

## Review of Recommendations on Prophylactic Antibiotic Use in Cesarean Section -A Review Article

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### Abstract

The significant rise in Cesarean Section (CS) rates in both developing as well as developed countries mandates a definitive protocol for preoperative preparation, intra-operative surgical principles and postoperative care. Apart from surgical and anesthesia related complications, post-operative infections following a CS can lead to puerperal sepsis, near-miss maternal morbidity and mortality. Post cesarean section infections are likely to become a health and economic burden and their prevention remains a public health priority. One such preventive measure is appropriate and timely use of antibiotics in both elective and emergency cesarean sections. The infections are usually poly-microbial, involving aerobic and anaerobic organisms. Role of antibiotic prophylaxis in CS is clearly demonstrated in various studies, but the dosage and the ideal drug, its timing and frequency still remains debatable and controversy. This article reviews on various studies in the recent past regarding recommendations on prophylactic antibiotic use in cesarean section.

### Introduction

Women who deliver by Cesarean Section [CS] are 5-20 times more predisposed to postpartum infections including endometritis, urinary tract infections, surgical site infections than women who deliver vaginally<sup>[1,2]</sup>. The incidence of infection varies widely from 2.5% to 20.5% and 40 to 75% in developed countries and developing countries respectively. With antibiotic prophylaxis, the post cesarean infectious morbidity was reduced in both in high risk and low risk patients<sup>[3]</sup>. The infection rate was reduced by half and more from a very high baseline of 20-50%<sup>[4,5]</sup>.

Organisms of the lower genital tract are common source of infection, and the risk is higher with ruptured membranes or with a preterm birth. Anaerobes and gram negative aerobes like species of *Escherichia coli*, *Enterobacter*, *Klebsiella*, *Proteus* and anaerobes like *Bacteroides*, *Clostridium*, and *Fusobacterium* are the common isolates<sup>[6]</sup>. Skin contaminants like *Staphylococcus aureus* may be isolated as a result of an interruption in the sterility, in the surgical technique, especially following an emergency or complicated surgery.

The need for antibiotic prophylaxis, the type and route of drug including timing and frequency, the cost-effectiveness, effects of antibiotics on the mother-child dyad and the development of antimicrobial resistance remains a major concern. Considering the fact that, surgical site infections are preventable but prevention is complex requiring integration of preoperative, in-

tra-operative and postoperative events. The rates of surgical site infection especially in the presence of other risk factors like anaemia, CS in labor, woman on immunosuppressive therapy may be decreased with effective antibiotic usage. Moreover, neonatal survival is best when there is no maternal jeopardy. Till date there is no evidence based global guidelines regarding choice of antibiotic, epidemiological data including bacteriology and sensitivity patterns of these infections, especially in resource limited countries so as to identify an ideal drug. A cost effective prophylactic antibiotic regimen with safe maternal and neonatal outcomes should be sought. Here in this review we discussed the recommendations by various organizations and randomized controlled studies (Table 1) over the period of time.

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**Table 1:** RCT on antibiotic usage in cesarean section

YEAR	STUDY BY	TYPE OF STUDY	OUTCOME
1991	Ruiz- Moreno et al. <sup>[8]</sup>	RCT comparing i.v. metronidazole vs placebo	Endometritis(14% vs 30%), wound infection(2% vs 8%) are less in metronidazole group when compared to placebo group.
2001	Pitt et al. <sup>[19]</sup>	Double blinded RCT comparing intravaginal metronidazole vs placebo	7% developed endometritis in metronidazole group as compared to 19% of those receiving placebo gel.
2003	Andrews et al. <sup>[20]</sup>	Double blinded RCT comparing cefotetan with doxycycline+ azithromycin	Post CS endometritis (16.9% vs 24.7%, p= .02), wound infections( 0.8% vs 3.6% and p=.03) were significantly less in doxycycline +azithromycin group.
2003	Mayer et al. <sup>[21]</sup>	Double blinded prospective RCT comparing cefazolin versus cefazolin plus metranidazole	Significant reduction in postoperative infection rate (14% vs 32%) and duration of hospital stay(3.12% vs 4.46%) with cefazolin plus metronidazole group
2008	Alekwe et al. <sup>[22]</sup>	RCT comparing single dose of ceftriaxone vs multiple doses of ampiclox, gentamycin, metronidazole.	Incidence of endometritis (14% vs 15%), UTI(11% vs 15%) and SSI(7% vs 6%) are not significantly different in both the groups.
2009	Tita et al. <sup>[14]</sup>	RCT comparing i.v.azithromycin vs placebo	Infectious morbidity(6.1% vs 12%, p< 0.001), endometritis is(3.8% vs 6.1%, p = 0.002), wound infection is(2.4% vs 6.6%, p< 0.001), adverse maternal events is(1.5% vs 2.9%, p = 0.03) are significantly less in azithromycin group.
2013	Lyimo et al. <sup>[23]</sup>	RCT comparing single i.v. dose of gentamycin+ metronidazole vs 8 hrly administration of the same antibiotics for 24 hrs.	SSI occurred in 4.8% in 1st group compared to 6.4% in 2ndgroup.
2017	U p T o - Date <sup>[24]</sup>	Preferred Regimen-Cefazolin Dose-<120kg 2gm intravenous;>120kg 3gm intravenous	Alternative regimens-i) Ampicillin-sulbactam 3gm intravenous ii) clindamycin 600-900mg intravenous or vancomycin 15 mg/kg plus one of the following gentamycin 5 mg/kg or aztreonam 3 gm iv iii) Metronidazole 500 mg i.v plus gentamycin 5 mg/kg

## Discussion

In Cochrane review (2014) of 95 studies enrolling more than 15,000 women, the use of prophylactic antibiotics in woman who underwent CS reduced the incidence of wound infection (RR 0.40, 95% CI 0.35 to 0.46, 82 studies, 14,407 women), en-

dometritis (RR 0.38, 95% CI 0.34 to 0.42, 83 studies, 13,548 women) and maternal serious infectious complications (RR 0.31, 95% CI 0.20 to 0.49, 32 studies, 6159 women) when compared with no treatment. Gerstner, et al (1980) and Ruiz-Moreno, et al (1991) showed that when metronidazole was given intravenously, the chances of endometritis, surgical site infection, and rate of postoperative febrile morbidity was reduced<sup>[7]</sup>. In a prospective comparative study by O’Leary et al in 1986, post cesarean morbidity was lesser in ampicillin-gentamycin group as compared to ampicillin alone<sup>[8,9]</sup>. Metronidazole, when used as a prophylactic agent administered intravenously or rectally gave mixed results for post caesarean endometritis and wound infection. The timing of administration of antibiotic was also a concern. Cochrane (2002) and ACOG (2003) recommended administering prophylactic antibiotics after cord clamping<sup>[10]</sup>. Cochrane Database of Systematic Reviews (2003) and CDC (2006) recommended administration of cephalosporins of first generation like cefazolin after clamping of umbilical cord as prophylaxis against post- caesarean infections rather than a pre-surgical prophylaxis. Cefazolin was considered as it was equally effective and cheaper than broad-spectrum antibiotics<sup>[3,5]</sup>. A retrospective study conducted in Pittsburgh, USA (2002 - 2007), reviewed the cases of cesarean deliveries where antibiotic was given before the skin incision in first group and after clamping of cord in second group. First group had lower rates of endometritis and wound infection. Further, it had no adverse effect on the neonate. Similar findings were observed by Yokoe in 2001<sup>[10]</sup> and Sullivan, et al (2008) when cefazolin was given 15-60 minutes preceding an incision or at the time of clamping of cord with no increase in rates of neonatal sepsis.

A questionnaire based study published in Journal of Indian Medical Association (2008) evaluated the antibiotic prescriptions of obstetricians working in different centers in Delhi, (India) in vaginal deliveries (episiotomies) and cesarean sections. A single antibiotic cefazolin 1gm every 12<sup>th</sup> hourly intravenously for three days was used by 34.4% and 33.3% of practitioners in planned and non-elective cesarean sections respectively. The antibiotic was used for five days by 35.5% and 41.1% doctors respectively. A triple antibiotic regimen of ampicillin, metronidazole and gentamycin was used by 30% and 25.5% doctors for planned and non-elective and Cesarean respectively for five days.

ACOG (2010) recommended cefazolin 1 - 2 g IV one hour prior to the surgery or as soon as possible if it is an emergency cesarean<sup>[11]</sup>. SOGC (2010) recommended, all parturient scheduled to elective or emergency CS should be given antibiotic as prophylaxis not more than 60 minutes prior to skin incision with first-generation cephalosporin and single drug dose is sufficient if total duration of surgery is less than three hours and the total blood loss is less than one and half liter when a repeat dose is advised. In case of allergy to penicillin, clindamycin or erythromycin can be used<sup>[12]</sup>.

Baaqeel, H and Baaqeel, R in 2013 systematic review regarding the timing of administration of prophylactic antibiotics in CS confirmed that the pre-incisional use and not after cord clamping, had less post CS maternal infectious morbidity and no immediate untoward effects on the newborn<sup>[13]</sup>. A RCT by Tita, et al in 2013 assigned women with a singleton pregnancy of ≥ 24 weeks period of gestation undergoing CS in labor with or

without leakage of amniotic fluid to azithromycin plus standard antibiotic versus placebo versus standard antibiotic groups. Incidence of endometritis, wound complications, and serious maternal adverse events were significantly lower in azithromycin added group. The neonatal outcome was same in both the groups<sup>[14]</sup>. Systematic review of Cochrane database (2014) of 7299 women provided a comparison between the use of cephalosporins versus penicillin's for antibiotic prophylaxis for CS<sup>[15]</sup>. The efficacy of cephalosporins and penicillin's was comparable in preventing immediate post cesarean infections.

Pinto-Lopes R et al in 2017 in his review article included 16 studies, involving 2695 women and no significant difference was observed between single dose and multiple dose antibiotic prophylaxis in the incidence of postpartum infectious morbidity, endometritis, and wound infection. A trend towards lower risk of urinary tract infection was seen with multiple dosing<sup>[16]</sup>.

Cefazolin belongs to first generation of cephalosporin and is a Category B drug in pregnancy. Its t<sub>1/2</sub> is 1.8 hours. Coverage for gram positive organisms including mycoplasma and urea plasma is good and modest for gram negative organisms. The concern with its use was an increase in the resistant strains of anaerobes which may be dealt with adding metronidazole, clindamycin, or azithromycin. Many center's now practice a single dose of 2 gm cefazolin for all women undergoing CS as a standard regime. The higher dose of cefazolin 3 grams for obese women is supported by a study in which  $\geq 20$  percent of obese when body mass index is 30 to 39.9 kg/m<sup>2</sup> and extremely obese women with body mass index of  $\geq 40$  kg/m<sup>2</sup> did not achieve therapeutic levels for Gram-negative rods with a 2 gm dose. Despite these recommendations, there is ongoing debate concerning the use of more effective prophylaxis with newer and extended-spectrum drugs like cefotetan as endometritis is predominately a polymicrobial infection. The woman with high risk of postoperative infection like CS in labor or had ruptured membranes for more than four hours may benefit from an extended-spectrum regimen, but available data do not mandate a change in practice at this time.

Thus, as per recommendations, the duration of antibiotics usage in caesarean section has been reduced from more than 5 days to a single dose. But the older practice of multiple doses of antibiotics is still lingering on with a potential for development of antimicrobial resistance and harmful sequelae in the near future.

A survey (2005) of SEA-ORCHID project team in South East Asia on reviewing the medical reports of 9550 and found that antibiotic prophylaxis for CS was administered over more than one dose pre-orpost-operatively in majority<sup>[17]</sup>.

The goal of antibiotic therapy is to achieve sufficient tissue levels at the time of microbial contamination, and the ideal drug should be long acting, inexpensive, and have a low side effect profile. The wrong choice of antibiotic may result in the neonate being exposed to resistant strains of bacteria which may lead to a worse neonatal outcome and/or the need for extensive neonatal septic screens and infection work-ups. The confounding factors leading to difficulty in implementing a universal approach to antibiotic prophylaxis are complex and need to be studied. Moreover, the existing differences in the socio-economic status of the patients, feasibility and utilization of health

resources in developing and developed world may lead to difficulty in having a universal regimen of antibiotic prophylaxis. Though single dose cefazolin has been recommended by various bodies for pre-surgical prophylaxis in CS, data on efficacy of a single drug as antibiotic prophylaxis is limited in developing countries and use of multiple drug regimens may evolve over time considering the high rates of post-cesarean morbidity in third world countries. Further knowledge of antibiotic susceptibility and resistant strains is to be considered. In a prospective study to evaluate the clinical profile and bacterial isolates among women with puerperal sepsis in a tertiary hospital in North India by Jayasree Vankuru et al, *E. coli* was the commonest pathogen isolated and was uniformly sensitive to amikacin which may be included among the initial antibiotics to treat puerperal sepsis in India<sup>[18]</sup>. More randomized trials targeting these population should be done so as to globally recommend an ideal antibiotic.

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