent neonatal sepsis syndrome and BPD.

In Mozambique a study compared single dose preoperative Gentamicin and Metronidazole with a week long conventional course of prophylactic antibiotics [48]. Women completing the study (n = 241) were distributed into group 1 (n = 116) and group 2 (n = 125). No significant differences were found in the prevalence of postoperative infection nor in the mean hospital stay. The cost of the single dose of prophylactic antibiotics was less than one-tenth of the cost of the standard postoperative scheme.

A 2010 Cochrane review looked at different classes of antibiotics given to women routinely for preventing infection at caesarean section [49]. 29 studies were included of which 25 provided data on 6367 women. There was a lack of good quality data and important outcomes often included only small numbers of women. The evidence showed no overall difference between the different classes of antibiotics in terms of reducing maternal infections after caesarean sections. None of the studies looked at outcomes on the baby, nor did they report infections diagnosed after the initial postoperative hospital stay. It was not possible to assess impact of different classes of antibiotics on bacterial resistance. It was concluded that cephalosporins and penicillins have similar efficacy at caesarean section when considering immediate postoperative infections.

Costs involved

It would not make sense to use prophylactic antibiotics without considering its cost. When looking at the costs of using a certain prophylactic antibiotic regimen, it is not enough to look at the cost of acquiring the antibiotic. Complications that may arise as a result of poor efficacy of the antibiotic, prolonged hospital, investigations and subsequent treatment all add to the costs of using that antibiotic regimen, if the same costs can be

avoided by using alternative antibiotics. A typical antibiotic regimen is one that is cheap to acquire and its use is associated with normal length of hospital stay with no extra expenses of investigating and treatment of infective mobidity.

There are studies which have looked at the cost – effectiveness of of using prophylactic antibiotics [50]. They conducted an economic analysis of prophylactic antibiotic administration for elective cesarean delivery. Costs were based on the hospital's accounting system. Cost of an uncomplicated elective cesarean delivery was $1638.57. Fever evaluation added $125.91. Elective procedure complicated by endometritis cost $2327.29. Cefazolin administration cost $1.01. The following estimates were used: relative risk (RR) of endometritis with antibiotics was 0.18 (95% CI 0.07-0.45), fever 0.47 (95% CI 0.32-0.68), risk of endometritis without prophylaxis 4.8% (95% CI 0.9%-43%), and fever without prophylaxis 14.4% (95% CI 4%-33%). Cost of an average case without prophylaxis was $1683.72; prophylaxis reduced this to $1653.06. Sensitivity analysis over the ranges above still yielded cost savings. Therefore in this study administration of prophylactic antibiotics for elective cesarean delivery reduced costs by $30.66 per case, approximately 2% of the total cost.

An earlier study in 1986 compared the costs of using four different drugs [51]. In this study ampicillin was noted to be the most expensive drug because of its high failure rate. Piperacillin was the least expensive. It was suggested that highly effective prophylaxis with an antibiotic agent such as piperacillin can result in significant cost savings when used for high-risk patients undergoing cesarean section.

An Irish study in 1993 showed use of prophylactic antibiotics was associated with increased costs to the patient [52]. This was from data gathered from The National Maternity Hospital in Dublin. A prospective audit of 200 patients was undertaken to determine the effectiveness of prophylactic antibiotics at caesarean section in reducing the cost of postnatal care. The main outcome measures were the cost-effectiveness of this treatment in reducing the cost of care and incidence of infection. The results show that the routine administration of prophylactic antibiotics had no significant effect on

infection rates, the prescribing of puerperal antibiotics or the duration of stay in the postnatal period. The total cost of antibiotics in the prophylaxis group was over four times that in the non-prophylaxis group.

CHAPTER 2

METHODOLOGY

Study design

A prospective Randomized Clinical Trial evaluating two prophylactic antibiotic regimens for caesarean section.

Study setting

The study was done at Parirenyatwa and Harare Hospitals. These are two major referral, tertiary institutions in Zimbabwe. In 2011, there were 13060 deliveries at Harare hospital. Of these, 2573 were caesarean sections. This gives a caesarean section rate of 19.7%. At Parirenyatwa, there were 8994 deliveries in 2011. 2403 were caesarean sections giving a caesarean section rate of 26.7%. There are 53 midwives at Parirenyatwa hospital out of the required 103. Harare hospital had 46 midwives by end of 2011 out of the required 156. There is a general increase in the number of deliveries in both hospitals since 2008.

Participants

- Women who undergo caesarean sections at Parirenyatwa and Harare hospitals regardless of indication

Inclusion criteria

- Elective caesarean sections
- Emergency caesarean sections

Exclusion criteria

- Patients who do not want to participate in the study
- Severe immunosuppression of any cause
- Stage 3 and 4 HIV infection
- Prolonged rupture of membranes more than 12hours
- Surgery longer than 3hours
- Chorioamnionitis diagnosed preoperatively
- Obvious infection that requires therapeutic antibiotics

Sampling method

Simple randomization

- Randomization was done by picking a raffle ticket from a box. The ticket picked would determine which arm the patient would be allocated to.

INTERVENTIONS

Arm 1

The patients in this arm were given ceftriaxone and metronidazole preoperatively as follows:

- Ceftriaxone 1g intravenously
- Metronidazole 500mg intravenously

No more antibiotics were given except for the intention to treat

Arm 2

The patients in this arm were given antibiotics for one week as follows

a) Preoperatively

- Benzyl penicillin 5MU intravenously
- Chloramphenicol 1g intravenously

b) Postoperatively within 24 hours of the operation

- Benzyl penicillin 2.5MU 6 hourly for 3 doses iv
- Chloramphenicol 500mg 6 hourly for 3 doses iv

c) Oral antibiotics from day 1 postoperatively

- Amoxicillin 500mg tds for 7 days
- Metronidazole 400mg tds for 7 days

All patients were observed for 4days in hospital then discharged. Those who were kept in hospital for various reasons, beyond the mandatory 4days were followed up until discharge. At 6weeks from the day of delivery, all patients were followed up at the postnatal clinic or by telephone.

OUTCOMES

The following outcomes were monitored for.

1 Pyrexia >38^{o}C

- This was monitored for during the initial hospital stay after caesarean section
- Only the morning temperature done at about 6am was considered
- There were 3 types of thermometers used on these two hospitals. Two were digital and one was a mercury thermometer. They were all tested on the patients and gave similar readings.
- For the purposes of this study, the temperature was measured in the armpit
- One or more readings greater than 38^{o}C were considered significant

2 Admission with puerperal sepsis

- Any patients admitted with 2 or more of the following parameters within the first 42days after delivery:

a) Pelvic pain
b) Fever i.e. temperature 38.5°C or higher
c) Abnormal vaginal discharge
d) Abnormal smell of the vaginal discharge
e) Delay in the rate of uterine involution (<2cm/day during the first 8 days)

3 Wound sepsis

- Presence of pus or necrotic tissue on the caesarean section wound
- Gapping of the suture line

4 Death

- Only death caused by infection which started in the pelvis or the surgical wound was considered.

5 Hospital stay

- We looked at the total number of days in hospital during the first 42 days after delivery
- The standard hospital stay was 4 days. Any patient with more than 4 days in hospital was considered here if the reason for prolonged stay was pyrexia, puerperal sepsis, wound sepsis or pelvic abscess

6 Laparotomy for pelvic abscess

- In this case, the pelvic abscess had to be confirmed by the presence of pus in the pelvis at laparotomy.

Sample size determination

We used a *two sided, two independent samples test for proportions* formula to calculate the sample size.

$$n_i=[\{\sqrt{(pq2)}Z_{1-(\alpha/2)} + \sqrt{(p_1q_1+p_2q_2)}Z_{1-\beta}\}/ES]^2$$

We estimated that 10% of patients in ARM 2 will have puerperal infection by six weeks of follow up (from literature). To demonstrate non-inferiority of ARM 1, 1-sided α = 0.025 with 80% power we will require 108 patients per arm. After adjusting for 20% attrition, we got a sample size of 130 per arm, giving a total sample size of 260 participants.

Randomization procedure

- There was an A4 envelope of raffle tickets at each of the 2 maternity units at which the study was carried out.

- Each envelope contained 75 tickets marked ARM 1 and 75 marked ARM 2. The ticket for ARM 1 was identical to that of ARM 2 in size, shape and material.

- When a patient agreed to participate, a single ticket was picked blindly. This determined the arm to which the patient was allocated. The tickets were not replaced after they were picked.

- This was continued until the time the researchers decided to close recruitment

Statistical Analysis

All participants were analyzed according to the study arm to which they were randomized. The proportions of patients who developed hyperpyrexia (temperature more than 38^{o}C), those who were admitted with puerperal sepsis, those who had wound sepsis, laparotomy for pelvic abscess and those had prolonged hospital stay (more than the standard 4 days) were compared by randomization arm using the standard methods for comparing proportions (χ^2 test). Equivalence was regarded as proven if the proportion in arm 1 is the same as in arm 2 and the p-value is not less than 0.05.

All statistical analysis were performed using Stata version 12.0 (Stata Cooperation, College Station, Texas USA). All P-values are two sided. And were evaluated at p=0.05 level of significance and 95% confidence interval.

Ethical considerations

The study was approved by the hospital ethics committee before commencement. Patients were informed of the risks of taking part in the study. They were also informed that they were free to pull out of the study at any point. The patients were treated for any infections if it was necessary during the course of the study. Their names were not recorded in the data collection sheets. Only their hospital numbers and phone numbers were recorded in the data collection sheets.

CHAPTER 3

RESULTS

A total of 280 patients were enrolled into the study. The total number of patients who completed the study was 232. This was after 15 patients were incorrectly recruited and 33 were not followed up to the end of the study. It was impossible to contact these 33 patients after 6 weeks although they had been followed up until discharge following the caesarean section. 112 patients in arm 1 and 120 patients in arm 2 completed the study. (see Patient flow diagram). The total number of patients who had at least one of the outcome parameters looked at was 28 out of 232 (12%). The commonest finding was hyperpyrexia which affected 15 patients.

DEMOGRAPHIC DATA (see table 1).

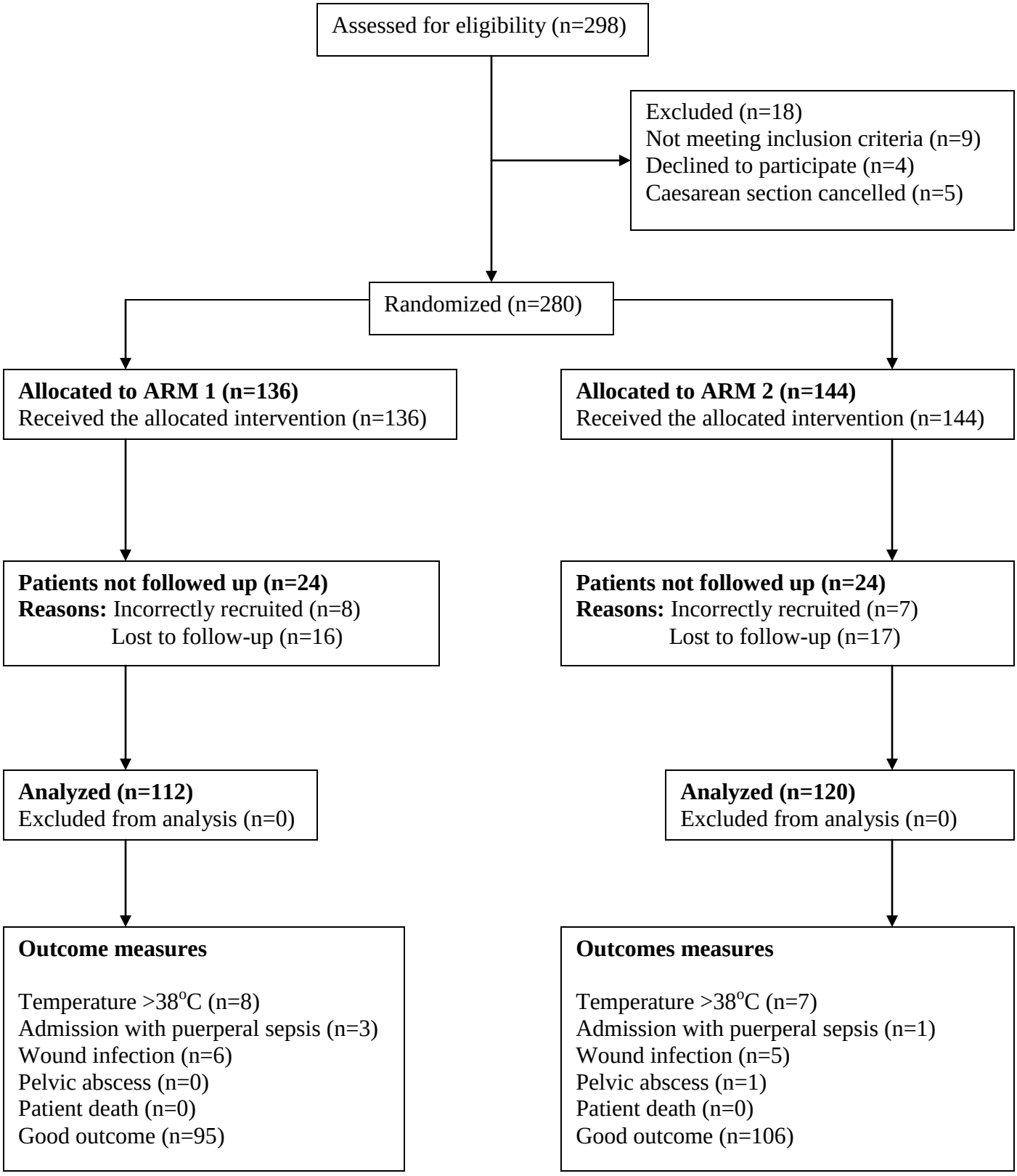
Number of patients recruited

Slightly more patients were recruited at Parirenyatwa hospital than at Harare hospital. This would be unexpected as Harare hospital manages more patients than Parirenyatwa. This is because the study at Parirenyatwa started about 10days earlier than at Harare hospital after the pharmacy had availed the drugs earlier. The number of patients recruited at Parirenyatwa was 127 which was 55% of the total. The number of patients recruited at Harare hospital was 105 (45%). There was no significant difference in the number of patience recruited in each arm with 51.7% in arm 2 and 48.3% in arm 1. This means the randomization was satisfactory.

Age distribution

The median age in both ARM 1 and ARM 2 was 27. The interquartile range for ARM 1 was 22-32 years while that for ARM 2 was 21-31 years. There was no significant age difference between the 2 arms.

Patient flow diagram



Educational status

Most of the women recruited went to school at least up to O' level (n=207 or 89%). The number of women in Arm 1 with at least O' level qualification was 101 (90%) while that in Arm 2 was 106 (88%). There was no significant difference in the level of education between the two arms.

Marital status

99% of women recruited to arm 1 were married. Of those recruited to arm 2, 95% were married. There was no significant difference in this aspect between the 2 arms.

Occupation

73% of the women in arm1 and 81% of those in arm 2 were housewives who were not formally employed. There was no significant difference between the two arms.

Booking status

The number of patients booked in arm 1 was 107 (96%) while that in arm 2 was 106 (88%). A woman who had at least 1 antenatal visit was considered to be booked. There was no significant difference between the 2 arms and bias was not to be expected.

HIV status

In arm 1, 93 patients (83%) were HIV negative while in arm 2, the number was 103 (86%). The number of those who were HIV positive was 12% in arm1 and 8% in arm 2. The HIV status was not known in 5% and 6% for arm 1 and arm 2 respectively. There was no significant difference in HIV status between the 2 arms.

Characteristics	Arm 1 n(%)	ARM 2 n= 120
Age-(years), median (IQR)	27 (22-32)	27 (21-31)
Number of patients		
Parirenyatwa	61 (54)	66 (55)
Harare	51 (46)	54 (45)
Marital Status		
Married	111 (99)	114 (95)
Single	1 (1)	5 (4)
Divorced	-	1 (1)
Education Level		
Below Grade 7	0 (0)	1 (1)
Primary	11 (10)	13 (11)
Secondary	99 (88)	105 (87)
College/University	2 (2)	1 (1)
Occupation		
Unemployed/ Housewife	82 (73)	97 (81)
Formally employed	30 (27)	23 (19)
Booking Status		
Booked	107 (96)	106 (88)
Not Booked	5 (4)	14 (12)
HIV Status		
Negative	93 (83)	103 (86)
Positive	13 (12)	10 (8)
Unknown	6 (5)	7 (6)

Table 1: Socio-demographic characteristics of patients

Indication for the caesarean section (see table 2)

The commonest indications for caesarean section were previous caesarean section (58 patients, fetal distress (35 patients), CPD (34 patients), dysfunctional labour (25 patients), malpresentation (23 patients) and hypertensive disease (20 patients). There was an acceptable balance of these indications between the 2 arms.

The numbers recruited for each indication for the caesarean section were relatively small especially for certain uncommon indications like, fibroid uterus and bad obstetric history. This meant that these indications would be seen in one arm and not in the other arm. However this would not be expected to cause any bias in the results.

A better comparison in relation to each indication would be achieved with much bigger sample size. This however was not necessary for this particular study because the main objectives would be met with the sample size used.

In summary, there was a fair distribution of the indications the 2 arms and we would not expect any bias affecting the results.

Table 2: Indications for Caesarian Section

Indication	ARM 1 n=112 (%)	ARM 2 n=120 (%)
Previous C/S or uterine scar	30 (27)	28 (23)
Fetal distress	17 (15)	18 (15)
Malpresentation	8 (7)	15 (12)
CPD	16 (14)	18 (15)
Thick MSL	5 (4)	8 (7)
Dysfunction labour	10 (9)	15 (12)
APH	4 (3)	1 (1)
PMTCT	2 (2)	6 (5)
Hypertensive disease	13 (12)	7 (6)
Multiple pregnancy	6 (5)	3 (2)
Bad Obstetric History	1 (1)	-
Fibroids	-	1 (1)

OUTCOMES (see tables 3 and 4)

Pyrexia

The number of patients who had pyrexia more than 38^{o}C was 15. Of these, 8 were in arm 1 while 7 were in arm 2. There was no statistically significant difference between the two arms. The two arms were equivalent in preventing pyrexia in women undergoing caesarean section. The p-value was 0.685.

Admission with puerperal sepsis

Total number of patients admitted with puerperal sepsis was 4. Three of these were in arm 1 and one was in arm 2. There was no statistically significant difference between the two arms, which means the two prophylactic antibiotic regimes were equivalent in preventing puerperal sepsis. The p-value was 0.281.

Wound sepsis

Eleven patients developed wound sepsis during the follow up period. 6 were in arm 1 and 5 were in arm 2. There was no statistically significant difference between the 2 arms which was a demonstration of equivalence in the prevention of wound sepsis. The p-value was 0.669.

Hospital stay

Fourteen patients had prolonged hospital stay as a result of infection. Nine of these were in arm 1 and 5 of them were in arm 2. There was no statistically significant difference between the two arms. The p-value was 0.216.

Table 3 Adverse outcomes by study arm

Outcome	ARM 1	ARM 2	P-Value
Temperature			
$>38^{0c}$	8	7	0.685
$\leq 38^{0c}$	104	113	
Admission with puerperal sepsis			
Yes	3	1	0.281
No	109	119	
Wound sepsis			
Yes	6	5	0.669
No	106	115	
Hospital stay			
More than 4 days	9	5	0.216
Standard (4 days)	103	115	
Laparotomy for pelvic abscess			
Yes	0	1	0.330
No	112	119	

.

Laparotomy for pelvic abscess

Only one patient had a laparotomy for a pelvic abscess that confirmed the presence of pus in the pelvis. This was a patient in arm 2. This was a patient who had been admitted with puerperal sepsis. There was no statistically significant difference between the 2 arms in preventing pelvic abscesses. The p-value was 0.330.

Mortality

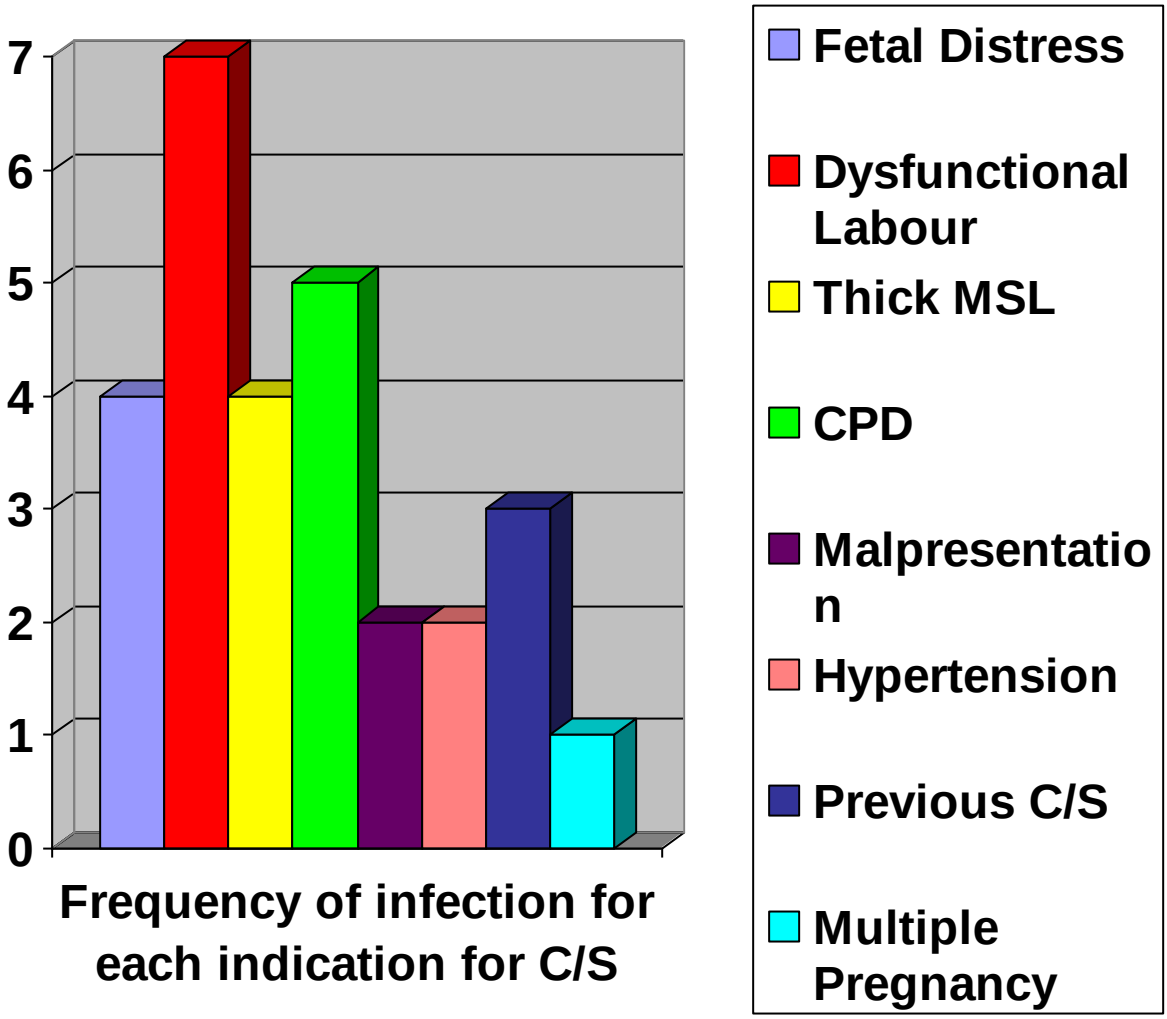
None of the patients died during this study.

Table 4: Frequency of events for indications of C/S in each randomization arm (n)

Caesarian-section indication	Hyperpyrexia		Puerperal sepsis		Wound Sepsis		Hospital stay > 4 days		Laporotomy pelvic /absc	
	Arm 1	Arm 2	Arm 1	Arm 2	Arm 1	Arm 2	Arm 1	Arm 2	Arm 1	Arm2
Fetal distress	1	1	1		1	1	2	1		
Malpresentation	3				1	1	1	1		
CPD		2								
Thick MSL		1	1		1	1	2			
PMTCT										
BP					2		2			
Fibroids										
Multipregnancy	1									
Dysfunctional Labour	3	2	1	1		1	1	2		1
Previous C/S		1			1	1	1	1		
TOTAL	15		4		11		14		1	

Figure 1 shows the number of patients who had infective morbidity in each indication for caesarean section.

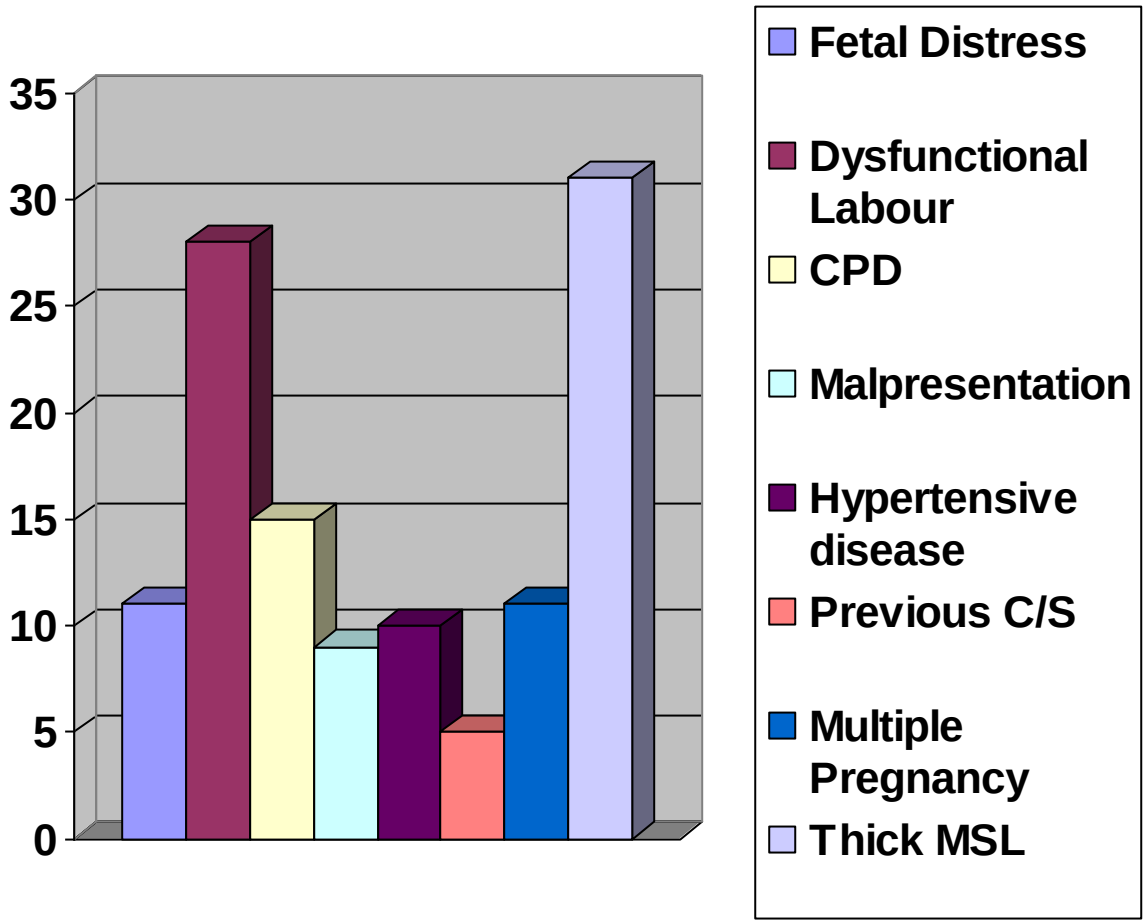
Figure 1



This graph shows the indications which were associated with some form of infective morbidity. However it is difficult to make any conclusion about the risks of infective morbidity associated with any of these indications for caesarean section based on this graph.

Figure 2 gives a better interpretation of the information in figure 1 by giving proportions of women who developed some form of infective morbidity for each indication for caesarean section.

Figure 2



Percentage of women affected for each indication for caesarean section

The above graph shows that 31% of women with thick meconium stained liquor had some form of infective morbidity.

For those with dysfunctional labour, 28% were affected. These are significant proportions which suggest increased risk of infective morbidity in these two scenarios.

The proportions for other indications were relatively small and probably not of much significance.

CHAPTER 4

DISCUSSION

Puerperal sepsis is the 4th cause of maternal mortality in Zimbabwe according to the 2007 study of maternal mortality in Zimbabwe. Caesarean section is a major risk factor of puerperal infection. From studies which have been done, the incidence of puerperal infections following caesarean section varies mainly depending on the definition used. In our study the rate was 12%. According literature, the prevalence of wound infection and endometritis after cesarean section without preoperative antimicrobial prophylaxis varies from 5 to 85% depending on definition and study population. In a Mozambique study, the incidence of infections following caesarean section was 5.2 and 6.4% with two different antibiotics regimens (48).

Our study has shown that the two arms are equivalent in preventing infective morbidity. A vial of 1 gram of ceftriaxone costs US$1.50 and a vial of 500milligrams of metronidazole sosts US1.50. The cost of antibiotics for a patient on ARM 1 would be US$3. A patient of ARM 2 regimen would spend $10 on antibiotics which is more than 3 times the cost for ARM 1. It obviously makes financial sense to recommend the use of preoperative ceftriaxone 1 gram and metronidazole 500mg for women undergoing caesarean section as antibiotic prophylaxis.

The two hospitals are generally understaffed and the nurses and doctors are often overwhelmed with work. Some of the necessary duties are often not emplemented as a result of this understaffing. A patient who is in ARM 2 needs to receive at least 13 doses of antibiotics during her hospital stay. This is all a burden for the nursing staff to monitor the administration of these antibiotics. The use of ARM 1 would significantly reduce the duties of the nurses. This would also reduce the responsibilities of the doctors who may have to establish intravenous access for those patients who are still on intravenous antibiotics. With the patient going home on oral antibiotics comes the challenge of compliance and the risks of increasing antibiotics resistance which is a major challenge in

use of antibiotics. All these problems can be avoided by using single dose of antibiotics given preoperatively.

Ceftriaxone and metronidazole are a good combination of antibiotics for prophylaxis in women undergoing caesarean section. They are available at a reasonable cost in Zimbabwe. Cefalosporins are recommended as alternatives to equally efficacious penicillins for surgical prophylaxis. First generation cephalosporins are recommended over broader spectrum cefalosporins like ceftriaxone, as they are equally effective and less costly than the latter [11, 24]. However in our hospitals, ceftriaxone is the only readily available cephalosporin. It is also a relatively new antibiotic in Zimbabwe and is still very efficacious in treating most infections. The available penicillins like benzyl penicillin have been is use for a long time and their efficacy as single agents needs to be reassessed in randomized control trials. There are fears or increased resistance which however need to be confirmed

Traditionally, most centres have been using either a cephalosporin or a penicillin for surgical prophylaxis. Accumulating evidence from randomized clinical recommend the addition of azithromycin, gentamycin or metronidazole. This is associated with better outcomes than using a cephalosporin or a penicillin alone [25, 26]. Azithromycin has been noted to be superior to gentamicin and metronidazole. It has a longer half-life of 68 hours, higher tissue concentration and lower potential for fetal transfer than the other antibiotics in published studies [42-43]. However in Zimbabwe azithromycin is significantly more expensive than metronidazole and gentamicin. A single dose of azithromycin costs at least US$18 which is more than 10 times the cost of metronidazole. Azithromycin is also not readily available in most government hospitals in Zimbabwe. Gentamycin would have been a good alternative to metronidazole although this study chose to look at metronidazole which has generally been used in this context in most hospitals in Zimbabwe. The efficacy of both gentamycin and metronidazole has also recently been proven in a study which was done in Zimbabwe's neighbour, Mozambique. This however used the two drugs as a combination [48]. Although both metronidazole

and gentamycin have been in use for a long time, antibiotic resistance against these two drugs is generally limited.

An important factor in the administration of prophylactic antibiotics is the correct timing of administration of the drugs. For the best results, antibiotics are best given preoperatively. In this research some anaesthetists were anxious about administration of antibiotics around the time they were supposed to anaesthetize the patients. Although local guidelines recommend antibiotics to be given not more than 15minutes before the initial incision, this has not been the practice and some junior anaesthetists had to be reassured of the safety of this practice. It is important to watch out for allergic reactions though in all patients who are given antibiotics. Such allergic reactions are not common and their rare possibility should not be reason for failure to administer antibiotics preoperatively. There is need to allow the antibiotics to reach peak plasma concentrations and research shows this is superior to intraoperative and postoperative administration even when given up to 2hours before the incision. It was very feasible to administer the antibiotics within the 30 minutes that were recommended in this study and the best time to give the antibiotics was after the anaesthetist has given his spinal or general anaesthetic. None of the patients in this study developed any allergic drug reactions. It is however important for the anaesthetist to monitor the patient closely after administration of the antibiotic and to be prepared for any adverse outcomes.

Most of the patients who were admitted with postpartum infections were admitted within 1 to 2 weeks of being discharged. This was a general trend noted although this study was not designed to look closely at that. It would probably mean monitoring of these patients for up to 2 weeks would result in early detection of infections. However, considering the cost of keeping the patients for long, complications of prolonged hospital stay and the relatively low incidence of puerperal infections, this would not be cost effective. We suggest the 10day visit should try to screen for these infections instead of just concentrating on the welfare of the neonate. It would most likely be cost effective. Other researches have also shown that infections generally manifest early in the postnatal period. In a New Zealand study, only 36% of infections manifested after discharge [53].

However a study in Mozambique showed that most wound infections occurred after discharge [48]. In that study patients were discharged after 7 days. They however did not give information on exactly how many days after discharge the infections manifested.

The rate of puerperal infections were noted to be higher in certain circumstances of the caesarean sections. Patients with thick meconium stained liquor and those who had caesarean section for dysfunctional labour generally had higher rates of puerperal infections in this study. The numbers of patients seen for each indication for caesarean section were however were small in this study and it would be difficult to make firm conclusions based on this evidence. A study done in the USA in 2003 however showed an increased risk of infection in women who had meconium stained liquor. (Am J Obstet Gynecol. 2003 Sep;189(3):746-50. Meconium-stained amniotic fluid is associated with puerperal infections. Tran SH, Caughey AB, Musci TJ Department of Obstetrics and Gynecology, Kaiser Permanente, San Francisco, CA, USA). The risk of infection seemed to increase with the amount of meconium in the liquor. In this study, both antibiotic regimes showed equal efficacy in patients with thick meconium stained liquor. A 2010 systematic review showed that antibiotics may reduce the risk of infections in women with meconium stained amniotic fluid when compared to placebo (Cochrane Database Syst Rev. 2010 Dec 8;(12):CD007772. Antibiotics for meconium-stained amniotic fluid in labour for preventing maternal and neonatal infections. Siriwachirachai T, Sangkomkamhang US, Lumbiganon P, Laopaiboon M).. However there was no reduction in the incidence of postnatal endometritis. These patients probably need close monitoring. At Parirenyatwa and Harare hospital, the practice is to give these patients intravenous antibiotics for an unspecified number of days followed by oral antibiotics for 5 to 7 days. This evidence identifies the need for more well-designed, adequately powered randomized control trials to assess the effect of various prophylactic antibiotics in the incidence of maternal complications for women with meconium stained amniotic fluid. Such studies need to be done also on other indications for caesarean section like dysfunctional labour to be able to have a clearer picture of the risks of infection.

Patients who were HIV positive did not show a significant risk of puerperal infection in our study. None of the patients who were HIV positive had any postpartum infections. However the numbers looked at were small to make any conclusion. HIV status probably does not affect the risk of postpartum infections except for those with severe immunosuppression who were not included in this study. There is need for more well designed randomized control trials to assess the risk associated with positive HIV status.

CONCLUSION AND RECOMMENDATIONS

- There was no statistically significant difference in the efficacies of the two arms in preventing infective morbidity

- Because of reduced costs, better convenience for the patients and less burden on the nursing staff, we recommend the use of the single dose regime of ceftriaxone for prophylaxis in women undergoing caesarean section. These drugs should be given within 30minutes of the initial incision by the surgeon.

- The incidence of puerperal infections as defined by our study was 12%.

- Particular care has to be given to women who have had caesarean section for thick meconium stained liquor and dysfunctional labour as they seemed to be at increased risk for infection. None of the 2 arms showed superiority in managing these patients in our study. More research is however needed. We suggest a more prolonged monitoring to enable early treatment for any infections that are suspected or diagnosed.

References

1 Berg CJ, Chang J, Callaghan WM, Whitehead SJ. Pregnancy-related mortality in the United States, 1991–1997. Obstet Gynecol. 2003;101(2):289–96.

2 Gibbs RS. Clinical risk factors for puerperal infection. Obstet Gynecol. 1980;55(5 Suppl):178S–184S.

3 Perencevich EN, Sands KE, Cosgrove SE, Guadagnoli E, Meara E, Platt R. Health and economic impact of surgical site infections diagnosed after hospital discharge. Emerg Infect Dis. 2003;9(2):196–203.

4 Smaill F, Hofmeyr GJ. Antibiotic prophylaxis for cesarean section. Cochrane Database Syst Rev. 2002;(3):CD000933.

5 Mangram AJ, Horan TC, Pearson ML, Silver LC, Jarvis WR. Guideline for Prevention of Surgical Site Infection, 1999. Centers for Disease Control and Prevention (CDC) Hospital Infection Control Practices Advisory Committee. Am J Infect Control. 1999;27(2):97–132. quiz 133–4; discussion 96.

6 Opoien HK, Valbo A, Grinde-Andersen A, Walberg M. Post-cesarean surgical site infections according to CDC standards: rates and risk factors. A prospective cohort study. Acta Obstet Gynecol Scand. 2007;86(9):1097–102.

7 Martin JA, Hamilton BE, Sutton PD, et al. Births: Final data for 2005. Natl Vital Stat Rep. 2007;56 (6):1–103.

8 Hamilton BE, Martin JA, Ventura SJ. Births: Preliminary data for 2006. Natl Vital Stat Rep. 2007;56 (7):1–18.

9 MacDorman MF, Menacker F, Declercq E. Cesarean birth in the United States: epidemiology, trends, and outcomes. Clin Perinatol. 2008;35(2):293–307.

10 American Society of Health System Pharmacists. ASHP Therapeutic Guidelines on Antimicrobial Prophylaxis in Surgery. American Society of Health-System Pharmacists. Am J Health Syst Pharm. 1999;56(18):1839–88. Review.

11 American College of Obstetricians and Gynecologists. ACOG practice bulletin number 47, October 2003: Prophylactic Antibiotics in Labor and Delivery. Obstet Gynecol. 2003;102(4):875–82.

12 Classen DC, Evans RS, Pestotnik SL, Horn SD, Menlove RL, Burke JP. The timing of prophylactic administration of antibiotics and the risk of surgical-wound infection. N Engl J Med. 1992;326(5):281–6.

13 Centers for Medicare & Medicaid Services. Physician Quality Reporting Initiative (PQRI) Quality Measures Specifications. 2008. [Accessed June 18, 2008]. http://www.cms.hhs.gov/PQRI/downloads/2008PQRIMeasureSpecifications123107.pdf

14 Smaill FM, Gyte GM Antibiotic prophylaxis versus no prophylaxis for preventing infection after caesarean section. Cochrane Database Syst Rev. 2010 Jan 20:CD007482.

15 Med J Malaysia. 1992 Dec;47(4):273-9. The role of prophylactic antibiotics in caesarean section--a randomised trial. Ng NK, Sivalingam N. Kinta Medical Centre, Ipoh, Perak Darul Ridzuan

16 Mahomed K. Br J Obstet Gynaecol. 1988 Jul;95(7):689-92. A double-blind randomized controlled trial on the use of prophylactic antibiotics in patients undergoing elective caesarean section.

17 BJOG. 2001 Feb;108(2):143-8. A randomised controlled trial of antibiotic prophylaxis in elective caesarean delivery. Bagratee JS, Moodley J, Kleinschmidt I, Zawilski W.

18 Am J Obstet Gynecol. 2001 Mar;184(4):656-61. Prophylactic use of antibiotics for nonlaboring patients undergoing cesarean delivery with intact membranes: a meta-analysis. Chelmow D, Ruehli MS, Huang E.

19 Cunningham FG, Leveno KJ, DePalma RT, Roark M, Rosenfeld CR. Perioperative antimicrobials for cesarean delivery: before or after cord clamping? Obstet Gynecol. 1983;62(2):151–4.

20 Am J Obstet Gynecol. 2008 Sep;199(3):301.e1-6. Timing of perioperative antibiotics for cesarean delivery: a metaanalysis. Costantine MM, Rahman M, Ghulmiyah L, Byers BD, Longo M, Wen T, Hankins GD, Saade GR.

21 Ann Fr Anesth Reanim. 2009 Oct;28(10):855-67. Epub 2009 Sep 19. Antimicrobial prophylaxis for caesarean delivery: before or after cord clamping? A meta-analysis Boselli E, Bouvet L, Rimmelé T, Chassard D, Allaouchiche B.

22 Am J Obstet Gynecol. 2008 Sep;199(3):310.e1-5. Effect of a change in policy regarding the timing of prophylactic antibiotics on the rate of postcesarean delivery surgical-site infections. Kaimal AJ, Zlatnik MG, Cheng YW, Thiet MP, Connatty E, Creedy P, Caughey AB

23 Obstet Gynecol. 2010 Sep;116(3):791-2. Committee opinion no. 465: antimicrobial prophylaxis for cesarean delivery: timing of administration. [No authors listed]

24 Hopkins L, Smaill F. Antibiotic prophylaxis regimens and drugs for cesarean section. Cochrane Database Syst Rev. 2000;(2):CD001136.

25 O'Leary JA, Mullins JH, Jr, Andrinopoulos GC. Ampicillin vs. ampicillin-gentamicin prophylaxis in high-risk primary cesarean section. J Reprod Med. 1986;31(1):27–30.

26 Andrews WW, Hauth JC, Cliver SP, Savage K, Goldenberg RL. Randomized clinical trial of extended spectrum antibiotic prophylaxis with coverage for Ureaplasma urealyticum to reduce post-cesarean delivery endometritis. Obstet Gynecol.

27 Tita AT, Hauth JC, Grimes A, Owen J, Stamm AM, Andrews WW. Decreasing incidence of post-cesarean endometritis with extended-spectrum antibiotic prophylaxis. Obstet Gynecol. 2008;111(1):51–6.

28 Tita AT, Owen J, Stamm AM, Grimes A, Hauth JC, Andrews WW. Impact of Extended-Spectrum Antibiotic Prophylaxis on Incidence of Post-Cesarean Surgical Wound Infection. Am J Obstet Gynecol. 2008;199(3):303, e1–3.

29 Newton ER, Wallace PA. Effects of prophylactic antibiotics on endometrial flora in women with postcesarean endometritis. Obstet Gynecol. 1998;92(2):262–8.

30 Hoyme UB, Kiviat N, Eschenbach DA. Microbiology and treatment of late postpartum endometritis. Obstet Gynecol. 1986;68(2):226–32.

31 Sherman D, Lurie S, Betzer M, Pinhasi Y, Arieli S, Boldur I. Uterine flora at cesarean and its relationship to postpartum endometritis. Obstet Gynecol. 1999;94(5 Pt 1):787–91.

32 Watts DH, Eschenbach DA, Kenny GE. Early postpartum endometritis: the role of bacteria, genital mycoplasmas, and Chlamydia trachomatis. Obstet Gynecol. 1989;73(1):52–60

33 Emmons SL, Krohn M, Jackson M, Eschenbach DA. Development of wound infections among women undergoing cesarean section. Obstet Gynecol. 1988;72(4):559–64.

34 Roberts S, Maccato M, Faro S, Pinell P. The microbiology of post-cesarean wound morbidity. Obstet Gynecol. 1993;81(3):383–6.

35 Rosene K, Eschenbach DA, Tompkins LS, Kenny GE, Watkins H. Polymicrobial early postpartum endometritis with facultative and anaerobic bacteria, genital mycoplasmas, and Chlamydia trachomatis: treatment with piperacillin or cefoxitin. J Infect Dis. 1986;153(6):1028–37.

36 Watts DH, Eschenbach DA, Kenny GE. Early postpartum endometritis: the role of bacteria, genital mycoplasmas, and Chlamydia trachomatis. Obstet Gynecol. 1989;73(1):52–60.

37 Andrews WW, Shah SR, Goldenberg RL, Cliver SP, Hauth JC, Cassell GH. Association of post-cesarean delivery endometritis with colonization of the chorioamnion by Ureaplasma urealyticum. Obstet Gynecol. 1995;85(4):509–14.

38 Keski-Nisula L, Kirkinen P, Katila ML, Ollikainen M, Suonio S, Saarikoski S. Amniotic fluid U. urealyticum colonization: significance for maternal peripartal infections at term. Am J Perinatol. 1997;14(3):151–6.

39 48. Yoon BH, Romero R, Park JS, et al. Microbial invasion of the amniotic cavity with Ureaplasma urealyticum is associated with a robust host response in fetal, amniotic, and maternal compartments. Am J Obstet Gynecol. 1998;179(5):1254–60.

40 Watts DH, Krohn MA, Hillier SL, Eschenbach DA. Bacterial vaginosis as a risk factor for post-cesarean endometritis. Obstet Gynecol. 1990;75(1):52–8.

41 Archer GL. Alteration of cutaneous staphylococcal flora as a consequence of antimicrobial prophylaxis. Rev Infect Dis. 1991;13(Suppl 10):S805–9. Review. [PubMed]

42 Whitman MS, Tunkel AR. Azithromycin and clarithromycin: overview and comparison with erythromycin. Infect Control Hosp Epidemiol. 1992;13(6):357–68. Review. [PubMed]

43 Ramsey PS, Vaules MB, Vasdev GM, Andrews WW, Ramin KD. Maternal and transplacental pharmacokinetics of azithromycin. Am J Obstet Gynecol. 2003;188(3):714–8. [PubMed]

44 Pitt C, Sanchez-Ramos L, Kaunitz AM. Adjunctive intravaginal metronidazole for the prevention of postcesarean endometritis: a randomized controlled trial. Obstet Gynecol. 2001;98(5 Pt 1):745–50.

45 Meyer NL, Hosier KV, Scott K, Lipscomb GH. Cefazolin versus cefazolin plus metronidazole for antibiotic prophylaxis at cesarean section. South Med J. 2003;96(10):992–5.

46 Goldenberg RL, Andrews WW, Goepfert AR, Faye-Petersen O, Cliver SP, Carlo WA, Hauth JC. The Alabama Preterm Birth Study: umbilical cord blood Ureaplasma urealyticum and Mycoplasma hominis cultures in very preterm newborn infants. Am J Obstet Gynecol. 2008;198(1):43, e1–5.

47 Schelonka RL, Waites KB. Ureaplasma infection and neonatal lung disease. Semin Perinatol. 2007;31(1):2–9. Review.

48 Acta Obstet Gynecol Scand. 2003 Jul;82(7):636-41. Choice of antibiotics for infection prophylaxis in emergency cesarean sections in low-income countries: a cost-benefit study in Mozambique. Kayihura V, Osman NB, Bugalho A, Bergström S.

49 Alfirevic Z, Gyte GML, Dou L. Different classes of antibiotics given to women routinely for preventing infection at caesarean section. Cochrane Database of Systematic Reviews 2010, Issue 10. Art. No.: CD008726. DOI: 10.1002/14651858.CD008726

50 Am J Obstet Gynecol. 2004 Nov;191(5):1661-5. Prophylactic antibiotics for non-laboring patients with intact membranes undergoing cesarean delivery: an economic analysis. Chelmow D, Hennesy M, Evantash EG.

51 Drug Intell Clin Pharm. 1986 Jul-Aug;20(7-8):592-3. Cost of antibiotic prophylaxis in cesarean section. Ford LC.

52 Health Trends. 1993;25(3):84-7. Prophylactic antibiotics at caesarean section do not reduce costs. Keane D, James D

53 Beattie PG, Ring TR, Hunter MF, Lake Y. Risk factors of wound infection following caesarean section. Aust N Z J Obst Gynaecol 1994; 34: 398–402.

54 Am J Obstet Gynecol 1990 Jun;162(6):1398-403; discussion 403-5. Vaginal birth after cesarean or repeat cesarean section: medical risks or social realities? Kirk EP, Doyle KA, Leigh J, Garrard M. Department of Obstetrics and Gynecology, Oregon Health Sciences University, Portland 97201-3098.

55 Boggess KA, Watts DH, Hillier SL, Krohn MA, Benedetti TJ, Eschenback DA. Bacteremia shortly after placental separation during cesarean section. Obstet Gynecol 1996;87:779-784

56 MacLean A. B. (1990) Puerperal pyrexia. In Clinical Infection in Obstetrics and Gynaecology. Blackwell Scientific Publications, Oxford , p. 199.

QUESTIONNAIRE **DATE :……. ARM …….**

Patient ID …… Hospital Number…… Patient's Age:…….
Marital status:…… **Parity**……..……...
Level of Education…… **Occupation**……
Address:……
Telephone number(s)…….

Booked □ **Not booked** □

Indication for caesarean section

Fetal distress □
Dysfunctional labour □
Antepartum Haemorrhage □
Cephalo – pelvic disproportion □
Hypertensive disease in pregnancy □
PMTCT □
Other …….

HIV Status

Positive □ Negative □ Unknown □ CD4……

ARV use

Full ART □ PMTCT regimen □ None □

Did the patient have any of the following during admission and during the 6weeks period?

Pyrexia ≥38^{O} C during index admission (post C/S)	Yes	□	No	□
Admission for pueperal sepsis/ endometritis	Yes	□	No	□
Wound sepsis	Yes	□	No	□
Patient died of puerperal infection	Yes	□	No	□

Number of extra days in hospital due to infection……

Surgery done for puerperal infection during the 6weeks (tick appropriate box).

Exploratory Laparotomy □ EVAC for RPOCs □ Other surgery ……
Pelvic abscess confirmed at surgery □
Other outcomes (specify)……

END OF QUESTIONAIRRE

INFORMATION FOR PARTICIPANTS – ENGLISH AND SHONA

NAME OF RESEARCHER: Dr A Ziruma

Phone Number: 0772429843

Project Description:

You are requested to particitpate in thus study which compares "Ceftriaxone and Metronidazole" prophylaxis for caesarean section versus the current regimen of prolonged course.

Tsananguro yewongororo iyi

Munokumbirwa kupinda muongororo ino yokuona mushonga uri nani wekushandisa kudzivirira utachiona kumadzimai anosunungutswa nekuchekwa. "Ceftriaxone ne Metronidazole" dzinoenzaniswa nemishonga yagara ichishandiswa.

……

Procedures involved in the study

You will be given only one of the two option of antibiotics that are being compared. What you will be given will be determined randomly and you will not be able to chose which option you prefer. If you are allergic to any of the drugs mentioned above, you should not participate in this study. You will be kept in hospital for 5days or more if there is a problem that needs to be treated while you are in hospital. This means you stay 1 day more than usual so that the doctors can closely monitor and manage accordingly. After 6 weeks you will be required to come back to this hospital for the final assessment.

Zvichaitwa muongororo iyi

Hamugoni kusarudza mushonga wamuchapiwa pamiviri yataurwa pamusoro. Munopiwa zvichienderana nepepa ranhongwa mubhokisi. Kana ropa renyu risingapindirani neumwe wemishonga iyi hamufaniri kupinda muongororo iyi. Muchagara muchipatara kwemazuva mashanu kana pasina chimwe chinenge chichida kurapiwa muri muchipatara. Zvinoreva kuti muchawedzera zuva rimwechete pamazuva amanga muchifanira kugara. Kwapera masvondo matanhatu munotarisirwa kudzoka kuchipatara chino kuzoonekwa kekupedzisira

……

About the drugs

Both are safe to be given to pregnant women but we don't know which of the two is better than the other. If you are given either of the 2 options, it doesn't mean you will not be affected by infection of the operation site but the chances of infection are reduced

Pamusoro pemishinga iyi

Mishonga iyi haina njodzi kupiwa kumadzimai akazvitakura asi hatizivi kuti uri nani kupinda umwe ndeupi. Kana mukapiwa upi zvawo pakati peiyi mishonga hazvirevi kuti hamuchaiti utachiona panzvimbo yachekwa, asi mukana wekuita utachiona uhwu unenge wava mushoma

……

Benefits to you

There are no immediate or direct benefits to you. The only benefit you will have is when we start using the more effective of the 2 choices to the benefit of the community.

Mubairo wamungawana

Hakuna mubairo wamunopiwa. Kubatsirika kwamungaita ndekwekuti zvipatara zvinenge zvava kuziva mishonga inonyanya kubatsira zvinozobatsira vanhu vese pakurapwa nemishonga inesimba.

……

Withdrawal from study

You are free to decide that you no longer want to participate in the study at any point. This will not compromise the care given to you by the hospital

Kubuda muchirongwa

Munekodzero uye makasununguka kubuda muchirongwa panguva ipi zvayo. Izvi hazvikanganisi kurapwa kwenyu

……

THANK YOU!
TATENDA!