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Evolving Concepts in Antibiotic Prophylaxis for Cesarean Delivery: A Systematic Review

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Abstract

Objective—To review the current status of antibiotic prophylaxis for cesarean delivery, newly evolving strategies to enhance the effectiveness of antibiotic prophylaxis in reducing post-cesarean infection, and the implications of the emerging practices.

Data Sources—We conducted a full PubMed (January 1966–July 2008) search using the key words “cesarean section” and “antibiotic prophylaxis.” A total of 277 articles were identified and supplemented by a bibliographic search.

Methods of Study Selection—We selected a total of 15 studies which included all published clinical trials, meta-analyses of clinical trials, and observational studies evaluating either the timing of antibiotics or the use of extended-spectrum prophylaxis. We also reviewed nine reports involving national recommendations or technical reviews supporting current standards for antibiotic prophylaxis.

Tabulation, Integration, and Results—We conducted an analytic review and tabulation of selected studies without further meta-analysis. Although current guidelines for antibiotic prophylaxis recommend the administration of narrow-spectrum antibiotics (cefazolin) after clamping of the umbilical cord, the data suggest that antibiotic administration prior to surgical incision or the use of extended-spectrum regimens (involving azithromycin or metronidazole) after cord clamp may reduce postcesarean maternal infection by up to 50%. However, their impact relative to each other has not been studied. In addition, their impact on neonatal infection or infection with resistant organisms warrants further study.

Conclusion—The use of either cefazolin alone prior to surgical incision or an extended-spectrum regimen after cord clamp appears to be associated with a reduction in postcesarean maternal infection. Confirmatory studies focusing additionally on neonatal outcomes and the impact on resistant organisms, as well as studies comparing both strategies, are needed.

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Introduction

Prophylactic antibiotics reduce surgical site infections^{1–4} and evidence-based national guidelines recommend their administration *prior* to surgical incision.^{2–3,5} An exception to this pre-incision prophylactic approach is cesarean delivery, the most common major surgical procedure in the United States⁶ and elsewhere. Driven by concerns about the sequelae of fetal antibiotic exposure with pre-incision administration, for nearly 30 years, the standard to prevent post-cesarean infection has been the administration of narrow spectrum antibiotic prophylaxis after delivery of the baby and clamping of the umbilical cord.^{4,7} Meanwhile, US cesarean delivery rates are increasing - from 20.7% in 1996 to 31.1% in 2006, an absolute increase of 50% over a decade (Figure I).^{8–9} The overall increase mirrors increases in both primary (laboring and non-laboring) cesareans and repeat cesareans. Recent data also indicate that primary cesareans in the absence of obstetric indications are rapidly rising, reflecting both shifting obstetric practices and maternal preference.¹⁰ If these trends continue, cesareans will make up approximately 50% of the more than 4 million annual deliveries by 2020. Therefore, the health and economic burden of post-cesarean infection will likely continue to rise. In this article, we review the current status of antibiotic prophylaxis for cesarean delivery, newly evolving strategies to enhance the effectiveness of antibiotic prophylaxis in reducing post-cesarean infection, and the implications of the emerging practices.^{2–3,7}

Data Sources and Study Selection

We searched the entire PubMed computerized database from January 1966 through July, 2008, using the keywords “cesarean delivery” and “antibiotic prophylaxis.” All published studies (without restriction by national origin, language, and presence or absence of risk factors) focusing on national recommendations for antibiotic prophylaxis, timing of prophylaxis and/or extended spectrum regimens for cesarean delivery were selected for abstraction. Our definition of “extended-spectrum” antibiotic prophylaxis specifically refers to the combined use of the standard narrow-spectrum beta-lactam and a 2nd antibiotic of a different class. This is different from the use of broad spectrum penicillins (latter generation cephalosporins, ureidopenicillins or monobactams) or other single agents which have been generally demonstrated to be no more effective than the standard. A bibliographic review of selected studies was also used to supplement eligible studies.

The search produced 277 PubMed articles for preliminary abstract review. Case reports, descriptive studies, and letters to the editor as well as irrelevant studies were excluded. A total of 15 studies including all relevant clinical trials, metaanalyses or observational studies evaluating the timing of antibiotics or extended-spectrum prophylaxis for cesarean^{11–25} and 9 publications of national recommendations or metaanalyses supporting current standards for antibiotic prophylaxis were selected and fully reviewed.^{2–5,7,26–29} Key outcome measures were any post-cesarean maternal infection (primarily endometritis and wound infection based on standard definitions regardless of duration of follow-up), neonatal sepsis and sepsis work-ups. Descriptive data including study design, sample size and results for relevant studies were abstracted. Because of the varying study designs and the inclusion of metaanalyses, we conducted an analytic as opposed to a synthetic or metaanalytic review i.e. focused on analyzing study results without further metaanalysis. We present descriptive data for each study and comment on the relative risks of total maternal post-cesarean infection comprising endometritis and wound infection with or without other infections (e.g., urinary tract infection). We also present data for endometritis, wound infection; neonatal infection and/or hospital stay where available. Whenever possible we compute the relevant relative risk using data presented in the study reports. Finally we provide a review of the data supporting the rationale for each strategy (based primarily on bibliographic review of the selected articles) and comment on clinical and research implications for the use of the interventions.

Results

Current Standards for Cesarean Antibiotic Prophylaxis

Infections remain among the top 5 causes of pregnancy-related mortality and account for a disproportionate contribution to maternal morbidity, both in the US and around the world.³⁰ Cesarean delivery is the single most important risk factor for postpartum infection. Compared to women delivered vaginally, those delivered by cesarean classically face a 5 to 20-fold increase in risk.³¹ The most common post-cesarean infections are surgical site infections (endomyometritis and wound infection) and infection of the urinary tract. Pelvic abscess, septic pelvic phlebitis, pneumonia and sepsis, although rare, are also increased. These infections are associated with considerable health and economic burdens.³² The incidence of post-cesarean infection varies widely by population profile depending on several risk factors. Low socioeconomic status, unscheduled delivery (e.g., due to labor arrest, failed induction, and fetal emergencies), and obesity feature among these risk factors for post-cesarean infection.^{31,33–34}

Routine use of prophylactic antibiotics reduces the risk of post-cesarean fever and infections by over 50% from baseline rates as high as 20–50%.⁴ Based on systematic reviews of over eighty clinical trials, this benefit applies to both non-elective and elective (scheduled) procedures.^{4,26} Because antibiotic prophylaxis shortens overall length of hospitalization and reduces treatment costs associated with cesarean, it is highly cost-effective.^{27–28} Consequently, antibiotic prophylaxis is recommended for all women undergoing cesarean section.⁷ The American College of Obstetricians and Gynecologists (ACOG) specifically recommends a narrow-spectrum 1st generation cephalosporin (cefazolin) over ampicillin as the regimen of choice because of increasing microbial resistance to the latter.⁷

Despite currently recommended antibiotic prophylaxis protocols, at least 10% of cesareans overall are complicated by infection, and over 15% by fever.⁴ Fifteen to 80% of post-cesarean infections, particularly those involving wounds, may actually occur after initial discharge from the hospital.^{2,35} Therefore, underestimation of the incidence of post-cesarean infection is pervasive, particularly when based solely on in-patient data and/or follow-up duration of less than 4–6 weeks. Given the rising rates of cesarean delivery (Figure I), prevention of post-cesarean infection remains a public health priority.³⁶ Evolving concepts affecting both the timing of antibiotic administration and the selection of antimicrobial agents have implications for addressing this priority.

Pre-Incision Antibiotic Prophylaxis

Rationale—Both animal models and clinical studies in non-pregnant patients suggest that prophylactic antibiotics are more effective if administered just prior to surgery (as opposed to long before, during, or after the procedure).^{1,37} Administration within 30–60 minutes of surgery is optimal; this maximizes tissue and blood antibiotic concentrations at surgical sites.^{2–3,5,29} Antibiotics commonly used for cesarean prophylaxis are rapidly transferred to the fetal compartment (within 2 hours for cefazolin) raising concerns that fetal exposure to antibiotics might mask infection in the neonate and promote the selection of resistant organisms.⁷ Thus, historically, pediatricians were inclined to perform invasive and costly sepsis work-ups on neonates who were exposed to antibiotics immediately prior to delivery.¹² Moreover, 2 non-randomized studies of timing of antibiotic prophylaxis for cesarean (Table I) suggested that while pre-incision administration did not reduce post-cesarean infection,^{11–12} it did increase invasive neonatal sepsis evaluations and costs.¹⁰

Therefore, to prevent fetal exposure, the traditional practice has been to administer antibiotics only after delivery of the infant and clamping of the umbilical cord,^{4,7} and federal and national

organizations including the CDC, the Center for Medicaid and Medicare Services and the American Society of Hospital Pharmacists all identify cesarean as the exception to general recommendations to administer antibiotic prophylaxis *prior* to surgical incision.^{2–3,5,29} Although ACOG currently does not make an explicit recommendation regarding timing, it recognizes that prophylactic antibiotics for cesarean delivery are generally administered after cord clamping.⁷ The most recent Cochrane systematic review, involving over 80 clinical trials, recommended administration after cord clamp pending further studies of pre-incision administration.⁴

Study Findings—Compared with the older studies,^{11–12} 4 more recent studies of antibiotic prophylaxis for cesarean delivery suggest that prophylactic antibiotics administered prior to incision are more effective in preventing post-cesarean infection than administration after umbilical cord clamping (Table I).^{13–18} These studies do have sample size limitations and were not all randomized trials. The largest and most recent randomized trial reported by Sullivan involved 357 patients from a single center.¹⁶ Significant reductions in the pre-incision group were observed in endometritis and total infection (endometritis, wound infections, urinary infections and pneumonia) but not in wound infections alone.¹⁶ A meta-analysis of all 3 randomized trials found a 50% reduction in post-cesarean infection associated with pre-incision antibiotic administration.¹⁷ Although antibiotic exposure did not appear to influence neonatal sepsis in any single trial or in the metaanalysis (n=759), none of these studies was sufficiently powered to determine a clinically significant difference in this rare 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. One retrospective cohort study has also associated pre-incision antibiotic prophylaxis with greater than a 50% reduction in maternal infection compared to prophylaxis after cord clamp.¹⁸

Extended Spectrum Antibiotic Prophylaxis

Study findings—First generation cephalosporins (primarily cefazolin) are recommended over broader spectrum antibiotics, as they are equally effective and less costly than the latter.^{7,19} However, the broad-spectrum antibiotics that have been evaluated are mainly single-agent extended-spectrum penicillins, or 2nd or 3rd generation cephalosporins (i.e. beta lactams).¹⁹ In one small trial, ampicillin alone (compared to ampicillin plus gentamycin) was associated with significantly higher risk of endometritis, febrile morbidity and longer hospitalization.²⁰ Indeed, accumulating evidence from the preceding and other randomized clinical trials (Table II) suggest that such extended-spectrum regimens (i.e., 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 (and costs) than narrow-spectrum agents alone.^{20–23} Furthermore, a recent cohort study confirmed a corresponding drop in rates of post-cesarean endometritis with increasing use of azithromycin-based extended spectrum prophylaxis (Figure II) at one US center over a period of 14 years.²⁴ The incidence of wound infection also decreased from 3.2 to 1.3% over the same time period.²⁵ These findings are limited by the possibility, albeit unlikely, that they are entirely due to other concurrent changes during the time periods.

Rationale—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.^{2–3,7} Post-cesarean infections are polymicrobial, involving aerobes, anaerobes and *Ureaplasma* (or *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.^{38–41} The most common organisms isolated from wound infections also include *Ureaplasma* as well as staphylococci and enterococci.^{42–43} 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.^{44–48} Bacterial vaginosis is also associated with as much as a 6-fold increased risk of post-cesarean endometritis.⁴⁹ Therefore, the recommended narrow-spectrum regimen of cefazolin alone does not cover frequent isolates or risk factors such as *Ureaplasma* and anaerobic bacteria. Indeed, narrow-spectrum antibiotic prophylaxis modifies flora towards the increased presence of resistant organisms such as anaerobes.^{38,50} While azithromycin or metronidazole appropriately suppresses ureaplasma or anaerobes respectively, it is likely that the origin of the observed benefits extends to the suppression of other susceptible organisms. The use of an extended-spectrum regimen involving a 2nd antibiotic is not an entirely new concept in surgical antibiotic prophylaxis. The addition of vancomycin to cefazolin is recommended for other surgeries (e.g. cardiothoracic surgery) when MRSA is a frequent cause of infection.² Also, extended-spectrum prophylaxis is well established for non-surgical obstetric antibiotic prophylaxis: ampicillin + erythromycin (or azithromycin) for preterm premature rupture of membranes to reduce maternal and fetal infectious morbidity, and to prolong the time from membrane rupture to delivery.^{7,51}

Antibiotic selection—Azithromycin appears to be the leading option for the 2nd antibiotic for extended-spectrum regimens for cesarean delivery. It has a longer half-life (68 hours), higher tissue concentration and lower potential for fetal transfer than the other antibiotics in published studies.^{52–53} In addition, azithromycin has both aerobic and some anaerobic coverage, uniquely covers *Ureaplasma*, and is the only choice associated with significantly reduced incidence in both endometritis and wound infection.^{20–25} The main advantage of metronidazole over azithromycin is lower antibiotic cost. Furthermore, in light of evidence suggesting that greater than 20% of preterm neonates may have *Ureaplasma* bacteremia,⁵⁴ and suggestions that bronchopulmonary dysplasia (BPD) is associated with neonatal *Ureaplasma* infection,⁵⁵ pre-incisional use of azithromycin-based extended spectrum prophylaxis may theoretically prevent neonatal sepsis syndrome and BPD. However, this hypothesis needs to be tested.

The rationale and evidence for azithromycin-based extended-spectrum antibiotic prophylaxis for cesarean delivery are demonstrated in a series of studies conducted at one center.^{23–25, 46} First in a cohort study of 575 women undergoing cesarean with intact membranes and without any clinical evidence of infection, those with positive chorioamnion cultures for *Ureaplasma* (with and without other bacteria) were three times more likely to develop post-cesarean endometritis than those with negative *Ureaplasma* cultures.⁴⁶ In a subsequent clinical trial involving 597 cesareans, azithromycin-based extended-spectrum prophylaxis significantly reduced incidence of post-cesarean endometritis and wound infection, and shortened hospital stay compared to the use of a cephalosporin only.²³ Finally, institutional surveillance studies demonstrated significant reductions in endometritis and wound infection.^{24–25}

Conclusion

A recent joint publication by ACOG and the American Academy of Pediatrics included new wording that “... an antibiotic before the procedure [cesarean] has been demonstrated to be more effective than administration immediately after umbilical cord clamping.”⁵⁶ Still, none of the major national guidelines on antibiotic prophylaxis, including ACOG’s, explicitly recommends pre-incision administration of antibiotic prophylaxis (or use of an extended-

spectrum regimen) for cesarean. Nevertheless, after some 25–30 years of narrow-spectrum prophylaxis after cord clamping, interventions to improve on this clinical standard are emerging.

We acknowledge that our review findings are inherently limited by the likelihood of publication bias; studies with negative findings are less likely to be published. The inclusion of observational studies further raises the possibility of bias.

Amongst the published studies of timing of antibiotic prophylaxis for cesarean, one well-designed and implemented randomized trial provides evidence that pre-incision administration is superior to administration after cord clamp in preventing post-cesarean endometritis and total infectious morbidity.¹⁶ The study's power to delineate the impact on wound infections alone, or on neonatal outcomes, was limited. Universal use of pre-incision administration will expose all neonates delivered by cesarean (1.3 million annually in the US for example) to prenatal antibiotics. The already widespread prenatal use of antibiotics for preterm membrane rupture and to prevent GBS sepsis (both of which are without demonstrable neonatal harm), and commitments from pediatricians to avoid invasive neonatal sepsis evaluations solely because of antibiotic exposure, may serve to diminish concerns regarding safety. However, conclusive information regarding the safety of pre-incision prophylactic antibiotics, and their potential impact on the rate of neonatal infections, and emergence of anti-microbial resistance or selection of known resistant organisms is not available. Specifically, given reports suggesting an increase in *E. coli* neonatal sepsis with GBS prophylaxis, attention should be paid to the possibility of resistant infections.^{57–58} Obstetric and neonatal antibiotic practices, by inducing early abnormal gut colonization, have also been implicated in the significant rise in childhood allergy and asthma.^{59–60} Consequently, adoption of these emerging strategies for antibiotic prophylaxis during cesarean should be tempered by caution. Follow-up studies addressing these concerns including additional well-designed trials to confirm the effectiveness and neonatal safety of pre-incision timing of antibiotic prophylaxis for cesarean delivery are prudent. It is important to verify that neonates are not subjected to invasive and costly sepsis work-ups solely because of antibiotic exposure under the non-blind conditions of routine clinical practice.

The available experimental evidence supporting extended-spectrum prophylaxis for cesarean comes from single centers using varying antibiotic regimens.^{20–23} Given the marked inter and intra-regional variation in populations and rates of post-cesarean infection, additional trials are needed to assess the generalizability of the benefit observed with extended regimens administered after cord clamping, and to compare the strategy to pre-incision administration of cefazolin alone. Furthermore, considering the potential for a shift in practices to pre-incision antibiotic prophylaxis for cesarean delivery, studies assessing whether pre-incision administration of extended-spectrum antibiotics provides additional benefits over pre-incision administration of cefazolin only may also be indicated. Such studies should assess the impact on maternal and neonatal infection, and monitor for disparities in microbial resistance and pseudomembranous colitis. Because the overall incidence of post-cesarean infections will vary immensely by socio-demographic profile and other risk factors within populations, the urgency with which to adopt and/or further evaluate these emerging strategies may vary by setting. Nonetheless, efforts to optimize the impact of antibiotic prophylaxis should obviously be part of a comprehensive strategy to reduce surgical site infections including improved patient preparation and surgical technique.²

The use of either cefazolin alone prior to surgical incision or an extended-spectrum regimen after cord clamp appears to be associated with a reduction in postcesarean maternal infection. Confirmatory studies focusing additionally on neonatal outcomes and the impact on resistant organisms, as well as studies comparing both strategies, are needed.

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Figure 1.

Trends in total cesarean delivery rate, US 1996–2006. Data from Martin JA, Hamilton BE, Sutton PD, Ventura SJ, Menacker F, Kirmeyer S, Munson ML. Births: Final data for 2005. Natl Vital Stat Rep 2007;56:1–103, and Hamilton BE, Martin JA, Ventura SJ. Births: Preliminary data for 2006. Natl Vital Stat Rep. 2007;56:1–18. {AQ: Figure 1 redrawn by editorial office. Please review and indicate approval.}

Figure 2.

Annual incidence of post-cesarean endometritis for three time periods, categorized according to type of prophylactic antibiotics at University of Alabama at Birmingham. The line is the moving average trend line for successive years within each period of antibiotic prophylaxis. 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.* 2003;101:1183–9.

Overview of Published Studies of Timing of Antibiotic Prophylaxis for Cesarean

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Table 1

Study Description				Study Outcomes			
Study	Design	Sample Size	Antibiotic Prophylaxis (dose)	Total Infection [*]	Endometriti ^s	Wounds [*]	Neonatal Sepsis ^{*,†}
Gordon, 1979 ¹⁰	RCT (Un-blinded) 2 ^o analysis of 2 clinical trials	78	Ampicillin (1g)	1.40 (0.3, 5.9)	N/A	N/A	0 vs. 2.7%
Cunningha m, 1982 ¹¹		305 (642 neonates)	Cefamandale or Penicillin G & Gentamycin	N/A	1.09 (0.6, 1.9)	N/A	9.2 vs. 6.7%
Feigin, 1993 ¹²	Cohort (Historical comparison)	435	A cephalosporin (Cefonicid, ceftriaxone or cefamezine)	0.40 (0.20, 0.81)	0.40 (0.12, 1.3)	0.11 (0.01, 0.9)	N/A
Wax, 1997 ¹³	RCT	90	Cefazolin (1g)	0.28 (0.03, 2.6)	0.84 (0.05, 13.0)	0.42 (0.04, 4.5)	3.35 (0.8, 14.9)
Thigpen, 2005 ¹⁴	RCT	303	Cefazolin (2g)	0.58 (0.34, 1.0) [‡]	0.67 (0.42, 1.1)	0.84 (0.45, 1.6)	0.96 (0.68, 1.3)
Sullivan, 2007 ¹⁵	RCT	357	Cefazolin (1g)	0.40 (0.18, 0.87)	0.20 (0.2, 0.94)	0.52 (0.18, 1.5)	1.0 (0.67, 1.55)
Costantine, 2008 ¹⁶	Metaanalysis (the 3 preceding RCTs)	749 (771 neonates)	Cefazolin	0.50 (0.33, 0.78)	0.47 (0.26, 0.85)	0.60 (0.30, 1.21)	0.93 (0.45, 1.96)
Kaimal, 2008 ¹⁷	Cohort (Historical)	1316	Cefalozin	0.33 (0.14, 0.76)	0.34 (0.13, 0.92)	N/A	N/A

^{*} RR (95% CI) for “Before Incision” vs. “After Cord Clamping” extracted from published reports or calculated using the reported data (Referent is the “After cord clamping” group)

[‡] Calculated assuming that no patient had both wound infection and endometritis;

[§] Neonatal sepsis: either proven or suspected

RCT= Randomized clinical trial; N/a = Relevant data “Not available”;

Table 2

Overview of Published Trials of Extended-Spectrum Antibiotic Prophylaxis for Cesarean

Study Description			Study Outcomes				
Study	Design	Sample size	Antibiotics	Total Infection [*]	Endometritis [*]	Wounds [*]	Hospital stay ^{**}
O'Leary 1986 ¹⁹	RCT	123	Gentamycin (+ Ampicillin)	0.42 (0.17, 1.03) [†]	0.38 (0.14, 0.99) [*]	0.98 (0.06, 15.0) [*]	1.4 days shorter
Pitt, 2001 ²⁰	RCT	224	Vaginal metronidazole (+ Cefazolin)	N/A	0.42 (0.19, 0.92)	1.67 (0.41, 6.81)	No difference
Meyer, 2003 ²¹	RCT	160	Metronidazole (+ Cefotetan)	N/A	0.43 (0.23, 0.82)	N/A	1.4 days shorter
Andrews, 2003 ²²	RCT	597	Azithromycin/Doxycycline (+ Cefotetan)	0.68 (0.50, 0.94)	0.68 (0.49, 0.94)	0.22 (0.05, 0.99)	½ day shorter

^{*} RR (95% CI) for "Extended spectrum" vs. "standard narrow spectrum" prophylaxis from published reports or calculated based on reported data (Referent is the narrow-spectrum only group corresponding to the antibiotic in parentheses);

[†] Calculated assuming that no patient had both wound infection and endometritis

^{**} Shorter hospital stay with extended-spectrum compared to narrow spectrum prophylaxis;
RCT= Randomized clinical trial; N/a = Relevant data "Not available"