PHARMACY PRACTICE

Postpartum Endometritis: A Proposal for Improved Patient Care and Reduced Costs

Anita Kozyrskyj and Greg Ryan

Guidelines for the prophylaxis and treatment of postpartum endometritis have been in place in the Perinatal Unit at Mount Sinai Hospital since the 1980s. During this time they have been continuously evaluated and revised in order to provide postpartum patients with optimal pharmacotherapeutic care, while containing treatment costs. Consistent with these goals, the guidelines were again revised with the additional objective of introducing oral drug therapy as first line. In order to evaluate outcomes of the existing guidelines, antibiotic usage and costs were determined in postpartum patients for the time period July to December 1993 using the drug utilization report capabilities of the Digimedics computer system. Presented here are the questions asked during the revision process, the resultant changes to the guidelines and the rationale for change.

Should prophylaxis be extended to all caesarean section patients?

For the most part, antibiotic prophylaxis of caesarean section has been limited to high-risk caesarean section patients, for example those with prolonged premature rupture of membranes. Prophylaxis of these patients reduces the incidence of postpartum endometritis by 50%.[1] However, a recently published meta-analysis showed that prophylaxis of elective (low-risk) caesarean section patients also reduces the incidence of postpartum endometritis by at least 58%.[2]

The prophylaxis of high-risk caesarean section patients with one to three doses of cefazolin 1g starting at cord-clamping was the established practice at Mount Sinai Hospital. During the time period July to December 1993, patients who had not received cefazolin prophylaxis at cord clamping and were subsequently treated with intravenous antibiotics for postpartum endometritis represented 5% of all postpartum patients. Based on the antibiotic treatment costs for these patients, which include drug acquisition, preparation, administration and laboratory monitoring costs, the annual treatment costs were projected to be $27,500. Therefore, cefazolin prophylaxis was extended to all caesarean section patients with the aim of decreasing postpartum morbidity and associated treatment costs.

Could oral antibiotic therapy be used as first line therapy in the treatment of mild to moderate infections?

Traditionally intravenous antibiotics had been used to treat postpartum endometritis, with ampicillin as the drug of choice,[3] followed by cefotetan or clindamycin and gentamicin if no response was seen in 24-48 hours. As most patients are healthy and able to take medications orally, oral antibiotic therapy as a first line therapy was entertained. Experience with oral antibiotics as first line therapy for postpartum endometritis was limited. Amoxicillin, replacing intavenous ampicillin in the original guidelines, was considered a possibility. However, the ideal oral agent would have activity against most of the pathogens isolated in postpartum endometritis, such as *group B Streptococcus*, *Staphylococcus epidermidis*, *Escherichia coli*, *Bacteroides*[4] and especially *Streptococcus faecalis* which can be selected out during cefazolin prophylaxis.[5] Oral amoxicillin-clavulanic acid represents such an agent. In a study by Fernandez et al, 73 postpartum patients with mild endometritis, defined as a temperature less than 38.5°C, were treated with either amoxicillin-clavulanic acid 500 mg orally q8h or amoxicillin 500 mg/ metronidazole 500 mg orally q8h. There was no difference between the groups in the number of days to defervescence or the infection rate.[6] Our guidelines were subsequently changed to oral amoxicillin-clavulanic acid for mild to moderate endometritis. Oral amoxicillin was included as an alternative to amoxicillin-clavulanic acid. Oral clindamycin was reserved for penicillin-allergic patients.

Anita Kozyrskyj, B.Sc. Phm., was Supervisor, Perinatal Pharmacy Services, Mount Sinai Hospital, Toronto, Ontario. Ms. Kozyrskyj is now a Master's candidate, Dept. of Community Health, University of Manitoba.
Greg Ryan, M.B., is Staff Obstetrician, Perinatal Unit, Mount Sinai Hospital, Toronto, Ontario.
Address correspondence to: Anita Kozyrskyj, B.Sc.Phm., 505-44 The Promenade, Winnipeg, Manitoba, R3B 3H9.

Should cefotetan be recommended as a first line agent for severe endometritis and at what dose?

From the Digimedics drug utilization reports it was revealed that the majority of patients were treated with intravenous clindamycin and gentamicin. There was poor compliance with the exisiting guidelines recommending the use of ampicillin initially or the use of cefotetan as an alternative to clindamycin and gentamicin. As cefotetan has documented efficacy in postpartum endometritis[7,8] it was recommended as the treatment of choice for severe infections because of its convenient q12h dosing. Although mainly administered as a 2 g dose in clinical trials,[7,8] as a beta-lactam, cefotetan exhibits time-dependent, not concentration-dependent bacterial killing. Higher serum concentrations achieved with the 2 g dose do not result in greater efficacy, provided that trough levels exceed the MIC of the infecting organisms.[9] A serum trough concentration of 7.4 mg/L is achieved 12 hours after a 1 g dose, greater than the MIC of Bacteroides and other susceptible bacteria.[10,11] Moreover, uterine and parametrial tissue levels far exceed the MIC following a 1 g dose.[12] Therefore, it was also proposed that the cefotetan dose be modified from 2 g to 1 g q12h.

What place in therapy do clindamycin and gentamicin have?

Consistent with the previous guidelines, clindamycin and gentamicin were reserved for patients with penicillin allergies or those not responding to cefotetan after 48-72 hours of therapy. Once daily gentamicin dosing was proposed for these patients, following dosing recommendations used at Mount Sinai Hospital. As there was little experience with the once daily regimen in the postpartum population,[13] a pilot study of peak and 12-hour serum gentamicin levels in the first 10 patients was planned.

Is it necessary to switch to oral therapy once the patient was afebrile or could therapy be stopped?

In the past, all postpartum patients on intravenous therapy who were afebrile for 24-48 hours were switched to oral therapy. There was some evidence to indicate that switching to oral therapy was not necessary in this population. In two randomized studies, one of which was placebo controlled, the efficacy rate was similar in groups switched to oral antibiotics and those receiving no oral antibiotics after patients were afebrile for 48-72 hours on intravenous therapy.[14,15] Only a 50% compliance rate was documented in mothers discharged on oral antibiotics.[15] Moreover, it has been shown that breast-feeding mothers discharged on oral antibiotics discontinued the antibiotic or stopped breast-feeding despite reassuring advice that they could breastfeed while taking these antibiotics.[16] Therefore, discontinuation of therapy once the patient was afebrile on intravenous antibiotics was included as an option.

What were the outcomes of the proposed changes?

The new guidelines were approved by the Antibiotic Subcommittee of the Pharmacy and Therapeutics Committee and updated in the annual edition of the Hospital Drug Formulary in July 1994 (see Figure 1). Ongoing review of antibiotic utilization in postpartum patients and monitoring of health outcomes, such as the incidence of endometritis, was recommended to evaluate the new guidelines.

REFERENCES

1. Monga M, Oshiro B. Puerperal infections. Semin Perinatol 1993;17(6):426-31.
2. Smaill F. Antibiotic prophylaxis and caesarian section. *Br J Obs Gyn* 1992;99:789-90.
3. Pond DG, Bernstein PE, Love KR, et al. Comparison of ampicillin with clindamycin plus gentamicin in the treatment of postpartum uterine infection. *CMAJ* 1979;120:533-7
4. Martens M, Faro S, Maccato M, et al. Susceptibility of female pelvic pathogens to oral antibiotic agents in patients who develop postpartum endometritis. *Am J Obstet Gynecol* 1991;164(5):1383-6.
5. Stiver HG, Forward KR, Tyrrell DL, et al. Comparative cervical microflora shifts after cefoxitin or cefazolin prophylaxis against infection following caesarean section. *Am J Obs Gyn* 1984;149(7):718-21.
6. Fernandez H, Claquin C, Guibert M, et al. Suspected postpartum endometritis:a controlled clinical trial of single-agent antibiotic therapy with Amox-CA (Augumentin) vs ampicillin-metronidazole+-aminoglycoside. *Eur J Obstet Gynecol Reprod Biology* 1990;36:69-74.
7. MacGregor R, Graziani A, Samuels P. Randomized, double-blind study of cefotetan and cefoxitin in post-caesarian section endometritis. *Am J Obstet Gynecol* 1992;167(1):139-43.
8. Hemsell D, Wendel G, Gall S, et al. Multicenter comparison of cefotetan and cefoxitin in the treatment of acute obstetric and gynecologic infections. *Am J Obstet Gynecol* 1988;158:722-7.
9. Vogelman B, Gudmundsson S, Leggett J, et al. Correlation of antimicrobial pharmacokinetic parameters with therapeutic efficacy in an animal model. *J Infect Dis* 1988;1 58(4):831-47
10. Martin C, Thomachot L, Albanes J. Clinical Pharmacokinetics of cefotetan. *Clin pharmacokinet* 1994:26(4):249-58.
11. Ward A, Richards D. Cefotetan, a review of its antibacterial activity, pharmacokinetic properties and therapeutic use. *Drugs* 1985;30:382-426.
12. Orr J, Sisson P, Barrett J, et al. Pharmacokinetics and tissue kinetics of 1 gm cefotetan prophylaxis in adbominal or vaginal hysterectomy. *Am J Obstet Gynecol* 1988;158(3):742-3.
13. Bourget P, Fernandez H, Delouis C, et al. Pharmacokinetics of tobramycin in pregnant women, safety and efficacy of a once-daily dose regimen. *J Clin Pharm Therap* 1991;16:167-76
14. Hager W, Pascuzzi M, Vernon M. Efficacy of oral antibiotics following parenteral antibiotics for serious infections in obstetrics and gynecology. *Obstet Gynecol* 1989;73:326-9
15. Dinsmoor M, Newton E, Gibbs. A randomized, double-blind, placebo-controlled trial of oral antibiotic therapy following intravenous antibiotic therapy for postpartum endometritis. *Obstet Gynecol* 1991;77:60-2
16. Ito S, Koren G, Einarson T. Maternal noncompliance with antibiotics during breastfeeding. *Ann Pharmacother* 1993;27:40-2.

Figure 1: Guidelines for the use of antibiotics in obstetrics