

# Preoperative Administration of Cephalosporins for Elective Caesarean Delivery

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## SUMMARY

**Introduction** Antibiotic prophylaxis means administration of antibiotics in prevention of infections.

**Objective** To investigate the efficacy of a single dose preoperative administration of ceftriaxone and cefazolin in the prevention of intra- and postoperative infections in the parturients without high risk of inflammation.

**Methods** The first group of 45 pregnant and 4 non-pregnant women were preoperatively administered ceftriaxone in a dose of 2 g, i.v., 10 minutes before the planned surgery. The second group of 45 pregnant and 4 non-pregnant women were preoperatively administered cefazolin in a dose of 2 g i.v., 10 minutes before the planned surgery. The concentrations of antibiotics were estimated immediately and 6 hours following the operation, as well as in the amniotic fluid and umbilical cord in the group of pregnant women. The estimation of antibiotic concentration was done by the method of liquid chromatography.

**Results** The mean concentrations of antibiotics in the patients following the elective caesarean section were as follows: ceftriaxone – 22.7 µg/l. vs cefazolin – 44.8 µg/l. Six hours later, the concentration of antibiotic decreased, but the concentration of cefazolin was still over the MIC for sensitive bacteria. The mean concentrations of antibiotics following gynaecological surgery in the non-pregnant patients were as follows: ceftriaxone – 12.0 µg/l vs cefazolin – 30.1 µg/l. Six hours later, the concentration of antibiotic decreased.

**Conclusion** It is most optimal to administer a single-dose of the first generation cephalosporins -cefazolin- immediately following the clamping of the umbilical cord as well as in preoperative prophylaxis in gynaecological operations.

**Keywords:** caesarean section; antibiotic prophylaxis; cephalosporins; cefazolin; ceftriaxone

## INTRODUCTION

Antibiotic prophylaxis means administration of antibiotics in prevention of infections. It can be a primary, secondary (suppression) and eradicating one. Basic questions related to antibiotic prophylaxis are as follows: the timing of prophylactic administration of antibiotics, duration of antibiotic prophylaxis and the choice of antibiotics for antibiotic prophylaxis [1]. While we are deciding about antibiotic prophylaxis, someone has to make a decision in the estimation of the real benefit of this administration in the view of the consequences regarding the broader biological sense.

Inflammatory complications which follow the caesarean section can occur in 30 to 85 % of operated patients [2, 3]. The most frequent complications which follow the caesarean sections are as follows: endometritis, urinary infections, wound infections and peritonitis.

The basic significance of antibiotic in the prevention of surgical infection is based on the reduction of endogenous and exogenous bacterial contamination during the surgical procedure. The proper antibiotic can be maintained only by the knowledge of the risk levels of infection of each operation and condition of the patient [4]. Antibiotic prophylaxis at emergency caesarean

section has been shown to reduce the postoperative infective morbidity. There is a wealth of data on antibiotic usage at caesarean section, but the value of antibiotic prophylaxis in elective caesarean section and "low risk" groups remains unsettled. However, there is controversy about which antibiotics should be used. According to current recommendations, the literature supports usage of single dose of the first-generation cephalosporin immediately after clamping the umbilical cord [4, 5].

## OBJECTIVE

The aim of this investigation was to compare the efficacy and safety of a single dose application of antibiotics in the prevention of infections in the patients with caesarean section: 1. to investigate the efficacy of a single dose preoperative administration of ceftriaxone and cefazolin in the prevention of intra- and postoperative infections in the parturients without high risk of inflammation; 2. to investigate the effect of pregnancy on single-dose pharmacokinetics of ceftriaxone and cefazolin after elective caesarean section and gynaecological operations; and 3. to estimate the concentrations of antibiotics in the amniotic fluid and the newborn infant blood

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(umbilical cord), as to determine the quantity of antibiotics passed into the newborn infant and the safety of the administered antibiotics.

## METHODS

Pregnant women were enrolled into the study when the decision for caesarean section was made. The inclusion criterion of the patients into the study was women undergoing elective caesarean section at the Department of Obstetrics and Gynaecology, the Clinical Centre of Vojvodina, Novi Sad, Serbia. The trial was approved by the institutional review board of the hospital and each woman gave informed consent. The exclusion criteria were: the use of therapeutic antibiotics, allergy to cephalosporins or concurrent use of other prophylactic antibiotic regimens.

A prospective investigation comprised 90 healthy pregnant women at term planned for elective caesarean section vs 8 non-pregnant women planned for gynaecological surgery. The first group of 45 pregnant women (group A) and 4 non-pregnant women (group C) were preoperatively administered ceftriaxone in a dose of 2 g i.v., 10 minutes before the planned surgery. The second group of 45 pregnant women (group B) and 4 non-pregnant women (group D) were preoperatively administered cefazolin in a dose of 2 g i.v., 10 minutes before the planned surgery. All patients were followed up for clinical postoperative course and possible incidence of infection. The concentrations of antibiotics were estimated immediately and 6 hours following the operation (in 36 pregnant and 8 non-pregnant women) and also in the amniotic fluid and in the umbilical blood of the newborn infants. The estimation of antibiotic concentration was done by the method of liquid chromatography [6].

## RESULTS

The women in the two groups were comparable. In tables 1 and 2 are shown: patient characteristics, parity, indication for caesarean section, duration of caesarean section, estimated blood loss, the number of postoperative days and infection morbidity. There were no significant differences as regards (median) maternal age, body mass index, parity, indications for caesarean section, the mean blood loss, duration of caesarean section and the number of postoperative days. These parameters did not influence the total number of postoperative infective complications. In our study, the total number of infective complications in the patients of two groups was about 4.4% (4 patients) (Table 2).

The mean concentrations of antibiotics in the patients following the elective caesarean section were as follows: ceftriaxone – 22.7 µg/ml and cefazolin – 44.8 µg/ml. Six hours later, the concentrations of antibiotics were decreased: ceftriaxone – 13.2 µg/ml and cefazolin – 24.8 µg/ml, which is still over the MIC for intermediary sensitive bacteria (Tables 3 and 4). The mean concentrations of antibiotics following the gynaecological surgery in non-pregnant patients were as follows: ceftriaxon – 12.0 µg/ml and cefazolin –

30.1 µg/ml. Six hours later, the concentrations of antibiotics were decreased: ceftriaxone – 5.7 µg/ml and cefazolin – 17.3 µg/ml. In the group of non-pregnant women the concentration of cefazolin was above the MIC for sensitive bacteria (Tables 3 and 4).

Pharmacokinetic parameters of ceftriaxone and cefazolin in caesarean section and non-pregnant sectioned women are presented in Table 5. Pregnancy influenced ceftriaxone pharmacokinetics but not those of cefazolin. Ceftriaxone constant of elimination decreased significantly from  $0.18 \pm 0.05/h$ , in non-pregnant sectioned women, to  $0.11 \pm 0.04/h$  in the caesarean sectioned group ( $t=3.04$ ;  $p<0.01$ ).

**Table 1.** Patients' characteristics\*

Parameter	Group 1	Group 2	
General data	Age (years)	30.8±5.7	28.9±6.1
	Body weight (kg)	83.0±12.6	80.0±11.9
	Body height (cm)	166.2±6.8	167.6±6.9
	BMI (kg/m <sup>2</sup> )	30.2±5.1	28.4±4.1
Parity	Nullipara	16 (35.5%)	17 (37.7%)
	Secundipara	23 (51.1%)	26 (57.7%)
	Multipara	6 (13.3%)	2 (4.4%)
Indications for caesarean section	Repeat	25 (55.5%)	26 (57.7%)
	Disproportion	5 (11.1%)	8 (17.7%)
	Breech presentation	6 (13.3%)	6 (13.3%)
	Other	9 (20.0%)	5 (11.1%)

\* Data are expressed as mean value with standard deviation and number of patients with per cent.

**Table 2.** Hospital course of all patients according to prophylactic regimen\*

Parameter	Group 1	Group 2
Operative time (minute)	31.9±11.2	30.0±9.4
Estimated blood loss (ml)	391.1±211.9	424.4±213.8
Postoperative days in hospital	4.2±0.1	4.7±1.8
Infection morbidity	2 (4.4%)	2 (4.4%)

\* Data are expressed as mean value with standard deviation and number with per cent

**Table 3.** The concentration of ceftriaxone in pregnant (group A) and non-pregnant patients (group C) immediately after the operation and 6 hours after application

Concentration of ceftriaxone (µg/ml)	Group	$\bar{X}$	SD	Min	Max
After the operation	A	22.7	20.4	2.4	82.4
	C	12.0	9.8	3.8	25.3
6 hours after application	A	13.2	11.2	1.0	37.3
	C	5.7	5.0	1.2	12.2

MIC for ceftriaxone (µg/ml): susceptible ≤8; intermediate 16-31; resistant ≥64

**Table 4.** The concentration of cefazolin in pregnant (group B) and non-pregnant patients (group D) immediately after the operation and 6 hours after application

Concentration of cefazolin (µg/ml)	Group	$\bar{X}$	SD	Min	Max
After the operation	B	44.8	22.0	16.8	102.5
	D	30.1	13.7	18.7	49.2
6 hours after application	B	24.8	9.2	10.2	47.8
	D	17.2	8.1	10.8	29.1

MIC for cefazolin (µg/ml): susceptible ≤8; intermediate 16; resistant ≥32

**Table 5.** The pharmacokinetic parameters of ceftriaxone and cefazolin in pregnant and non-pregnant patients (mean value and standard deviation)

Parameters	Ceftriaxone		Cefazolin	
	Group A	Group C	Group B	Group D
$k_e$ (1/h)	0.11±0.04	0.18±0.05	0.10±0.05	0.11±0.01
$T_{1/2}$ (h)	7.34±3.31	4.00±1.00	8.33±6.30	6.34±0.97
$V_d$ (L)	189.84±197.73	234.37±166.96	48.29±19.81	66.78±23.14
Cl (L/h)	24.42±34.38	48.24±41.47	4.89±2.32	7.50±2.95

The mean concentration of the administered antibiotics in the umbilical cord was high (ceftriaxone – 29.0 µg/ml and cefazolin – 54.3 µg/ml) suggesting that there is a good transfer of all drugs across the fetoplacental barrier and there might be possible negative side effects in the newborn infants. The mean concentrations of the administered antibiotics in the amniotic fluid were low (ceftriaxone – 1.6 µg/ml and cefazolin – 6.8 µg/ml) and below the MIC for sensitive bacteria. Our study was done on the low risk population for development of infection (elective caesarean section), without starting a labour or rupture of membranes. Also, in our study, the low concentration of administered antibiotic in the amniotic fluid did not have any clinical importance.

## DISCUSSION

In our study, the total number of infective complications in the patients of two groups was about 4.4% (4 patients). In the first group of pregnant women who were preoperatively administered ceftriaxone, the total number of infective complications was 4.4% (2 patients). Post-operative febrile morbidities were found in one of the patients (2.2%) and also one of the patients had wound infection (2.2%). In the second group of pregnant women who were preoperatively administered cefazolin, the total number of infective complications was 4.4% (2 patients). Post-operative febrile morbidities were found in one of the patients (2.2%) and also one of the patients had urinary tract infection (2.2%).

High incidence of infection-related morbidity was encountered by following caesarean section [4]. In a large prospective study of Nielsen and Hökegård [7], they demonstrated an overall infection rate of 13.3%. In the study of Hagglund and et al. [8], the total number of infections after elective caesarean section was 9%. The infections after caesarean section were polymicrobial, i.e. the combination of anaerobic and aerobic bacteria [9]. Many studies investigated the efficacy of antibiotic prophylaxis on the high risk population for development of infection (emergency caesarean section) [2, 10]. A lower number of studies investigated the efficacy of antibiotic prophylaxis on the low risk population for development of infection (elective caesarean section) [11]. There is a controversy regarding the use of antibiotic prophylaxis in elective caesarean section [3, 4]. The proportion of obstetricians who use antibiotic prophylaxis routinely is small. A survey of all maternity clinics in Denmark showed that 4 (8%) departments used prophylactic antibiotic in elective caesarean section and 25 (52%) departments used prophylactic antibiotic in emergency caesarean section [12]. There was considerable variation on the rate of use of antibiotic prophylaxis (0-58.7%) between hospitals. The routine use of cefazolin is not recommended in elective caesarean section when febrile morbidity is low [3].

Although the doses of antibiotics per kg/BW were decreased in pregnant women, the mean concentrations of prophylactically administered antibiotics, estimated 6 hours following the application, were lower in non-pregnant women and higher in the parturient, which is suggesting that there is no need for any increase of the common dose of antimicrobial drugs in pregnancy [13]. In the study of Lang et al. [14] the concentration of ceftriaxone in mother's blood after application of 1 g i.v. before emergency caesarean section was enough for an adequate protection from infection morbidity. In Novelli study [15], pharmacokinetics and half-life of antibiotics in plasma are in direct connection to the activity of antibiotics in tissue of the patient and the single dose of antibiotic prophylaxis was enough to stop the infection even in long-lasting operation.

Our results suggest that ceftriaxone excretion may be slower in caesarean sectioned women relative to the controls, so that there is a potential risk of over-dosage. Therefore, individual antibiotic monitoring after caesarean section is recommended [13]. One possible explanation for different effects of pregnancy on ceftriaxone pharmacokinetics may be because of albumin changes during pregnancy. Because of ceftriaxone's high and saturable binding to albumin, its free fraction varies with time, dose and albuminaemia [16]. Also, body-fluid shifts may have a dramatic impact on serum drug concentrations [17].

In our investigation, the mean concentration of the administered antibiotics in the umbilical cord was high (ceftriaxone – 29.0 µg/ml and cefazolin – 54.3 µg/ml) suggesting that there is a good transfer of all drugs across the fetoplacental barrier and there might be possible negative side effects in the newborn infants. This is a reason why antibiotic prophylaxis should be given intravenously by the anaesthetist at caesarean section after clamping of the umbilical cord [18, 19, 20].

## CONCLUSION

On the basis of the analysis results of the obtained pharmacokinetic parameters and taking into account the ratio of potential risks and benefits, it can be concluded that the preoperative administration of a single-dose of the first generation cephalosporins – cefazolin has been the most optimal choice, both in obstetrical and gynaecological operations.

## NOTE

This paper is the part of the PhD thesis by its first author, Assist. Prof. Dr. Zorica Grujić.

## REFERENCES

- Hopkins L, Smaill F. Antibiotic prophylaxis regimens and drugs for cesarean section. *Cochrane Database Syst Rev.* 2000; 2:CD001136.
- Meyer NL, Hoser KV, Scott K, Lipscomb GH. Cefazolin versus cefazolin plus metronidazole for antibiotic prophylaxis at cesarean section. *South Med J.* 2003; 96(10):992-5.
- Rouzi AA, Khalifa H, Ba'aqeel H, Al-Hamdan HS, Bondagji N. The routine use of cefazolin in cesarean section. *Int J Gynaecol Obstet.* 2000; 69:107-12.
- Grujić Z. Antibiotiska profilaksa kod elektivnih carskih rezova. Beograd: Zadužbina Andrejević; 2007.
- Smaill F, Hofmeyr GJ. Antibiotic prophylaxis for cesarean section. *Cochrane Database Syst Rev.* 2002; 3:CD000933.
- Hakim L, Bourche DWA, Triggs EJ. High-performance liquid chromatographic assay of cefotaxime, desacetylcefotaxime and ceftriaxone in rat plasma. *J Chromatogr.* 1988; 424:111-7.
- Nielsen TF, Hökegård KH. Postoperative cesarean section morbidity: a prospective study. *Am J Obstet Gynecol.* 1983; 146:911-6.
- Hägglund L, Christensen KK, Christensen P, Kamme C. Risk factors in cesarean section infection. *Obstet Gynecol.* 1983; 62(2):145-50.
- Stein GE. Patient costs for prophylaxis and treatment of obstetric and gynecologic surgical infections. *Am J Obstet Gynecol.* 1991; 164:1377-80.
- Olsen IP, Augensen K, Jensen A, Njølstad I. Is antibiotic prophylaxis in Cesarean section necessary? *Tidskr Nor Laegeforen.* 2002; 122(19):1864-6.
- Racinet C, Mallaret MR, Favier ML, Berthet J, Morel I, Fauconnier J, et al. Antibiotic prophylaxis in cesarean sections without high risk of infection. Therapeutic trial of cefotetan versus placebo. *Presse Med.* 1990; 19(38):1755-8.
- Pedersen TK, Blaakaer J. Antibiotic prophylaxis in cesarean section. *Acta Obstet Gynecol Scand.* 1996; 75:537-9.
- Popović J, Grujić Z, Sabo A. Influence of pregnancy on ceftriaxone, cefazolin and gentamicin pharmacokinetics in caesarean vs. non-pregnant sectioned women. *J Clin Pharm Ther.* 2007; 32:595-602.
- Lang R, Shalit I, Segal J, Arbel Y, Markov S, Hass H, et al. Maternal and fetal serum and tissue levels of ceftriaxone following preoperative prophylaxis in emergency cesarean section. *Chemotherapy.* 1993; 39(2):77-81.
- Novelli A. Antimicrobial prophylaxis in surgery: the role of pharmacokinetics. *J Chemother.* 1999; 11(6):565-72.
- Lagneau F, Marty J, Beyne P, Tod M. Physiological modeling for indirect evaluation of drug tissue pharmacokinetics under non-steady-state conditions: an example of antimicrobial prophylaxis during liver surgery. *J Pharmacokinet Pharmacodyn.* 2005; 32:1-32.
- Markantonis SL, Kostopanagiotou G, Panidis D, Smirniotis V, Voros D. Effects of blood loss and fluid volume replacement on serum and tissue gentamicin concentrations during colorectal surgery. *Clin Ther.* 2004; 26:271-81.
- Gilbert DN, Moellering RC, Eliopoulos GM, Sande MA. *The Sanford Guide to Antimicrobial Therapy.* 34th ed. Antimicrobial Therapy Inc. USA; 2004.
- Fejgin MD, Markov S, Goshen S, Segal J, Arbel Y, Lang R. Antibiotic for cesarean section: the case for „true“ prophylaxis. *Int J Gynaecol Obstet.* 1993; 42:257-61.
- Grujić Z, Bogovac M, Grujić I, Hrabovski I. Antibiotic prophylaxis in elective cesarean section: is it worth? Third South East European Congress in Perinatal Medicine. Belgrade, 2009.

## Једнократна примена цефалоспорина пре порођаја елективним царским резом

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### КРАТАК САДРЖАЈ

**Увод** Антибиотска профилакса је примена антибиотика ради спречавања инфекција.

**Циљ рада** Циљ рада је био да се испита да ли је једнократна примена цефтриаксона и цефазолина пре операције довољна за спречавање инфекција током и после царског реза код породилца без високог ризика за развој инфекције.

**Методе рада** Испитано је укупно 90 трудница и осам болесница које нису биле трудне а подвргнуте су гинеколошком хируршком лечењу. Испитанице су сврстане у две групе од по 45 трудница и четири жене које нису биле трудне. Испитаницама прве групе примењен је цефтриаксон у дози од 2 g интравенски 10 минута пре планираног хируршког захвата, а испитаницама друге групе цефазолин, такође у дози од 2 g интравенски 10 минута пре операције. Концентрација антибиотика одређивана је одмах након хируршког захвата и шест сати од почетка операције, док је код трудница утврђивана и концентрација антибиотика у плодовој води и крви пупчаника. Одређива-

ње концентрације антибиотика вршено је методом течне хроматографије под високим притиском.

**Резултати** Просечна концентрација цефтриаксона после елективног царског реза била је 22,7 µg/ml, а цефазолина 44,8 µg/ml. Шест сати после операције концентрације антибиотика су биле ниже, али је ниво цефазолина и даље био изнад прага минималне инхибиторне концентрације за осетљиве бактерије. Просечна концентрација цефтриаксона после гинеколошких операција испитаница које нису биле трудне била је 12,0 µg/ml, а цефазолина 30,1 µg/ml. Шест сати после операције концентрације антибиотика су биле ниже.

**Закључак** Резултати истраживања су доказали да је постигнута антибиотска профилакса једнократним режимом – цефазолином након клемовања пупчаника довољна да спречи могућност продора патогених микроорганизама са коже.

**Кључне речи:** царски рез; антибиотска профилакса; цефалоспорици; цефазолин; цефтриаксон