CHAPTER 2

REVIEW OF LITERATURE

2.1 Introduction

Surgeon has the most important role in preventing postoperative infection, and antibiotic prophylaxis serves only an adjunct to the surgeon's abilities. The surgeon must be meticulous in handling tissues, good hemostasis must be achieved, tissue pedicle should be small. Tissue should not be strangulated and dead space should be obliterated[5].

Prophylaxis is defined as "measure necessary to preserve health and prevent the spread of disease[6]". Antibiotic prophylaxis is defined as the administration of an antimicrobial agent known to have minimal toxicity to the patient but that is effective in reducing the risk of post operative infection. The patient receiving antibiotic prophylaxis should not be infected at the time of the

operation but is known to be at considerable risk for infection.[5]

2.2 Concept of prophylactic antibiotics

Principles regarding the use of antibiotic prophylaxis were developed by Mill and Burke. They demonstrated in separate experiments that if antibiotics were to be effective in preventing a wound infection, the drug should be present in the tissue before the bacteria could invade and established an infection[7,8].

The guidelines for antibiotic prophylaxis were originally proposed by Ledger in 1975 that are still applicable today. The antibiotics utilized as a prophylactic agent must

(1) have a spectrum of activity effective against those bacteria most likely to cause or initiate infection.

(2) be present in tissue at the operative site in concentration that will be effective against the most frequent infecting organisms.

(3) have been demonstrated to be clinically effective.

(4) not be responsible for toxicity to the patient.

(5) not cause the emergence of resistant bacteria or cause super infection.

(6) be the least expensive but the most efficacious agent utilized[9]

There were special conditions regarding the use of antibiotics in gynecological patients. First, most gynecological patients were healthy and free of serious underlying disorder. Second, although the lower genital tract was a contaminated field, resistant gram negative organisms were not found except under special circumstance. Third, operation through or adjacent to these contaminated fields led to moderate to high incidence of infection, but serious infection measured by abscess formation or death was unusual[10].

The flora of the operative site was determined to be the critical factors in the development of postoperative infection after elective procedures in non-infected patients. This focused attention on the

importance of microbiology of the operative site and initiated the development of a rationale for prophylactic antibiotics in cases in which the vagina was entered. Slotnick and colleague found that the female genital tract had an average of 6-7 organisms resided in vagina and cervix and these endogenous microflora of endocervix mirrored the microflora of the vagina[11]. Anaerobes were the most prevalent organisms and outnumber the facultative bacteria by the factor of 10 to 1. The anaerobic bacteria commonly identified in normal microflora include, anaerobe gram positive cocci (peptostreptococci) and Prevotela (formerly Bacteroides species) P.bivia had been identified as a major component of anaerobic vaginal flora. The most common facultative bacteria of the normal vagina and cervix appeared to be lactobacilli, streptococcus, Staphylococcus epidermidis and Gardnerella vaginalis. E. coli was recovered in 5-30 % of healthy females. Other enterobacteriaceae were generally found in less than 10 %. Alteration of the normal environment as a result of operative intervention could produce condition appropriate for selective anaerobic survival and proliferation. The

presence of traumatized or necrotic tissue, and when blood supply to the distal end of surgical pedicle was interrupted and such pedicle have been exposed to bacteria of lower genital tract during surgery, infection wound be occurred[2]. There was no disagreement on whether most post operative infections originate from the ascending of this endogenous bacteria from the vagina to the pelvic cavity during the operative procedure.

2.3 Anaerobe Progression Theory

The majority of infections in Obstetric and Gynecology were polymicrobial disease that genesis with multiple bacteria whose ability to replicate at different oxygen level vary significantly. The catalytic event that took an endogenous bacterial flora and gives it pathogenicity was an alteration in the oxidation-reduction potential of the microbiologic environment. Iatrogenic lowering the oxidation-reduction potential often occurs during an operation when tissue was crushed by clamps, devitalized by loss of blood supply, and/or subjected to microhematoma formation or the development of serous fluid collection. A given disease could similarly lower the

oxidation-reduction potential and initiate the anaerobic progression. With the lowering the oxidation-reduction potential, acidification of the local environment and removal of molecular oxygen, the polymicrobial flora of vagina underwent selective change. Aerobic bacteria underwent a process of sequential autoelimination. The process was termed 'the anaerobe progression'. The effectiveness of antimicrobial for polymicrobial infection was influenced by the existing oxidation-reduction potential. When the oxidation-reduction potential was not yet in a critical zone, anaerobic infection could be effectively dealt with by eradicating the major constituent of the facilitating bacterial flora in the anaerobic progression. In this situation it was not necessary to eradicate each bacteria constituent. It only interrupted the potential for anaerobic progression. To eradicate the 'facilitating flora' which might transform the microbiologic environment into the one which was conductive for the replication of obligated anaerobes. The study of the use of antibiotics in Obstetrics and Gynecology seem to corroborate this hypothesis.

Prophylactic antibiotics eradicated selective constituents of the vaginal flora. The bacteria which had been eliminated were not usually considered to have pathogenic significance. To eradicate facilitating bacterial flora, one could abort the progression to anaerobic infection[1].

2.4 Review of relevant research

Apuzzio and Mickal in 1982 found the data support the use of antibiotic prophylaxis for the patients undergoing cesarean section or vaginal hysterectomy[12,13]

Duff et al. in 1982 use one gram dose of ampicillin intravenously every six hours for three doses to prevent post cesarean section endometritis[14]. Elliot et al. in 1982 compared ampicillin in short and long course, and found that no significant difference in post cesarean section endometritis[15]. Padilla and colleagues in 1983 found that a single 2 g. dose of ampicillin was effective in decreasing the incidence of postpartum endometritis[16].

Jakobi in 1988 did a randomized controlled trial to compare single dose and multiple dose cefazolin prophylaxis in cesarean section. He found no significant difference in rate of post partum endometritis[17].

In 1982 Shapiro et al. reported the results of a large study of risk factors for operative site infection following hysterectomy. Using logistic regression analysis in a series of more than 1400 patients, they show that factors significantly associated with operative site infections were a longer duration of operation, being a clinic patient, the lack of antibiotic prophylaxis, and an abdominal approach[18].

Hemsell et al. in retrospective analysis, found the postoperative antibiotic usage in women undergoing elective abdominal hysterectomy without prophylaxis to be 64%. With these level of infectious risk observed in their study group, they proceed to evaluate the utility of prophylaxis in a prospective fashion. They compared a three doses perioperative regimen of cefoxitin with placebo in a series of 100 women undergoing abdominal

hysterectomy. The incidence of major infection was 12% in antibiotic prophylaxis group, which was significantly less than the 32% rate observed in the placebo group[19]. Nonetheless, current available evidence would favor the use of an inexpensive, limited-spectrum antibiotics in a single dose.[20,21]

Grossman et al. in 1979 found that the organism recovered from vagina on admission to the hospital were not different from those found in antibiotics treated group. They concluded that hysterectomy itself rather than antibiotic prophylaxis altered the vaginal flora. And they also found that cefazolin and penicillin were equally effective in spite of the theoretical advantage of using cefazolin when one consider the potential pathogen normally colonized vagina[22].

Ohm and Galask in 1976 reported a series of a patients undergoing abdominal hysterectomy with and without cephalosporin prophylaxis. The incidence of operative site infections in the placebo group was 17% compared with 15% in the cephalosporin group[23]. Grossman et al. in 1979 examined morbidity following abdominal

hysterectomy in patients receiving prophylaxis with penicillin, cefazolin, or placebo. Using the number of patients developing postoperative infection for comparison, he noted a rate of 17% of those receiving penicillin, 22% of those receiving cefazolin, and 29% of those receiving placebo[22]. Duff in 1982 compared a short perioperative course of cefoxitin prophylaxis with placebo in a similar group of patients. He noted no difference between antibiotic prophylaxis and placebo group in the rate of pelvic cellulitis, vagina cuff abscess, or wound infection[24].

Polk in 1980 used perioperative cefazolin in 48 hours period in preventing infection after abdominal hysterectomy. He found that the patients who received cefazolin had significantly lower rate of wound and pelvic infection and febrile morbidity. The patients also had shorter length of hospital stay and received fewer antibiotic postoperatively[25].

Tuomala in 1986 did a randomized controlled trial to compare the efficacy of two regimens in preventing

infection after abdominal hysterectomy. He found that no significant difference in rate of infection after abdominal hysterectomy when prophylaxis with moxalactam and cefazolin[26].

Orr and Varner in 1986 compared two different cephalosporin as a prophylactic agent in abdominal hysterectomy. They found no significant difference in rate of post operative infection[27].

Mittendorf and Anderson in 1993 reported a meta-analysis of double-blinded randomized controlled trial study the effect of antibiotic prophylaxis in abdominal hysterectomy. They found 31 separated drug-placebo comparison in 25 trials. There were seven trials used multiple doses, parenteral injection of cefazolin. There were 5 trials used metronidazole, 3 trials used tinidazole. Others thirteen trials used different eleven drug regimens as prophylactic agents. In five of the study two different of the antibiotics were tested against a placebo, and in one study two different doses of the same drug were used. The over all serious infectious morbidity

occurred 21% in placebo group and only 9% in treatment group. When focus to cefazolin, rate of serious infection occurred 11%. They suggested the routine use of prophylactic antibiotics in abdominal hysterectomy[27].

When look at this meta-analysis, the overall rate of infectious morbidity in this article was high. The perioperative agents and doses of prophylactic antibiotics were varies. None in cefazolin trials used it as a single dose. Prophylactic antibiotics might be useful only in situation that high infection rate was expected. The result of this meta-analysis could not be applied to situation that infectious morbidity rate was not high. The single dose regimen that had proved its efficacy in vaginal hysterectomy and emergency cesarean section, might be tested in abdominal hysterectomy as well.

2.5 Cefazolin

The antibiotics which had been most extensively test for prophylaxis were the cephalosporin. There was no evidence that the newer extended spectrum cephalosporin

were more effective for prophylaxis than the first generation agent such as cefazolin. Most investigation had employed three perioperative dose of antibiotics. There was clearly no justification for administrating more than this number of dose. Longer course offer no therapeutic advantage and simply increased the expense of treatment and enhanced the probability of side effects[2].

Cefazolin was a drug to be used as prophylactic antibiotics in this research. Cefazolin was a first generation cephalosporin, comprise of 7-aminocephalosporanic acid with a D-aminodipic side chain. Cefazolin was active against a wide variety of aerobic gram positive constituents of vaginal flora (exclude enterococcus) that played role in anaerobe progression hypothesis[1]. This could subsequently inhibit infectious process. It also possessed activity against some aerobic gram negative rod, including many strains of E.coli, P. mirabilis and K. pneumonae. Although some anaerobes were susceptible to cefazolin but many resisted especially Bacteroides groups. Cefazolin interfered cell wall synthesis, resulting in bactericidal activity to sensitive

organisms. After one-gram of cefazolin intravenous injection, blood concentration exceeded 100 ugm/ml. within a few minutes and achieved its minimal inhibitory concentration (MIC.) level for susceptible organism but were undetectable after 4-6 hours. Cefazolin had a half-life of 106 minutes. Cefazolin binded about 80% of serum protein. It had the longest half-life among the first eneration cephalosporin. Susceptible organisms generally had MIC. below 4 ugm/ml. Cefazolin was excreted in unchanged form primarily through the kidney. Urinary excretion rate was up to 88% after seven hours of intravenous injection. Cefazolin were generally well tolerated. Reaction such as fever, eosinophilia and rash occur rarely and transient. Cross-reactivity between penicillin and cefazolin might exist. Patients with a history of penicillin allergy were contraindicated for cefazolin. There were no situations in which cefazolin was clearly the drug of choice for therapy. In most situations, other antibiotics were clearly preferable. Cefazolin might be used in treating some urinary tract infection because its high concentration in urine. It

might be used in initial treatment of post operative pneumonia since it might be caused either by gram positive cocci or by gram negative. Cefazolin was not expensive. According to anaerobe progression theory, cefazolin was an appropriate drug to be used as a prophylactic agent in abdominal hysterectomy.[1,2,11,].