Approach to Antibiotics in Obstetrics: Surgical Prophylaxis for Cesareans

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Objectives

• Review antibiotic prophylaxis for C-section
• Surgical site infection in pregnancy
• Special considerations for antibiotic prophylaxis in pregnancy
Prophylactic Antibiotics

• Goal to prevent infection
• Administered before microbial contamination
• Concerns about emergence of resistant strains of common bacteria

Obstetric specific
• Potential adverse effects of resistant bacterial infections on neonates
Prophylactic Antibiotics

• Goal is to have therapeutic tissue levels at time of microbial contamination

• Delaying administration reduces or eliminates benefit of prophylaxis

• Agent of choice should be long acting, narrowly focused on the likely bacteria, inexpensive, and have a low incidence of adverse effects
Resistant Organisms

• Antimicrobial prophylaxis results in:
  – Marked changes in skin flora with increase resistant flora

• In pregnancy adverse effects of resistant bacteria on neonates is increasing
  – VLBW (<1,500 g) reduction in early-onset GBS but increase in sepsis caused by *Escherichia coli*
Allergy and Anaphylaxis

• Anaphylaxis to penicillin occurs in 1 in 2,500–25,000 patients
  – Less severe reactions occur in 10% of patients

• Skin reactions (urticaria, rash, pruritus) to cephalosporins occur in 1–3% of patients
  – Risk of anaphylaxis is much lower (0.001–0.1%)

• Antibiotic use should be limited to the specific indications as outlined
Pharmacokinetics of Antibiotics in Pregnancy

- Glomerular filtration rates increased
- Increased plasma volume
- Hormone-mediated increases in binding proteins results in changes in the distribution of drugs
- Decreased in gastric emptying time and changes in gastric acidity changes oral absorption
- Result in a reduction in amount of drug available and potential need for increased dosages during pregnancy
Special Considerations in Pregnancy

- Choose agents with known trans-placental passage when therapeutic levels in amniotic cavity are desired
  - PPROM to prolong the latency period
  - Intra-partum prophylaxis for GBS

- Fetal concentrations of 30–90% of maternal serum
  - Ampicillin, cephalothin, clindamycin, and aminoglycosides

- Antibiotics that do not cross the placenta well
  - Erythromycin and Azithromycin
SURGICAL SITE INFECTION
Adverse Surgical Events

Impact of Surgical Site Infection

<table>
<thead>
<tr>
<th></th>
<th>Infected</th>
<th>Uninfected</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality</td>
<td>7.8%</td>
<td>3.5%</td>
</tr>
<tr>
<td>ICU adm.</td>
<td>29%</td>
<td>18%</td>
</tr>
<tr>
<td>Readmission</td>
<td>41%</td>
<td>7%</td>
</tr>
<tr>
<td>Median initial L.O.S.</td>
<td>11d</td>
<td>6d</td>
</tr>
<tr>
<td>Median total L.O.S</td>
<td>18d</td>
<td>7d</td>
</tr>
<tr>
<td>Initial excess cost</td>
<td>+$3,644 (median)</td>
<td></td>
</tr>
<tr>
<td>Total excess cost</td>
<td>+$5,038 (median)</td>
<td></td>
</tr>
</tbody>
</table>

* Pairs matched for procedure, NNIS index, age

Kirkland, Infect Control Hosp Epidemiol 1999; 20; 725
# Surgical Site Infection Rates

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Range of SSI*</th>
</tr>
</thead>
<tbody>
<tr>
<td>C-section</td>
<td>5-30% Endometritis</td>
</tr>
<tr>
<td></td>
<td>0-12% Wound</td>
</tr>
<tr>
<td>Vaginal hysterectomy</td>
<td>0.9-38% (~4-8%)</td>
</tr>
<tr>
<td>Abd hyst or mixed</td>
<td>2.8-23% (~5-10%)</td>
</tr>
<tr>
<td>Abd surgery, mixed</td>
<td>3.9-13%</td>
</tr>
<tr>
<td>Colorectal</td>
<td>4.4-22% (~10%)</td>
</tr>
</tbody>
</table>

*Includes wound infection and intra-abdominal infections/abscess
Pathogens in Ob/Gyn Infections

- Postpartum endometritis
  - *Peptostrep, Bacteroides, G vag, enterococci, GBS, enteric Gram negative rods*

- Wound infection
  - 25-50% *Staph aureus*, coag negative *Staph*
  - 50-75% vaginal flora

- Post hysterectomy
  - *Bacteroides, Peptostrep, G. vag, enterococci, enteric GNR*

Prophylactic Antibiotics: Timing and Dosing

• **Single** dose given 30 minutes or less before the skin incision provides adequate tissue concentrations.
  
  – Short half-life drugs:
    • Ampicillin
    • Cefoxitin/cefotetan

  – Long half-life drugs:
    • Cefazolin
    • Doxycycline
    • Metronidazole

• If surgery prolonged (>4 hours), major blood loss, or a short-half-life antibiotic used an additional dose is advisable

• **Postoperative dosing of antibiotics gives no additional benefit as “prophylaxis”**
Perioperative Prophylactic Antibiotics

Classen, NEJM 1992; 328; 281
Antibiotic Prophylaxis: Choice of Agents

• Likely pathogens: enteric gram-neg, aerobes, GBS, enterococci

• Cesarean section - clear benefit highest with active labor or ROM
  – Cefazolin 1-2 gms IV

• 3rd/4th generation cephalosporins have no role in prophylaxis
Evolution of Cesarean Prophylaxis

• Prior to 2000, research focused on benefit of prophylactic compared to no prophylaxis in reducing post-cesarean infectious morbidity
  – “Prophylaxis” occurred after incision, after cord clamp
  – Concerns/theoretical risks on neonate of pre-delivery antibiotics

• Early 2000’s more studies address concept of bringing timing of cesarean prophylaxis in line with other surgical prophylaxis regimens
Early Pre-Incision C/S Prophylaxis
Cunningham 1983

- Nonrandomized; 642 women at “high risk of infection” at time of c/s
  - 305 pts got perioperative abx doses (PCN/gent or cefamandole)
  - 255 pts got 1st dose 10-90 minutes before cord clamping
  - 50 pts got 1st dose within 90 minutes of cord clamping
- No difference between groups in rates of infection

Early Pre-Incision C/S Prophylaxis
Fejgin 1993

- Nonrandomized; data on pts given abx pre-op collected prospectively (n=241), post-cord clamping data retrospective/historical (n = 194)
  - Post-cord clamping group had higher mean BMI and longer op time
  - No differences in “febrile morbidity” or endometritis
  - Higher wound infection rates in post cord clamping group

Benefits of C-section Prophylaxis: Recent Reviews - Dinsmoor, 2009

- MFMU Network data: 9432 women who had pre-labor c/s
- 6006 women (64%) received perioperative antibiotic prophylaxis
  - Prophylaxis ↓ rates of PP endometritis by 60%
  - Rate of wound infection also ↓: 1% to 0.5% (OR 0.5; 0.28 – 0.86)

Benefits of C-section Prophylaxis: Recent Reviews- Smaill, 2010

- Meta-analysis of 86 studies involving > 13,000 women
- Antibiotic prophylaxis for c/s decreased infectious risks
  - Wound infx ↓ 61% (77 studies), endometritis ↓ 62% (79 studies), febrile morbidity ↓ 55% (50 studies), serious maternal infx ↓ 69% (31 studies)
- Elective vs labor- no difference
- Before vs after cord clamp- no difference

Smaill FM, Gyte GML. Cochrane Database, 2010
Randomized C-section Prophylaxis Trials
Sullivan 2007

- Randomized blinded trial \((n = 357)\)
  - Cefazolin 15-60 minutes before surgery vs after cord clamp
  - 80\% decrease in endometritis
  - 60\% decrease in surgical site infection
  - 65\% decrease in total infect morbidity

- No increased risks of neonatal sepsis, sepsis workup, length of stay

### Summary of post-cesarean infectious morbidity observed

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Study group (n = 175)</th>
<th>Control group (n = 182)</th>
<th>Relative risk 95% CI</th>
<th>Adjusted OR 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endomyometritis</td>
<td>2 (1%)</td>
<td>10 (5%)</td>
<td>0.2 (0.2 to 0.94)</td>
<td>0.22 (0.05 to 0.9)</td>
</tr>
<tr>
<td>Wound infections</td>
<td>5 (3%)</td>
<td>10 (5%)</td>
<td>0.52 (0.18 to 1.5)</td>
<td>0.4 (0.1 to 1.3)</td>
</tr>
<tr>
<td>Total infectious morbidity</td>
<td>8 (4.5%)</td>
<td>21 (11.5%)</td>
<td>0.4 (0.18 to 0.87)</td>
<td>0.35 (0.14 to 0.8)</td>
</tr>
</tbody>
</table>

Reviews and Protocol-Evaluation Studies
Costantine, 2008

– Meta-analysis of 3 prior RCTs (n = 749)

– Pre-incision antibiotics decreases
  • Endometritis
  • Overall infectious morbidity
  • Trend toward lower risk of wound infection
  • No effect on neonatal outcomes

### Summary of Maternal Outcomes Studies

<table>
<thead>
<tr>
<th>Reference</th>
<th>Endometritis</th>
<th>Wound Infection</th>
<th>Total Infectious Morbidity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre-op</td>
<td>Cord Clamping</td>
<td>Pre-op</td>
</tr>
<tr>
<td>Sullivan</td>
<td>2 (1%)</td>
<td>10 (5%)</td>
<td>5 (3%)</td>
</tr>
<tr>
<td>Wax</td>
<td>1 (2%)</td>
<td>1 (2.4%)</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Thigpen</td>
<td>12 (7.8%)</td>
<td>22 (14.8%)</td>
<td>6 (3.9%)</td>
</tr>
</tbody>
</table>
Protocol-Change and Cesarean Prophylaxis
Owens, 2009

• Review cesareans before and after pre-op antibiotic prophylaxis protocol change (Magee-Women’s): *n = 9010*
  – Pre-incisional at a single large center
  – BMI and rates of labor similar between groups

• Lower rates of endometritis and wound infection in pre-incisional antibiotics group

• Differences in infection rates unchanged in adjusted OR
  – Adjust for chorioamnionitis, trial of labor, gest age, maternal age/race, resident teaching service

Postpartum Endometritis by 3-month Intervals

**Group 1:** July 2002-Nov 2004, after umbilical-cord clamping

**Group 2:** June 2005-August 2007, before skin incision.

Current Cesarean Prophylaxis Recommendations

- Antimicrobial prophylaxis for cesarean delivery to reduce postoperative maternal infectious morbidity
- Preoperatively administered antimicrobial prophylaxis has no deleterious effects on mother or newborn
  - Endorsed by AAP
- Prophylaxis should be given for all cesareans
  - GBS prophylaxis will only be adequate for surgical prophylaxis if patient receiving cefazolin
- Prophylaxis should be given within 60 minutes of incision

ACOG, Committee Opinion #465, September 2010
The Bottom Line

Antibiotics prophylaxis for cesarean delivery should be administered pre-operatively and not delayed until after cord clamp.
Emerging Concepts in Cesarean Prophylaxis?

- Systematic review of pre-incisional prophylaxis and extended –spectrum regimens

- Focus on ureaplasma and/or anaerobic coverage (azithromycin, metronidazole)

- Evidence to suggest extended-spectrum antibiotics comes from single center
  - Need for head-to-head comparisons of 2 regimens pre-op (cefazolin vs azithromycin)
  - Impact of cefazolin pre-op appears to be comparable to azithromycin after cord clamping

Extended-Spectrum Prophylaxis

- Cesarean Section Optimal Antibiotic Prophylaxis (C/SOAP)  
  (PI: Alan Tita, UAB)

- Evaluate effectiveness/safety of cefazolin alone vs cefazolin + azithromycin pre-op  
  - Randomized placebo-controlled trial  
  - Enrolling only women with unscheduled/non-elective c/s

- Primary outcome measure: endometritis and/or wound infection

- Start date January 2011 (to January 2014)  
  - Estimate enrollment 2000
Preoperative antibiotic prophylaxis
SPECIAL CONSIDERATIONS
Antibiotic Dosing and Obesity

- Obesity is an independent risk factor for infection

- Increases in volume of distribution and drug clearance for cephalosporins in obese patients
  - Lower levels seen in bone, fat, and other tissues compared to non-obese pts *(Pai MP, Pharmacotherapy 2007)*

- Consider higher dosing of cefazolin for pre-operative cesarean prophylaxis if BMI > 30 (2 gm vs 1 gm ?)
  - 2-gm dose for obese bariatric pts shown to give comparable serum levels to 1-gm dose in non-obese pts *(Forse RA, Surgery 1989)*
Dosing of Antibiotic in Obesity

- Prospective cohort study of obese women to estimate adequacy of preoperative antimicrobial activity
- 29 subjects stratified by BMI category
  - less than 30 (n=10)
  - 30–39.9 (n=10)
  - 40 or higher (n=9)
- 2 g cefazolin 30–60 min before skin incision
- Collected adipose myometrium and serum samples, after skin incision and before skin closure

Pevzner et al. Obstet & Gynecol. VOL. 117, NO. 4, April 2011
Dosing of Antibiotic in Obesity- Results

• Cefazolin concentrations within adipose tissue at skin incision were inversely proportional to maternal BMI (r0.67, P<.001)

• Obese (20%) and extremely obese (33%) did not achieve minimal inhibitory concentrations for Gram-negative rods in adipose

• PK analysis suggests that antibiotic prophylaxis dosing may fail to provide adequate antimicrobial coverage in obese patients

Pevzner et al. Obstet & Gynecol. VOL. 117, NO. 4, April 2011
Antibiotic Prophylaxis in Obesity

• No official recommendations based on available data
• Cefazolin 3 grams in patients with elevated BMI
  – >40
Skin Preparation

• SSIs occur in 300-500K patients in U.S. per year despite povidone-iodine skin cleansing pre-op

• Improvement in skin antisepsis could decrease SSIs since skin in major source of pathogens

• No current CDC recommendations as to which antiseptics should be used for pre-op skin preps
Skin Prep Study and Surgical Site Infection Rates

• Randomized clinical trial of chlorhexidine-alcohol vs povidone-iodine for skin prep at 6 US university-affiliated hospitals (n = 849)

• Chlorhexidine-alcohol had significantly lower SSI rates for:
  – Any Surgical Site Infection (60% ↓ )
  – Superficial incisional infection (50% ↓ )
  – Deep incisional infection (67% ↓ )
  – No difference for sepsis or organ-space infection

• No cases of fire or chemical burns in OR

MRSA and Surgical Site Infection

• MRSA colonization rates in healthy pregnant women near term
  – 2% (R-V swabs) to 10% (nasal swabs)  
    (Creech CB, Am J Infect Control, 2010; Beigi R, Inf Dis Ob Gyn, 2008)

• Annual economic impact of MRSA infection in U.S. obstetric populations is $8.0-8.7 million
MRSA: Practical Considerations

- MRSA-colonized individuals may be chronically colonized and at risk for clinical infection
- No data to support routine screening of all patients
- If patient has recent history of invasive MRSA disease
  - Topical decolonization protocol for 5 days prior to surgery
- If history of serious MRSA infection and planned surgery
  - No data to guide altering surgical prophylaxis, but consider adding **single dose** of MRSA-active antibiotic (e.g. vancomycin) to pre-incision regimen
Summary: Decreasing Cesarean SSIs

• Consideration of chlorhexidine-alcohol as pre-op skin prep

• Pre-operative antibiotic prophylaxis: 1 dose within 60 minutes of incision
  – First-generation cephalosporin (cefazolin) as 1st choice

• Consider increase dose of antibiotics in obese patients

• Consideration of pre-operative (outpatient) bacterial decontamination protocols for MRSA carriers
ANTIBIOTIC USE - OTHER CONSIDERATIONS
Antibiotics in PTL and PPROM

• For patients with preterm labor with intact membranes
  – Use intrapartum antibiotics to prevent group B streptococcal perinatal infection.

• For patients with PPROM
  – antibiotics to prevent GBS perinatal infection
  – Broad-spectrum antibiotics during conservative management to prolong pregnancy and decrease short-term neonatal complications
3rd and 4th Degree Lacerations

- Single randomized trial suggests that a single dose of a second-generation cephalosporin (cefotetan or cefoxitin) was protective against perineal wound complications (8.2% vs 24.1%; \( P=0.04 \), RR 0.34; 95% CI, 0.12–0.96)

- This study had a follow-up loss rate of 27%, and its findings have not been replicated

- Recent meta-analysis suggests additional data needed before recommendations could be made
Cerclage

• Insufficient evidence to recommend perioperative antibiotic prophylaxis at the time of prophylactic or emergency cervical cerclage

• Antibiotic prophylaxis for abdominal cerclage via laparotomy is not recommended
Manual Removal of Placenta

- Several studies document the increased risk of postpartum endometritis after manual removal of the placenta during cesarean delivery
- No data exist to support the use of prophylactic antibiotics in this setting
Questions

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