

PROPHYLACTIC ANTIBIOTICS IN CESAREAN SECTION: A DOUBLE BLIND AND RANDOM STUDY ON 210 IRANIAN WOMEN

H. DABIRASHRAFI, M.D., K. MOHAMAD, Ph.D., M. MOHAMADI, M.S., N. MOGHADAMI TABRIZI, M.D., N. MOSLEMIZADEH, M.D., P. MALEKDAR, M.D.

From the Department of Obstetrics and Gynecology, Mirza Kouchek Khan (Zanan) Hospital, Tehran University of Medical Sciences, Tehran, Islamic Republic of Iran.

ABSTRACT

210 Iranian women participated in a study in two main categories (comprising six subgroups) for comparison of prophylactic antibiotic prescription by the intravenous route with the irrigation method together with control subgroups. Interesting results from our study were:

- 1- There was no significant statistical difference between subgroups with regard to infectious morbidity.
- 2- The rate of early infectious morbidity in our patients was lower than in American studies.
- 3- Late infections were more common than early infections in our study.
- 4- The rate of late endometritis in the irrigation subgroup under category of labor lasting less than six hours was significantly lower than the irrigation subgroup in the category of labor lasting more than six hours.

We think that the results of a particular study investigating the usefulness of prophylactic use of antibiotics at cesarean section from one country is not necessarily relevant for another country having a different culture and customs.

MJIRI, Vol. 2, No. 4, 269-274,

INTRODUCTION

Cesarean section has become a relatively safe and common operation with a three-fold increase in the past decade.¹ Following a cesarean section, women have an increase in not only the frequency but also the severity of puerperal infections.²

Miller³ published one of the first reports on the possible benefits of antibiotic prophylaxis in reducing postcesarean section infectious morbidity. But the choice of antibiotic, route of administration, and time of commencement are all controversial and subject to debate.

Jensen at the end of his article⁴ suggested that "a

prospective study comparing local application of antibiotics (irrigation) with intravenous antibiotic therapy together with untreated control groups is imperative before any definite conclusions can be drawn."

We followed the advice of Jensen and designed a prospective, double blind and random study with one month follow up to compare intravenous route with the irrigation method prescribing sodium cephalothin as the antibiotic of choice and having suitable control groups.

MATERIALS AND METHODS

The 210 patients participating in our study were

divided into two main categories: 1- duration of labor less than six hours (105 patients), 2- duration of labor more than six hours (105 patients). Then, each main category was subdivided into three subgroups: a) patients who received sodium cephalothin* (one gram) intravenously after clamping the umbilical cord, b) patients who were irrigated with 1 gr sodium cephalothin in 800 cc normal saline by the method of Long⁵, c) patients who received no prophylactic antibiotics.

During the study all the patients who needed primary or repeat cesarean section arrived in this study in a fashion that was determined by the use of two tables of random numbers provided by the biostatistic department.

All the cesarean sections were performed by residents under the supervision of staff members. After the completion of operation, another surgeon observed the patients (all 210 patients were followed up by the senior author of this article during the hospitalization period and for one month after the operation). The patients and senior author were unaware of the group assignment until after completion of the study and chart review by the authors. A routine protocol was used for management of all the patients. The patients who were excluded from the study were those who:

1) had received an antibiotic within 3 days prior to operation, 2) had an oral temperature of 38°C or greater within 24 hours before surgery, 3) had a history of hypersensitivity reactions or other adverse reactions to penicillin or cephalosporin type agents, 4) had expressed a wish not to participate in the study (only 5 patients).

Patients were examined daily during hospitalization and then three or four times after discharge until one month had elapsed after operation. Postoperative infection was suspected when a temperature of 38°C or more was recorded on two occasions during any 24-hour period after operation (excluding the first day).⁶ Temperature was measured four times daily by standard method. We used standard criteria for determining postoperative infections.⁷ We defined the early infections as those occurring up to 13 days post-operation and late infections as those occurring from 13 to 30 days.

For any patient with febrile morbidity of any cause a blood and differential count, chest X-ray, as well as a urine, blood, wound, feces and endometrial culture to search for aerobic and anaerobic microorganisms was routinely performed. Swab specimens in Stuart medium were transported to the laboratory within two hours. The specimens were inoculated on blood agar plates, both aerobically and anaerobically (Gaspak, BBL) and in Endo and thioglycolate tubes and incubated at 37°C for 48-72 hours. Isolated microorganisms

were identified according to standard methods.⁸ The usual treatment method for postoperative infections was a combination of gentamicin and clindamycin until the results of culture and sensitivity test were ready. Then, we changed to the antibiotic of choice if indicated.

After discharge from the hospital, the patients measured their temperature every night and reported any abnormal results immediately. We did not perform extensive bacteriological study in this outpatient period, mainly because of patient's reluctance. In the outpatient period we mostly prescribed doxycycline for the cases of endometritis. Nearly 90% of the patients came to the hospital to be visited by the senior author one month after the operation. Of the remainings, we gained information about 6% by telephone and through social workers. Nearly 4% of the patients were lost, during the one month follow-up period.

Most of our patients were of low socioeconomic status. Our hospital is a referral teaching hospital.

For qualitative variables, analysis of variance was used to assess statistical significance of differences between subgroups. For quantitative variables the χ^2 test was used to assess these differences except when the expected number in any cell was less than five, in which case the Fisher exact test was applied.

RESULTS

Table I shows the demographic and operative data of the two main categories, and their three subgroups. These distributions confirm the appropriate randomization of patients. Indications for cesarean section are shown in Table II. There were no significant statistical differences between the subgroups. The rate of postoperative infections is indicated in Table III. There is no statistical difference between the subgroups.

An interesting finding in our study is that the rate of early endometritis in the two main categories appears to be much lower than in the other reports.⁹⁻¹¹

The number of patients who came to the hospital to be visited by the senior author one month after operation was 82 (86%), 85 (79%), 85 (70%); and 91 (43%), 85 (70%), 88 (54%) in the two main categories, showing no significant statistical difference.

Another interesting finding in our study was that the rate of late endometritis was higher than the early cases, and also the rate of late endometritis in irrigation subgroup in the category of labor less than six hours was significantly lower than the irrigation subgroup in the category of labor more than six hours (Table III).

In the cases of early infectious morbidity all except two patients responded to gentamicin plus clindamycin. Most cases of late endometritis responded to

* Manufactured by Eli Lilly Italy, for the Islamic Republic of Iran.

Prophylactic Antibiotics in Cesarean Section

Table I. Demographic, preoperative and operative data.

Variable	Labor less than six hours			Labor more than six hours		
	control subgroup	irrigation subgroup	IV injection subgroup	control subgroup	irrigation subgroup	IV injection subgroup
Mean age (yr) \bar{X}	26,43	25	26,11	23,08	25,48	23,11
S	4,77	6,23	6,84	5,07	6,67	6,01
Parity P	5	7	9	16	19	17
Parity M	30	28	26	19	16	18
No of pelvic examination						
1-4	24	28	22	13	8	13
5-8	8	5	9	11	10	8
>8	3	1	3	11	17	14
Duration of membrane rupture						
<6	33	32	30	21	23	24
>6	1	2	2	10	11	10
Uterine incision						
transverse	34	33	34	34	35	33
vertical	0	0	1	0	0	1
Preoperative values						
Hemoglobin (gr/dL) \bar{X}	12,82	13,36	12,82	13,29	12,73	12,76
S	2,78	0,93	0,91	1,13	1,24	1,33
Hematocrit(%) \bar{X}	39,62	40,08	38,30	39,82	38,37	38,32
S	4,76	2,93	2,72	3,52	4,01	4,11
Postoperative values						
Hemoglobin (gr/dl) \bar{X}	12,34	12,77	12,14	12,11	12,10	12,16
S	1,54	1,73	1,78	1,84	1,20	1,20
Hematocrit(%) \bar{X}	37,18	38,32	36,37	36,36	35,96	36,36
S	4,67	5,06	5,35	5,40	3,62	3,71
Duration of operation						
<60 min	27	26	27	25	24	30
>60 min	6	8	8	8	12	5
Level of surgeon						
postgraduate year (1-2)	15	16	18	21	28	24
postgraduate year (3-4)	20	18	17	13	7	10
Postoperative length of stay, mean(day) \bar{X}	6,80	6,57	6,91	6,34	6,68	6,77
S	2,04	1,26	1,80	0,90	1,07	1,73

doxycycline.

Endometritis was found to be the major cause of postcesarean section febrile morbidity. The most common aerobic and anaerobic microorganisms that were isolated in early endometritis were *E. Coli* and peptostreptococci respectively.

There were no adverse reactions among patients receiving antibiotics. We had no severely ill patient with septic shock, pelvic abscess, or septic thrombophlebitis in our study.

DISCUSSION

Several well designed and well executed (randomized, double-blind, duration of prophylaxis < 24 hours) placebo-controlled clinical trials have evaluated the efficacy of prophylactic antimicrobial agents in preventing pelvic and wound infections after delivery by cesarean section.¹⁰⁻²² Seven of these trials demonstrated a significant reduction in pelvic and wound infections,^{9,13-18} and four did not.^{10,19-21} Our study

Table II. Indications for cesarean section.

Indication	Labor less than 6 hours			Labor more than 6 hours		
	control subgroup	irrigation subgroup	IV injection subgroup	control subgroup	irrigation subgroup	IV injection subgroup
Fetal distress	4	6	7	6	9	7
Breech presentation	3	1	3	5	8	7
Previous cesarean section	16	19	18	11	4	7
Caphalo-pelvic disproportion	2	1	2	9	11	12
Other causes	6	8	5	3	3	2

Table III. Postoperative infections.

	Labor less than 6 hours			Labor more than 6 hours		
	control subgroup No(%)	irrigation subgroup No(%)	IV injection subgroup No(%)	control subgroup No(%)	irrigation subgroup No(%)	IV injection subgroup No(%)
At the time of hospitalization						
Total number	35	35	35	35	35	35
Endometritis	3(8.57%)	1(2.86%)	2(5.71%)	3(8.57%)	2(5.71%)	2(5.71%)
Wound infection	1(2.86%)	0(0%)	1(2.86%)	0(0%)	0(0%)	2(5.71%)
Both infections	0(0%)	0(0%)	0(0%)	0(0%)	0(0%)	1(2.86%)
After discharge until one month after operation						
Total number	34	35	33	34	34	33
Endometritis	5(14.71%)	1(2.86%)	5(15.15%)	5(14.71%)	7(20.59%)	2(6.06%)
Wound infection	1(2.94%)	0(0%)	1(3.03%)	2(5.88%)	2(5.88%)	1(3.03%)
Both infections	0(0%)	1(2.86%)	1(3.03%)	0(0%)	1(2.94%)	1(3.03%)

* There is a statistically significant difference between these two subgroups.

shows that the results of prophylactic prescription of antibiotics is comparable with the control subgroups.

The results could be explained by one or more of the followings:

- 1- In our study the rate of morbidity is so low that the number of patients is not sufficient for comparison (we must extend our study).
- 2- Our study is performed in a new situation, and in this new situation the administration of antibiotics has no effect on reducing the rate of infections.
- 3- The administration of prophylactic antibiotics does not reduce the rate of infections in our patients.

In the Iranian gynecology service, prophylactic antibiotic therapy is not performed in the correct fashion. Very often, the patients receive antibiotics for long periods of time. Many of our gynecologists believe that for some undetermined reasons the incidence of postcesarean section infections must be higher than abroad or those reported from other countries.

On the other hand, most studies hither to published in the United States have shown a high rate of infection after cesarean section: frequencies above 50% are reported regularly.^{9-11,22} The frequency of infections has been significantly reduced by the administration of antibiotics before the cesarean section.^{9,11,17,19}

It is very interesting that in our hospital the rate of postcesarean section early endometritis in the control subgroups is both 8.57%. The rate of early infection in the other subgroups of our study is also very low (Table III). If the rate of infection in our study was high, and at the same time, the results of comparison in the subgroups had been similar, we could surely have said that the prophylactic antibiotic had no benefit to our patients. But in our study when the rate of early infection was low, and, at the same time, was similar in the subgroups, we can guess that this study in contrast to

American studies has been performed in a different environmental situation, and, in reality, the low rate of infection and its even distribution throughout the subgroups confirm each other.

What is the reason for the difference between the rate of late endometritis in the two irrigation subgroups? The irrigation method was introduced⁵ because, after delivery the uterus contracts and the antibiotics can not reach the superficial layer of the uterus in sufficient amount by the intravenous route. Our results show that the reverse is also true. In the category of labor more than six hours, probably because of the microorganism spread from the superficial to the deep uterine layers, the irrigated antibiotics can not penetrate to this depth after the contraction of the uterus, but this is not the case with the patients having labor of less than six hours duration when the infection is more superficial. This means that in the early phase of labor, the irrigation method is more effective than in the late phase.

One of the shortcomings in many of the studies about the effect of prophylactic antibiotics is that they only take into account early infectious morbidity. Rees et al²³ found that late postpartum infections occurred 13 to 38 days after delivery. In Polk's study 35% of all infection and 7% of cases of endometritis subsequent to cesarean delivery were first diagnosed after discharge of the patient from hospital.²⁴ It is an important finding that in our study the rate of late endometritis is higher than the rate of early infection. It is said that cesarean section increases the rate of an early postpartum infection five to ten fold over vaginal delivery.²⁵ 66% of cases of endometritis in our study were late infections. Many women with the late occurring infections were afebrile and had only mild symptoms. Genital mycoplasma and *Chlamydia trachomatis* have

generally produced mild clinical manifestations.²⁶ It was reported in a previous retrospective study,²⁵ that late postpartum endometritis was associated with *C. trachomatis* infections. In our study, the cases of late endometritis were mild and most responded very well to doxycycline, an antibiotic that is effective against genital mycoplasma and *C. trachomatis*.

One important question arises from our study: what is the reason for the very low rate of postcesarean section early infections in our patients, when we compare them with the western studies? For the following reasons it would be more logical to suppose that the rate of infection in our patients should be higher: 1- our hospital is a teaching referral hospital, 2- our patients are rarely operated on electively, 3- most of our patients are indigent, 4- our patients are crowded into rooms with 3 or 4 beds, 5- from the view point of nutrition, socioeconomic background, or hygiene it suffices to mention that our country has been at war, 6- good prenatal care is not usually practiced in our country. So, why should our rate of early infections be lower than in the American studies?

However, we know that in addition to the above factors, development of postoperative infections also depends on other factors that include: the number of microorganisms within the wound, virulence of these microorganisms, presence of substrate to support bacterial growth, and the efficacy of host factor in dealing with these microorganisms. In reality, the number of viable pathogenic microorganisms may be more important than the effect of antibiotics. Our early infections are fewer than late infections. So, we can say that the microorganisms that cause early infections play a less significant role in our patients. Although we feel the necessity of a study to be performed researching the species, number, and virulence of bacteria in the vagina and cervix of Iranian women immediately prior to cesarean section, and also their native immunological status, we think that the ethics and customs of Iranian women must be considered important in such a result. Multipartner sexual practice, alcohol addiction, and drug abuse are very rare among women in our society. The first sexual intercourse of Iranian women is often after marriage and intact hymen is an important and valued tradition in our country.

We, similar to Hagglund,²⁷ think that the results of postcesarean section infections studies obtained in one country is not necessarily useful in another geographical area or country having different social and cultural customs.

REFERENCES

1. Bottoms SF, Rosen MG, Sokol RJ: The increase in the cesarean birth rate. *N Engl J Med* 302 (10): 559-63, 1980.
2. Gibbs RS, Weinstein AJ: Puerperal infection in the antibiotic era. *Am J Obstet Gynecol* 124(7): 769-87, 1976.
3. Miller RD, Crichton D: Ampicillin prophylaxis in cesarean sections. *S Afr J Obstet Gynecol* 6:69, 1968.
4. Jensen LP, Dobin AJ, O'sullivan MJ, Hilsenbeck CE: Prevention of endomyometritis by local application of antibiotic solution during cesarean section. *Am J Obstet Gynecol* 1; 152(5): 565-8, 1985.
5. Long WH, Rudd EG, Dillon MB: Intrauterine irrigation with cefamandole nafate solution at cesarean section: preliminary report. *Am J Obstet Gynecol* 138:755, 1980.
6. Apuzzio JJ, Reyelt C, Pelosi M, Sen P, Louria DB: Prophylactic antibiotics for cesarean section: comparison of high- and low-risk patients for endomyometritis. *Obstet Gynecol* 59 (6): 693-8, 1982.
7. Levin DK, Gorchels C, Andersen R: Reduction of post-cesarean section infectious morbidity by means of antibiotic irrigation. *Am J Obstet Gynecol*. 147(3): 273-7, 1983.
8. Finegold SM, Martin WJ: *Diagnostic Microbiology*, St. Louis: The C.V. Mosby Company, 309-23, 1982.
9. Kreutner AK, Del Bene VE, Delamar D, Boddon JL, Loadholt CB: Perioperative cephalosporin prophylaxis in cesarean section: effect on endometritis in the high-risk patient. *Am J Obstet Gynecol* 134(8): 925-35, 1979.
10. Gibbs RS, DeCherney AH, Schwarz RH: Prophylactic antibiotics in cesarean section: a double-blind study. *Am J Obstet Gynecol* 114:1048-53, 1972.
11. Duff P, Park RC: Antibiotic prophylaxis for cesarean section in a military population. *Milit Med* 145(6): 377-81, 1980.
12. Harger J, English D: Perioperative cefoxitin prophylaxis in cesarean sections at high risk for infection. Interscience conference on antimicrobial agents and chemotherapy: abstract No 229, 1980.
13. Gibbs RS, Hunt JE, Schwarz RH: A follow-up study on prophylactic antibiotics in cesarean section. *Am J Obstet Gynecol* 117:419-22, 1973.
14. Wong R, Gee CL, Ledger WJ: Prophylactic use of cefazolin in monitored obstetric patients undergoing cesarean section. *Obstet Gynecol* 51(4): 407-11, 1978.
15. Gall SA: The efficacy of prophylactic antibiotics in cesarean section. *Am J Obstet Gynecol* 134(5): 506-11, 1979.
16. Larson P, Nelson KE, Ismail M, Geiseler PJ: A double-blind study of cefoxitin prophylaxis of post-cesarean section infection. International congress on chemotherapy and interscience conference on antimicrobial agents and chemotherapy, abstract No 649, 1979.
17. Rehu M, Jahkala M: Prophylactic antibiotics in cesarean section: effect of a short preoperative course of benzyl penicillin or clindamycin plus gentamicin on postoperative infectious morbidity. *Ann Clin Res* 12:45, 1980.
18. Dillon WR, Seigel MS, Lele AS, O'Leary JA: Evaluation of cefoxitin prophylaxis for cesarean sections. *Int J Gynaecol Obstet* 19:133, 1981.
19. Work B: Role of preventive antibiotics in patients undergoing cesarean section. *South Med J* 70: (suppl) 44, 1977.
20. Phelan JP, Pruyn SC: Prophylactic antibiotics in cesarean section: double-blind study of cefazolin. *Am J Obstet Gynecol* 133:(5) 474-8, 1979.
21. McCowan L, Jackson P: The prophylactic use of metronidazole in cesarean section. *N Z Med J* 92:153, 1980.
22. D'Angelo LJ, Sokol RJ: Short-versus long-course prophylactic antibiotic treatment in cesarean section patients. *Obstet Gynecol* 55(5): 583-6, 1980.
23. Rees E, Tait IA, Hobson, D, et al: Chlamydia in relation to cervical infection and pelvic inflammatory disease. In: Hobson D, Halmes KK, eds. *Nongonococcal Urethritis and Related Infections*, Washington DC: American society for microbiology,

- 67-76, 1977.
24. Polk BF, Karche M, Phillippe M, et al: Randomized clinical trial of perioperative cefoxitin in preventing maternal infection after primary cesarean section. *Am J Obstet Gynecol* 142(8): 983-7, 1982.
 25. Wager GP, Martin DH, Koutsky L, et al: Puerperal infectious morbidity: relationship to route of delivery and to antepartum Chlamydia trachomatis infection. *Am J Obstet Gynecol* 138:1028, 1980.
 26. Hoyme UB, Kiviat N, Eschenbach DA: Microbiology and treatment of late postpartum endometritis. *Obstet Gynecol* 68(2): 226-32, 1986.
 27. Hägglund L, Christensen KK, Christensen P, Kamme C: Risk factors in cesarean section infection. *Obstet Gynecol* 62(2): 145-50, 1983.