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Current Debate on the Use of Antibiotic Prophylaxis for Cesarean Section

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Abstract

Cesarean delivery is frequently complicated by surgical site infections (SSIs), endometritis and urinary tract infection. Most SSIs occur after discharge from hospital, and are increasingly being used as performance indicators. Worldwide, the rate of cesarean delivery is increasing. Evidence-based guidelines recommended the use of prophylactic antibiotics prior to surgical incision. An exception is made for cesarean delivery, where narrow-range antibiotics are administered post umbilical cord clamping because of putative neonatal benefit. However, recent evidence supports the use of pre-incision, broad-spectrum antibiotics which result in less maternal morbidity with no disadvantage to the neonate.

INTRODUCTION

Prior to the mid 19th century, surgical procedures commonly resulted in post-operative sepsis and death. In the 1860's, when Joseph Lister (1827-1912) introduced the principles of anti-sepsis (Table 1), the incidence of post-operative infectious morbidity and mortality fell markedly from 50% to 15%. In the 1960's, using an animal model, Burke demonstrated that if antibiotics were given before wound contamination, the rate of infection decreased.[1]

Following cesarean delivery (CD) maternal mortality and morbidity may result from a number of infections including endometritis, urinary tract infection (UTI) and surgical site infection (SSI).[2] In the 1980's, it was estimated that SSIs increased hospital stay by approximately 10 days, at an additional cost of around $2000 US per case.[3;4] By 1992, this figure had risen to $3152 US in extra charges for each SSI,[5-7] and deep SSI's involving organs or cavities, compared to superficial SSI's involving wound incisions, incurred even

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greater hospital stays and costs.[8-10] Approximately 1.7 million hospital-acquired infections occur in the USA annually,[9] and SSIs account for 20% of these cases.[11]

Following elective surgery, wound infection in patients who receive peri-operative antibiotics (within three hours following skin incision) occurs in 1.4% compared with 0.6% in those who receive antibiotics within two hours prior to skin incision.[12;13] Prophylactic antibiotics reduce the incidence of SSIs[14-16] and evidence-based guidelines recommend their use prior to incision as opposed to during or after the procedure.[14;15;17;18] Antibiotic prophylaxis is well established for gynecologic procedures such as abdominal hysterectomy, [19] and a single pre-operative antibiotic is recommended for abdominal and vaginal hysterectomy.[20] Cumulative meta-analysis data indicate that the benefits of antibiotic prophylaxis for abdominal hysterectomy were evident from the time of the first trial in 1972. Similarly, using cumulative meta-analysis data the individual benefits of cefazolin, metronidazole and tinidazole were evident in 1980, 1984 and 1986 respectively. This being the case, if the various studies had been pooled at an earlier date the use of controls in subsequent trials who received no treatment would have been unnecessary.[21] By the 1990's, 27 million surgical procedures were performed annually in the USA,[22] and SSIs accounted for approximately 15% of all nosocomial infections.[23] Moreover, 77% of deaths in surgical patients with nosocomial SSIs were related to infection.[15] While a proportion of SSIs is inevitable, adherence to evidence-based guidelines,[15] including prophylactic antibiotics, have been shown to reduce the rate of SSIs after elective surgical procedures.[24] Consistent with this notion, SSIs are increasingly used as performance indicators.[25] Post partum SSIs, especially those following CD are more common than those following other surgical procedures.[26] This may be due to the nature of intrapartum care, which is often prolonged, involves close contact with lay personnel (e.g. relatives who may not be familiar with hospital antiseptic measures), as well as a wide range of professionals from different departments in the hospital, which may increase the risk of cross-contamination. Labor and delivery are also associated with contamination by other body fluids, and are often unplanned or due to emergency situations.

OTHER INFECTIONS FOLLOWING VAGINAL OR ABDOMINAL BIRTH

For most pregnant women, SSIs are not life threatening, yet they have important implications on the length of hospital stay, hospital costs and social implications for the parents and the newborn.[27-29] Nonetheless, in low income countries, SSIs are still a major cause of mortality and morbidity, and infection remains among the top five causes of maternal mortality.[15;27] In the USA,[30] infection still accounts for a disproportionate contribution to pregnancy related mortality. Cesarean delivery is the single most important factor associated with post-partum infection,[31;32] and carries a 5-20 fold increased risk of infection compared to vaginal delivery.[32] The incidence of all maternal complications post-CD varies depending on definition, classification, and duration of observation,[31;33-44] but the rate of infection following CD is reported to be 1.1-25% as compared to 0.2-5.5% following vaginal birth.[27;31;32;34-36;39;43;45-49] The rate of infection after emergency and elective CD varied between 7.5-29.8% and 5.5-17.3% respectively.[28;47;50-56] The commonest infective complication following CD is endometritis, which occurs in up to 50% of cases,[16;57] though this can be reduced by 50% or more with the use of prophylactic antibiotics.[16;58-60] The prevalence of postpartum UTI and wound infection (WI) varies geographically,[35;43;45;47;50;56;61-64] and without antibiotic prophylaxis, WI or more serious infectious sequelae occurs in 10-25% of women post-CD. With or without endometritis, WI complicates more than 10% of CD despite the recommended antibiotic prophylaxis,[16] and is 50% higher in emergency compared with elective CD (OR = 1.47; 95% CI=1.14-1.90).[65] UTI occurs in 2.8% of CD compared to 1.5% of vaginal births (OR=1.68; 95% CI = 1.38-2.03), and WI is more than 60 times more common following CD than vaginal birth

(5.0% versus 0.08%). Infection within 30 days occurs in 7.6% of women following CD compared to 1.6% following vaginal birth (OR=4.71; 95% CI=4.08-5.43).[65] However, these numbers may be misleading since CD may be elective or as an emergency, each of which will carry a different risk of infection.

TIMING OF POSTPARTUM INFECTIONS

Up to 80% of infections occur after discharge from hospital;[15;35;39;47;50;55;56;61;62;65;66] therefore, post-CD infection rates may be underestimated if based on hospital discharge records. The guidelines for the prevention of SSI from the Centers for Disease Control and Prevention (CDC) require that WI which occur up to 30 days post-operatively will be classified as SSI.[15] By these criteria, 8.9% of infections occur post CD and only 1.8% occur before hospital discharge.[55] The rates of WI and and other post-CD infections peak after the fourth or fifth post operative day, a time at which most women delivered by CD will have been discharged home.[65]

RISK FACTORS

The risk factors associated with infection post-CD are extensive.[32;61;67-71] In the absence of risk factors, the National Nosocomial Infections Surveillance system reported an SSI rate of 3.4% for CD[72] and 8.1% following high-risk CD, both of which were higher than for non-CD surgical procedures. A major risk factor for post-operative infection is emergency CD (compared to elective).[40;46;48;73;74] In addition, high maternal body mass index (BMI), failure to use surgical drainage with subcutaneous tissue thickness of ≥3cm, as well as prolonged operating time and poor surgical technique, are established major risk factors for post-CD infections.[28;32;38;43;44;46;55;75-78]

INCREASING CESAREAN SECTION RATE

Despite the World Health Organization's estimate that CS rates should be no greater than 15%,[79] in the developed world CD rates are already above 20%.[55;65;80] The CD rate has increased by 50% in the USA (from 20-30% in the 10 years-period between 1996 and 2006[81]), such that CD is now the most common major surgical procedure carried out.[82] In 2006, 31% of births in the USA were by CD, which is equivalent to 1.3 million procedures annually.[66] If this trend continues, CD in the USA is likely to reach 50% by 2020, which would mean two million CDs each year.[83] With increasing CD rates, post-CD infections are likely to become an increasing health and economic burden,[30;66] and their prevention remains a public health priority.[66] Part of the reason for the increase in CD rates is the increased use of primary CD on maternal request,[65;84-87] which ranges from 4-15% of all CD in the USA. In a survey of obstetricians,[88] 53% of respondents confirmed they had performed such procedures, 58% recorded that the rate had increased in the last year and 41% said that they routinely discussed the topic with patients.[89] However, the rise in CD rates is more complex and includes clinical, medico-legal, financial, social and psychological factors.[84] As the proportion of women delivered by CD increases, strategies to reduce SSIs will have a substantial effect on the morbidity associated with CD.[66] Since CD is associated with a significant risk of infection compared to vaginal delivery, (mainly due to WI but also due to UTI following CD), and >75% of SSIs occur following discharge from hospital, this should form part of the discussion with patients who are contemplating CD on maternal request.[65;84;86;87]

ARE PROPHYLACTIC ANTIBIOTICS EFFECTIVE IN REDUCING INFECTIOUS MORBIDITY POST CD?

Antibiotic prophylaxis for women undergoing CD has been proven to be beneficial in decreasing post-CD infectious morbidity both in high-risk (in labor post membrane rupture), or low-risk patients, (non-laboring with intact membranes).[16;90-93] A single dose of antibiotics is as effective as multiple doses given peri-operatively,[94-97] and the routine use of prophylactic antibiotics reduces the risk of infection by more than 50% from a baseline as high as 20-50%.[98;99] In a systematic review of over 80 studies on the use of prophylactic antibiotics for CD, the Cochrane Collaboration specifically examined the effect of prophylactic antibiotics on the rate of maternal postpartum fever, WI, endometritis, UTI, serious infectious morbidity/death, as well as maternal side effects and length of hospital stay. For all CDs (both elective and emergency) the only outcome which increased following prophylactic antibiotics was maternal side effects, though this did not reach statistical significance. For all of the other outcomes, the use of antibiotics was associated with a statistically significant reduction, with an effect size of 40-65%. Endometritis and WI were reduced following both elective and emergency CD by 60-70% and 30-65% respectively.[16] While antibiotic prophylaxis for elective CD has been shown to be cost effective,[36;100] there has been reluctance in implementing the recommendations,[101;102] as well as inconsistency.[103;104] Several questions have been raised including the optimal indication, drug of choice and drug regimen,[105-108] and whether prophylaxis should be given to all women or only those considered to be at high risk.[36;109-111] These concerns underline the numerous variables involved in assessing the effects of antibiotic prophylaxis post-CD (presence or absence of membrane rupture, primary versus repeat CD, narrow-range versus broad-spectrum antibiotics, timing of administration whether pre-incision or post umbilical cord-clamping and others). Table 2 illustrates the effect of any prophylactic antibiotic on fever, WI, endometritis and UTI post-CD.[16]

CURRENT DEBATE ON THE USE OF ANTIBIOTIC PROPHYLAXIS FOR CD

Currently, the Cochrane Database of Systematic Reviews, the American College of Obstetrics and Gynecologists (ACOG) and the CDC recommend narrow-range first generation cephalosporins, like cefazolin, to be administered after umbilical cord-clamping for prophylaxis against infection post-CD.[16;90;112] This is because they are considered equally effective and less costly than broad-spectrum antibiotics.[90;113] However, despite the use of antibiotics, 10% of CD are still complicated by infection and 15% by fever.[16] The administration of antibiotics is not intended to sterilize tissues, but to act as an adjunct to decrease the intra-operative microbial load to a level which can be managed by the host innate and adaptive immune responses.[14;15;18;114] The goal of antibiotic therapy is to achieve sufficient tissue levels at the time of microbial contamination,[1] and the optimal agent should be long-acting, inexpensive, and have a low side effect profile.[90] Ampicillin reaches Group B Streptococcus (GBS) bactericidal concentrations in cord blood within five minutes of administration to the mother,[115] and cefazolin reaches the minimum inhibitory concentration for GBS in fetal blood within 30 minutes of administration.[13] Concerns about antibiotic intervention using broad-spectrum antibiotics center on infection with resistant organisms such as *Clostridium difficile* or methacillin resistant *Staphylococcus aureus*, but this is unlikely with single-dose prophylaxis.[15] In addition, the shorter hospital stay observed following antibiotic prophylaxis is not consistent with an increase in infections from resistant organisms.[98] Since there is overwhelming evidence for the need and effectiveness of prophylactic antibiotics to prevent infection following CD, the current debate focuses on the choice of antibiotic and the timing of administration. With respect to timing, the debate lies between pre-incision or post-clamping of the umbilical cord and the choice of antibiotic lies between narrow-range and broad-spectrum. Both of these debates

have been influenced by concerns that broad-spectrum antibiotics given pre-incision might mask neonatal infection or result in a neonatal infection in which no organism could be cultured. There are also concerns that the wrong choice of antibiotic may result in the neonate being exposed to resistant strains of bacteria,[90;116] which might lead to a worse neonatal outcome[117] and/or the need for expensive neonatal septic screens and infection work-ups.[118] This is supported by an observed shift in early neonatal sepsis from GBS to *Escherichia coli* and other Gram negative organisms, and a change in resistance patterns,[90;117;119-121] which may affect early gut colonization and has been implicated in early childhood asthma and allergy.[122;123]

TIMING OF ADMINISTRATION OF PROPHYLACTIC ANTIBIOTICS FOR CD

While regulatory agencies overwhelmingly advise prophylactic antibiotics to be given pre-incision to prevent SSIs,[14;15;18] an exception is made for CD, where the recommendation is to use these antibiotics post-clamping of the umbilical cord.[15;16] Recently, a systematic review of the literature has challenged this approach.[83] A total of 277 potentially relevant studies were identified, from which two non-randomized trials,[118;124] two retrospective-cohort studies,[24;125] and three randomized controlled trials (RCTs),[126-128] were selected to produce a meta-analysis.[129] The two non-randomized trials[118;124] concluded that there was no benefit of pre-incision versus post-clamping antibiotic prophylaxis with respect to overall infection rate or endometritis. However, one of the studies was unblinded,[124] with a small sample size, and the other was a secondary analysis of two trials,[118] one of which used narrow-range, and the other broad-spectrum antibiotics. Most meta-analyses or systematic-reviews would exclude such studies. The same is true of the two retrospective cohort studies, both of which used narrow-range cephalosporins,[24;125] yet found a significant reduction in overall infection rates. One showed a significant reduction in endometritis,[24] and the other reported a significant reduction in WI[125] when prophylactic antibiotics were given pre-incision rather than post-clamping. In the meta-analysis[129] of the three RCTs,[126-128] with a sample size of 749, the use of pre-incision cefazolin was associated with a 50% reduction in overall infection rate, a 53% reduction in the rate of endometritis and a non-statistically significant 40% reduction in the rate of WI compared to post-clamping administration. Neonatal sepsis rates were comparable between the two study groups.

Subsequently, a retrospective cohort study of 1316 term, singleton CDs at one institution reported on a policy change in timing of antibiotic prophylaxis from post-clamping to pre-incision, which resulted in a reduction of 60% in the rate of SSIs, a 50% reduction in the rate of endometritis and an 80% decrease in cellulitis.[24] Another recent study supports these findings,[130] though it was not a RCT. The observation arose from a change in policy from post-clamping administration of prophylactic antibiotics to pre-incision administration over two different time periods. With >4,000 CDs in each group and using the same antibiotics throughout (cefazolin), there were no adverse neonatal effects. Post-clamping antibiotics (n=4229) was associated with a 3.9% incidence of endometritis compared to 2.2% incidence for pre-incision cefazolin, (n=4781) (adjusted OR = 0.61; 95% CI=0.47-0.79) and post-clamping WI occurred in 3.6% compared to 2.5% following pre-incision antibiotics (adjusted OR= 0.70; 95% CI=0.55-0.90) (p=0.001 for the linear trend).[130] In contrast, using cefazolin in women undergoing elective CD, pre-incision antibiotics did not significantly reduce overall infection or endometritis. Nevertheless, the use of pre-incision antibiotics was not associated with an increase in neonatal sepsis, sepsis work-up, and admission or length of stay in the Neonatal Intensive Care Unit.[131]

CHOICE OF ANTIBIOTIC AND RATIONALE FOR THE USE OF BROAD-SPECTRUM ANTIBIOTICS

The main source of infection following CD is the lower genital tract[52;132] particularly if the membranes are ruptured, but this still occurs with intact membranes, especially following preterm birth.[133-135] The causative organisms are polymicrobial, particularly those responsible for bacterial vaginosis (BV), such as *Ureaplasmas*, *Mycoplasmas*, anaerobes or *Gardnerella vaginalis*[38;58;71;136-143] and these organisms are also commonly isolated from amniotic fluid and the chorioamnion at the time of CD.[58;71;144-146] When these organisms are detected, there is a 3-8 fold increased risk of endometritis or WI post CD,[58;83;144-147] and BV is associated with a 6-fold increase in post-CD endometritis.[71] WI is susceptible to skin contaminants as well as BV responsible organisms.[136;139]

The use of first generation cephalosporins such as cefazolin[90] provides antibiotic activity against *Ureaplasmas* and *Mycoplasmas* but may cause an increase in resistant organisms like anaerobes.[138;148] Hence, there is rationale for adding agents such as metronidazole, clindamycin, or azithromycin to extend the cover. The broad-spectrum antibiotics that have been evaluated are mainly single-agent extended-range penicillins, or second- or third-generation cephalosporins (β-lactams) which show no advantage.[113] However, four RCTs[98;149-151] compared the use of narrow-range antibiotic prophylaxis (first-generation cephalosporin or ampicillin) with broad-spectrum regimens which comprised narrow-range antibiotics with the addition of agents from a different class of antibiotics such as gentamycin,[150] metronidazole[149;151] or azithromycin and doxycycline.[98] Broad-spectrum antibiotics were associated with a statistically significant reduction in infection rates,[98] endometritis[98;149-151] and WI[98] compared to narrow-range. Length of hospital stay was significantly shorter when broad-spectrum antibiotics were used.[98;149;150]

USE OF AZYTHROMYCIN

The leading option as a second-line broad-spectrum antibiotic for CD appears to be azithromycin, which has a longer half-life (68 hours), higher tissue concentrations, and lower transplacental passage than several other antibiotics commonly used for this indication.[90] In addition, azithromycin is active against both aerobes and anaerobes, as well as *Ureaplasmas*, resulting in significantly less endometritis and WI than in studies in which other antibiotics were used.[98;149-153] Metronidazole is cheaper than azithromycin, but since 20% of preterm neonates may have *Ureaplasma* bacteremia[154] and it is suggested that neonatal *Ureaplasma* infection may be associated with bronchopulmonary dysplasia,[155] azithromycin based broad-spectrum prophylaxis may prevent neonatal sepsis and chronic lung disease, though this has not been tested. Addional support for the use of azithromycin-based broad spectrum antibiotic prophylaxis for CD has been demonstrated in a series of studies with experience of institutional surveillance.[58;98;152;153]

EXPERIENCE OF INSTITUTIONAL SURVEILLANCE

The first of these studies included 575 women undergoing CD with intact membranes and no evidence of chorioamnionitis. Colonization of the chorioamnion with *U. urealyticum*, irrespective of the presence of other organisms, was associated with a 3-fold increased risk of endometritis, which rose to an 8-fold increased risk if the women had gone into spontaneous labor.[58] Subsequently, in a RCT of 597 women undergoing CD, using broad-spectrum antibiotics known to be active against *U. urealyticum*, the prevalence of endometritis, WI, or either, was statistically significantly reduced compared to the use of cefotetan and placebo. Length of hospital stay overall, and the rate of endometritis, was also statistically significantly reduced.[98] Finally, institutional surveillance over a 14-year period,

demonstrated that when comparing the time during which narrow-range antibiotics were used, with the interim period of trials during which broad-spectrum antibiotics were tested, the latter was associated with a finite reduction in post-CD infection rate.[152;153] Endometritis rates fell from 23% with narrow-range, to 16% during the trial period, to 2.1% with routine use of broad-spectrum antibiotics.[153] Wound infection showed the same trend. During the use of narrow-range antibiotics, the rate of WI fell from 3.1% to 2.4% during the trial period, and to 1.3% with the routine use of broad-spectrum antibiotics.[152]

CONCLUSIONS

Cesarean delivery is associated with a significantly higher post-operative infection (SSI, WI, UTI) rate than following vaginal birth and other surgical procedures. With the increase in CD rates worldwide, post-CD infections (SSI, WI, UTI) are likely to become a significant health and economic burden. There is overwhelming evidence that antibiotic prophylaxis for CD is effective in preventive maternal infectious morbidity. However, concerns about neonatal infection have confined its use to narrow-range antibiotic administration post umbilical-cord clamping, instead of a regimen of pre-incision, broad-spectrum antibiotics which is being used in non-pregnant subjects undergoing major surgery. Recent evidence suggests that pre-incision broad-spectrum antibiotics are more effective in preventing post-CD infections than post-clamping narrow-range antibiotics, without prejudice to neonatal infectious morbidity. This strategy has been adopted by the ACOG and the American Academy of Pediatricians,[156] though national guidelines have yet to change. Nevertheless, the combination of broad-spectrum/pre-incision antibiotic prophylaxis for CD versus narrow-range/post-clamping has not been tested and there is an urgent need for this definitive study to be performed. Such a study would have to address both maternal and neonatal infectious morbidity as well as long term neonatal follow-up. Variables such as surgical technique (suture material, use of surgical drainage),[15;157] type of CD (elective vs. emergency; primary vs. repeat; with or without labor) and state of the chorioamniotic membranes would have to be addressed.

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Table 1

Innovations based upon antiseptic principles in the practice of surgery attributed to Joseph Lister (1827-1912) which reduced the rate of post surgical infectious mortality and morbidity (Guthrie d 1949; Baue AE 1909)

Carbolic acid (phenol) wound dressings
Absorbable (catgut) sutures soaked in carbolic acid
Surgical hand washing with carbolic acid
SAterilisation of surgical instrumentswith carbolic acid
Use of surgical drainage tubes
Use of gloves masks and gowns

Table 2

The effect of any prophylactic antibiotic on the rates of fever, wound infection, endometritis and urinary tract infection following cesarean delivery (adapted from Cochrane Systematic Review)[16]

Outcome	Elective CD RR (95% CI)	Emergency CD RR (95% CI)
Fever	0.49 (0.32-0.75)	0.40 (0.31-0.51)
Wound Infection	0.73 (0.53-0.99)	0.36 (0.26-0.51)
Endometritis	0.38 (0.22-0.64)	0.39 (0.34-0.46)
Urinary Tract Infection	0.57 (0.29-1.11)	0.43 (0.30-0.60)

RR = Risk Ratio

CI = Confidence Intervals

CD = Cesarean Delivery