Scholars Journal of Applied Medical Sciences (SJAMS) **ISSN 2320-6691 (Online)**
Sch. J. App. Med. Sci., 2015; 3(7B):2544-2551 **ISSN 2347-954X (Print)**

(An International Publisher for Academic and Scientific Resources)
www.saspublisher.com

Research Article

Optimal timing of peri operative antibiotics in caesarean section and risk of postpartum and neonatal infections

Dr. Alakananda, Dr. Gokul Ch. Das, Dr. Himleena Gautam
Department of Obstetrics & Gynaecology, Gauhati Medical College and Hospital (Bhangagarh, Guwhati-781032)
Under Srimanta Sankardev University of Health Sciences, Guwahati, Assam

***Corresponding author**
Himleena Gautam
Email: himleenaj@gmail.com

Abstract: The purpose of this study was to compare post partum infections and neonatal sepsis and bacteriology of cases with infections in relation to the timing of peri operative antibiotics at caesarean section. It was a prospective, Randomized Controlled Trial conducted in the Department of Obstetrics & Gynaecology, Gauhati Medical College. Group A received injectable antibiotic Ceftriaxone1gm 30-60mins before skin incision and Group B received the same antibiotic after cord clamping. Rates of post operative infections, endometritis, UTI and SSI and neonatal sepsis were compared in the two groups. In results Over a period of 12 months, 480 patients with singleton, live, term or near term pregnancies fulfilling the inclusion and exclusion criteria were included in the study (247- group A, 233- group B). Rates of endometritis (p=0.3182), UTI (p=0.4638), neonatal sepsis (p=0.8615 & 0.4919) and clinically probable sepsis (p=0.1984) were not significantly different in the two groups. However rates of SSI was significantly higher in group B. in conclusion there was no significant difference in maternal infectious morbidity and neonatal sepsis work up in relation to timing of administration of antibiotic in caesarean section, except in rates of SSI, which was more in group B. However the rates of infections were significantly higher in cases who underwent emergency caesarean (P= 0.0001), irrespective of timing of antibiotic.
Keywords: Caesarean section, endometritis, UTI, SSI, neonatal sepsis.

INTRODUCTION

An important risk factor of postpartum maternal infection is caesarean section [1]. Women undergoing caesarean section have a 5 to 20 fold increased risk for infection and infectious morbidity compared with a vaginal birth. Infections can affect the pelvic organs, the surgical wound and the urinary tract. Infectious complications that occur after caesarean births are an important and substantial cause of maternal morbidity and associated with a significant increase in hospital stay [2]. Worldwide, the rate of caesarean delivery is increasing [3,4]. The beneficial effect of prophylactic antibiotics in reducing the occurrence of infectious morbidity from caesarean section, whether elective or emergency is well established [5].

The goal of antimicrobial prophylaxis is to achieve for the duration of the operation, the serum and tissue drug levels that exceed the MICs for the organisms likely to be encountered during the operation [6, 7]. The timing of administration has been recognized to influence the efficacy of antimicrobial prophylaxis [8]. Evidence-based guidelines recommended the use of prophylactic antibiotics prior to surgical incision. An exception is made for caesarean delivery, where narrow-range antibiotics are administered post umbilical cord clamping because of putative neonatal benefit. Prophylactic antibiotics in most institutions is administered generally after clamping of the umbilical cord [9,10], as there is an argument to delay antibiotics until after cord clamping because relevant antibiotic plasma levels are seen in the neonate [11]. There are concerns that the wrong choice of antibiotic may result in the neonate being exposed to resistant strains of bacteria [12, 13], which might lead to a worse neonatal outcome (14) and/or the need for expensive neonatal septic screens and infection work-ups [15].

The most important source of micro-organisms responsible for post-caesarean section infection is the genital tract, particularly if the membranes are ruptured. Infections are commonly polymicrobial. However, inappropriate use of antimicrobials in surgeries, can select for resistant microorganisms [16] and it has been shown to result in marked changes in an individual's skin flora, with increases in resistant flora and strains with increased virulence seen postoperatively [17]. The

present study aims at comparing the timing of administering peri operative antibiotics in caesarean section, i.e. before skin incision and after cord clamping; and assessing risks of post operative maternal and neonatal infections.

MATERIALS AND METHODS

The Ethical Committee of Srimanta Sankardev University of Health Sciences, Guwahati, Assam, approved this Randomized Controlled study. Singleton, live, term or near term patients undergoing elective or emergency caesarean section in the Department of Obstetrics and Gynaecology in Gauhati Medical College and Hospital from June 2014 to May 2015 were included in the study. The exclusion criteria were- PPROM, PROM, cases with DM or GDM, prolonged labour, obstructed labour, suspected chorioamnionitis , cases with UTI, anemia (Hb < 10gm/dl), documented fever, penicillin or cephalosporin allergy cases who have received antibiotics in last 48 hours and pregnancies with IUGR babies. A non probability convenience sampling technique was used. Simple randomization was done avoiding bias and the cases were divided into 2 groups. Informed consent was taken from the cases. Necessary pre operative investigations were done. Inj. Ceftriaxone 1gm IV ANST was given to the patients before skin incision in group A and after cord clamping in group B. The duration of surgery was measured from the skin incision up to complete skin closure. All cases were done under spinal anaesthesia. Approximate blood loss during surgery was estimated by visual estimation by the obstetrician and nursing staff. Any intraoperative complication was noted. The patients and neonates were followed up for 5 days post-operatively Patients were assessed for any infectious complications (fever, endometritis, UTI, SSI) clinically. If the patient had positive clinical features, necessary investigations were done.

For detecting the outcome, the following definitions were used-

a. Fever- temperature of ≥ 100.4'F on two occasions 6 hours apart, excluding the first 24 hours of delivery. Standard mercury thermometer was used.
b. Endometritis- presence of fever with lower abdominal / uterine tenderness with tachycardia/ leukocytosis, sub involution of uterus and foul smelling lochia. High vaginal swab may or may not be positive.
c. UTI- presence of fever with lower abdominal or flank pain, burning micturition and/or increased frequency of micturition with positive findings in urine analysis.
d. Wound infection- purulent wound discharge with/without fever with erythema and tenderness in the wound, raised TC, CRP and/or positive pus culture.
e. Pneumonia- presence of fever with cough or respiratory distress with wheeze/crepitations on chest auscultation and consolidation in chest X-ray.

Neonates with positive sepsis screen but blood culture negative were labeled as clinically probable sepsis and those with positive sepsis screen and blood culture were labeled as either early onset sepsis or late onset sepsis, depending on whether culture was positive within 72 hours of birth or later respectively.

Normality of the data was tested with Kolmogorov-Smirnov and Chi-square tests when appropriate. Chi-square comparisons were performed for categorical variables and relative risks (RR) with 95% confidence interval were calculated. Analysis of variance testing was performed when multiple groups of categorical variables were encountered. Student t tests were used for continuous variable analysis. A logistic regression was also performed to obtain adjusted relative risk values. Chi-square test for independence was used for larger contingency tables. Data were presented as mean ± standard deviation for continuous variables and as frequency (percentage) for categorical variables. A P value of less than .05 was considered statistically significant.

RESULTS

480 subjects with all the inclusion criteria were included in this study. 247 were in group A and 233 in group B. As shown in table1, the 2 groups were comparable in age, gestational age, parity, BMI in the two groups. Also the two groups were comparable in terms of duration of labour, presence of draining P/V (per vagina), P/V examinations, and indications of C/S (caesarean section), duration of surgery and blood loss in surgery (table2).

Table 1: Comparison of demographic variables in the two groups

	GROUP A (n=247)	GROUP B (n=233)	P value (95%CI)
Age(mean in years)	25.57 ± 4.44	24.85 ± 4.37	0.054
Gestational age(mean in days)	274.18 ± 8.9	275.39 ± 9.39	0.163
Nulliparous (no.)	124	131	0.2007
BMI(mean in kg/m2)	25.93 ± 1.47	25.89 ± 1.58	0.955

Table 2: Comparison of obstetric variables in the two groups

	GROUP A (n=247)	GROUP B (n=233)	P value
Labour (mean in hrs)	1.98±2.41	2.09±2.52	0.5771
Presence of draining P/V	57	63	0.3164
>3 P/V examinations	207	199	0.6271
Operative time (mean in mins)	41.01±8.43	39.72±8.46	0.0938
Blood loss (mean in ml)	801.82±160.05	801.78.33±192.02	0.4974
Indication of C/S	76	92	0.3954
Fetal distress			
Oligohydramnios	30	30	
Malpresentations	27	26	
Emergency indications	173	168	0.6185

As shown in table3, 8.5% cases (i.e.21) in group A and 17.17% cases(i.e.40) in group B had post operative infections (p=0.7615). 2.83% in group A and 4.72% in group B had endometritis (p=0.3182 with RR of 0.7643 and 95% CI of 0.4252 to 1.374). 1.62% in group A and 2.58% in group B had UTI (p= 0.4638 with RR of 0.7737 and 95% CI of 0.3603 to 1.661). Though the rates were higher in group B, there was no statistically significant difference. However, 4.05% cases in group A and 9.87% in group B had SSI with p value of 0.0117 with RR of 0.5715 and 95% CI of 0.3381 to 0.9660, i.e. group B had significantly higher rates of SSI. There was no case of pneumonia and no sepsis related maternal mortality in the study.

Table 3: Comparison of post operative infections in two groups

	GROUP A (n=247)	GROUP B (n=233)	P value
Total infections	21	40	0.7615
Endometritis	7	11	0.3182
UTI	4	6	0.4638
SSI	10	23	0.0117

No significant relation was seen between development of post operative infections with variables like age of patient, BMI of patient, gestational age, presence of labour, presence of draining P/V, P/V examination, duration of surgery and blood loss during surgery in the two groups (table4).

Table 4: P values of post operative infections in relation to various variables

	P Values For Post Operative Infections In The Two Groups In Relation To The Various Variables			
Variables	Total Cases With Infections	Endometritis	UTI	SSI
Age	0.2747	0.7578	0.8390	0.2415
Gestational age	0.5503	0.4320	0.1084	0.7763
Parity	0.0630	0.6287	0.5982	0.1266
BMI	0.9636	0.7288	0.4292	0.2829
Presence of labour	0.5222	0.2796	0.7782	0.5615
Presence of draining	0.1535	0.1469	0.1967	0.0857
No. of P/V examination	0.2333	0.4117		0.4217
Duration of surgery	0.1607	0.3720	0.6062	0.1423
Blood loss during surgery	0.5684	0.6345	0.6342	0.5563

However on comparison of total elective and emergency cases, total post operative infections were significantly higher in the cases with emergency C/S. Only 2 elective cases out of 139 had infections; but 59 cases out of 341 emergency cases had infections. The P value comes out to be <0.0001 with RR of 0.08316 and 95% CI of 0.02060 to 0.3358. Thus emergency cases had significantly higher rates of infections.

As noted in table 5, both groups were comparable in terms of neonatal birth weight. There was no significant difference noted in EOS (p=0.8615), LOS (p=0.4919) and clinically probable sepsis (p=0.1984) in the two groups. Low birth weight babies (<2.5kg) and IUGR babies were not included in the study, considering that these babies are more prone for infection.

Table 5: Comparison of neonatal outcome

	GROUP A (n=247)	GROUP B (n=233)	P value
Birth weight (mean in Kgs)	2.89±0.33	2.88±0.34	0.9675
Clinically probable sepsis	20	27	0.1984
EOS	4	5	0.8615
LOS	5	7	0.4919

As shown in table6, in cases with endometritis, maximum cases showed no growth in high vaginal swab (57.14% in group A and 63.63% in group B). Growth of E.coli was found in 28.57% cases and 27.27% cases in groups A and B respectively. Other cases showed growth of Klebsilla. In cases with UTI, maximum cases had growth of E.coli (50% in each), followed by Klebsilla (25% and 33.33%) and Staph. Aureus (25% and 16.67%) in the two groups respectively. In cases with wound infection, maximum cases had growth of Staph. Aureus (40% and 39.13%), followed by coagulase negative staphylococci i.e. CONS (30% and 30.43%) and Klebsilla (20% and 17.39%) in the two groups respectively. No growth was detected in pus culture in 10% cases in group A and 13.04% in group B.

Table-6: Bacteriology of cases with infections

	GROUP A	GROUP B
BACTERIOLOGY IN ENDOMETRITIS	(n=7)	(n=11)
E. coli	2(28.57%)	3(27.27%)
Klebsilla	1(14.28%)	1(9.09%)
No growth	4(57.14%)	7(63.63%)
BACTERIOLOGY IN UTI	(n=4)	(n=6)
E. coli	2(50%)	3(50%)
Klebsilla	1(25%)	2(33.33%)
Staph. aureus	1(25%)	1(10.67%)
BACTERIOLOGY OF SSI	(n=10)	(n=23)
Staph. aureus	4(40%)	9(39.13%)
CONS	3(30%)	7(30.43%)
Klebsilla	2(20%)	4(17.39%)
No growth	1(10%)	3(13.04%)

Table 7: Rates of endometritis in different studies

STUDIES	YEARS	RATE OF ENDOMETRITIS IN GROUP A (%)	RATE OF ENDOMETRITIS IN GROUP B (%)	P value
Wax et al. (28)	1997	2	2.4	0.8984
Thigpen et al. (23)	2004	7.8	14.77	0.67
Sullivan et al. (24)	2007	1	5	0.0226
Kaimal et al. (26)	2008	2.1	4.8	0.014
Owens et al. (27)	2009	2.2	3.9	<0.0001
Yildrim *et al.;* [25]	2009	2.58	3.59	0.567
Witt et al. (29)	2011	0.27	0.27	0.9985
Macones *et al.;* [30]	2012	2.76	2.76	1
Present study	2015	2.83	4.72	0.3182

Table 8: Rates of UTI in different studies

STUDIES	YEARS	RATE OF UTI IN GROUP A (%)	RATE OF UTI IN GROUP B (%)	P value
Yildrim *et al.;* [25]	2009	1.55	2.56	0.4795
Witt et al. (29)	2011	2.16	1.08	0.2425
Macones et al. (30)	2012	0.92	0.92	1
Present study	2015	1.61	2.57	0.4638

Table 9: Rates of SSI in different studies

STUDIES	YEARS	RATES OF SSI IN GROUP A (%)	RATES OF SSI IN GROUP B (%)	P value
Wax et al. (28)	1997	2	4.9	0.4552
Thigpen et al. (23)	2004	3.92	5.37	0.84
Sullivan et al. (24)	2007	3	5	0.2144
Kaimal et al. (26)	2008	2.5	6.4	0.002
Owens et al. (27)	2009	2.5	3.6	<0.01
Yildrim et al. (25)	2009	3.1	4.1	0.5929
Witt et al. (29)	2011	2.43	2.43	0.9954
Macones et al. (30)	2012	0.46	1.34	0.3151
Brown et al. (31)	2013	1.8	10.3	0.0098
Present study	2015	4.04	9.87	0.0117

Table 10: Clinically probable sepsis in different studies

STUDIES	YRS.	CLINICALLY PROBABLE SEPSIS IN GROUP A	CLINICALLY PROBABLE SEPSIS IN GROUP B	P value
Thigpen et al. (23)	2004	7.19%	9.40%	0.76
Sullivan et al. (24)	2007	19%	18.5%	0.8999
Owens et al. (27)	2009	22.2%	24.1%	0.5655
Yildrim et al. (25)	2009	11.44	15.15	0.2751
Macones et al. (30)	2012	8.76	8.76	1
Present study	2015	8.10	11.59	0.1984

Table 11: Rates of neonatal sepsis in different studies

STUDIES	YEARS	NEONATAL SEPSIS IN GROUP A (%)	NEONATAL SEPSIS IN GROUP B (%)	P value
Thigpen et al. (23)	2004	4.58	4.7	0.96
Sullivan et al. (24)	2007	3	3.6	0.2223
Yildrim et al. (25)	2009	4.48	6.57	0.3609
Owens et al. (27)	2009	EOS- 0.7	EOS- 1.3	0.4133
		LOS- 1.8	LOS- 5.7	0.001
Present study	2015	Total- 3.64	Total -5.15	0.420
		EOS- 1.62%	EOS- 2.15%	0.6708
		LOS- 2.02%	LOS- 3%	0.4919

DISCUSSION

The administration of antibiotics is not intended to sterilize tissues, but to act as an adjunct to decrease the intra-operative microbial load to a level that can be managed by the host innate and adaptive immune responses [6, 18, 19]. In the 1960's, using a guinea pig model, Burke demonstrated that, when antimicrobials were administered before incision, experimental incisions contaminated with Staphylococcus aureus could not be distinguished from incisions that had not been contaminated [7]. This work was corroborated by Shapiro *et al.;* [20]. Classen *et al.;* found that administration of prophylactic antibiotics within a two-hour period preoperatively was associated with the lowest surgical wound infection rate [21]. Thus, evidence-based guidelines recommend the use of antibiotics prior to incision as opposed to during or after the procedure [6, 18, 22].

However, in the case of cesarean delivery, preoperative antibiotic dosing is associated with a substantial plasma level in the neonate [11]. Because

this therapeutic drug level in the newborn may alter blood culture results and, thus, perhaps delay, or mask the diagnosis of neonatal sepis, it is common practice to delay antibiotics until the baby is delivered and the umbilical cord clamped. But various studies [23, 24, 25] have shown that there is no difference in neonatal sepsis and sepsis work up in relation to timing of administration of antibiotics.

Sullivan *et al.;* [24], Kaimal *et al.;* [26], Owens *et al.;* [27] found significantly higher rates of endometritis and SSI in the group receiving antibiotic after cord clamping. But other studies [23, 25, 28, 29, 30] have found no difference. There was no significant difference in UTI in any study. Tables 7, 8, 9,10 & 11 show the various rates of post operative infections in different studies.

In two studies done by Brown et al. [31], higher rates of SSI were found in emergency cases. Out of the total cases in first study, 12.5% cases of SSI had emergency C/S as compared to 9.09% cases with elective indication. In the second study, all cases of SSI had emergency C/S.

In a study by Gibbs RS *et al.;* in 1985 [32], maximum cases(75%) with endometritis had anaerobic growth, 25% showed aerobic gram negative bacilli, out of which most common was E.coli. In the study by Gordon et al in 1979 [33], all cases with post operative UTI had E.coli in urine culture. In a study done by Steinberg et al in 2009 [34], 31.2% cases showed positive Staph. Aureus culture, followed by CONS with 15.6% and gram negative bacteria in 14.7%, cases. No organism was detected in 5.5% cases. In a study by Kaplan et al in 2003 [35] in Jordan, 42% had Staph. Aureus infection, followed by E.coli (27.7%) and Klebsilla (20.5%). This study considered CONS as a skin contaminant.

In the present study, we have used a third generation cephalosporin and we did not find any significant difference in rates of post operative infections, endometritis and UTI in the two groups. But the rate of SSI was significantly higher in the post cord clamping antibiotic group. There did not appear to be an advantage or disadvantage to the infant as far as infectious morbidity was concerned, regardless of when antibiotics were administered. Rates of neonatal sepsis and clinically probable sepsis were similar.

There are several study limitations that should be acknowledged. First the study was single blinded as only the patients did not know in which group they were. However, the pediatrician did not know whether the mother was given antibiotic or the timing of antibiotics in the neonates examined. Second, this study is limited to singleton term or near term pregnancies. We did not include parturient with prolonged labour (maximum duration of labour was 8 hours) and we did not include prolonged draining (maximum duration of draining was 4 hours), because in our set up these cases already received injectable antibiotic before being included in the study. So it may not be applicable to all cases (i.e. preterm gestation, prolonged labour or prolonged draining). Likewise the study could not find any significant difference in infections in relation to draining P/V, number of P/V examinations or duration of labour. Third, we could not do anaerobic culture, so probably we could not detect anaerobic organisms that are more common in endometritis.

It is possible the results might have been different if an antibiotic other than cefazolin had been used. A meta analysis of 51 antibiotic studies concluded that ampicillin, first, second-generation cephalosporins and third-generation cephalosporins like ceftriaxone had similar efficacy profiles when compared [36].

CONCLUSION

Rates of total post operative infections, endometritis and UTI and rates of clinically probable sepsis and neonatal sepsis were higher in the after cord clamping antibiotic group, but the difference was not significant. But, rates of SSI were significantly higher in the group receiving antibiotic after cord clamping. Thus there was no significant difference in the timing of administration of antibiotics in caesarean section, except in prevention of SSI. Also, post operative infections were significantly higher in emergency caesarean sections as compared to elective indications. In cases with endometritis and UTI, the common organism isolated was E.coli in both the groups. In cases with SSI, the most common organism isolated was Staph. Aureus in both the groups.

REFERENCES

1. Rasmussen SA, Maltau JM; Complications following cesarean section. Tidsskr Nor Laegeforen 1990; 110:351-3.
2. Henderson E, Love EJ; incidence of hospital acquired infections associate with caesarean section. J Hosp Infect 1995; 29:245-55.
3. Martin JA, Hamilton BE, Sutton PD, et al.; Births: Final data for 2005. Natl Vital Stat Rep. 2007; 56 (6):1–103.
4. Hamilton BE, Martin JA, Ventura SJ. Births: Preliminary data for 2006. Natl Vital Stat Rep. 2007; 56 (7):1–18.
5. Smaill F, Hofmeyr GJ; Antibiotic prophylaxis regimens and drugs for cesarean section. The Cochrane Database of Systematic Reviews 1996; Issue 2: Art. No.:CD001136. DOI: 10.1002/14651858.
6. Mangram AJ, Horan TC, Pearson ML, Silver LC, Jarvis WR; Guidelines for prevention of surgical

site infection, 1999. Hospital Infection Control Practices Advisory Committee. Infect Control Hosp Epidemiol 1999; 20:250-78.
7. Burke JF; The effective period of preventive antibiotic action in experimental incisions and dermal lesions. Surgery 1961; 50:161-8.
8. Page CP, Bohnen JM, Fletcher JR, McManus AT, Solomkin JS, Wittmann DH; Antimicrobial prophylaxis for surgical wounds. Guidelines for clinical care [published erratum appears in Arch Surg 1993; 128:410]. Arch Surg 1993; 128:79–88.
9. Festin M, Laopaiboon M, Pattanittum P, Ewens M, Henderson Smart D, Crowther C; Caesarean section in four South East Asian countries: reasons for, rates, associated care practices and health outcomes. BMC Pregnancy Childbirth 2009; 9:17–43.
10. Tita A, Rouse D, Blackwell S, Saade G, Spong C, Andrews W; Emerging concepts in antibiotic prophylaxis for cesarean delivery. A systematic review. Obstet Gynecol 2009; 113:675–82.
11. Fiore MT, Pearlman MD, Chapman RL, Bhatt-Mehta V, Faix RG; Maternal and transplacental pharmacokinetics of cefazolin. Obstet Gynecol 2001; 98:1075-9.
12. ACOG Practice Bulletin 47, October 2003: Prophylactic antibiotics in labor and delivery. Obstet Gynecol 2003; 102:875-82.
13. Edwards RK, Clark P, Sistrom CL, Duff P; Intrapartum antibiotic prophylaxis 1: relative effects of recommended antibiotics on gram negative pathogens. Obstet Gynecol 2002;100:534-9
14. Terrone DA, Rinehart BK, Einstein MH, Britt LB, Martin JN Jr, Perry KG; Neonatal sepsis and death caused by resistant Escherichia coli: possible consequences of extended maternal ampicillin administration. Am J Obstet Gynecol 1999; 180:1345–8.
15. Cunningham FG, Leveno KJ, DePalma RT, Roark M, Rosenfeld CR; Peri operative antimicrobials for cesarean delivery: before or after cord clamping? Obstet Gynecol 1983;62:151-4
16. Harbarth S, Samore MH, Lichtenberg D et al.; Prolonged antibiotic prophylaxis after cardiovascular surgery and its effect on surgical site infections and antimicrobial resistance. Circulation 2000; 101: 2916–21.
17. Archer GL; Alteration of cutaneous staphylococcal flora as a consequence of antimicrobial prophylaxis. Rev Infect Dis 1991; 13(suppl 10):S805-9. (Level III)
18. ASHP Therapeutic Guidelines on Antimicrobial Prophylaxis in Surgery. American Society of Health-System Pharmacists. Am J Health Syst Pharm 1999; 56:1839-88.
19. Agency for Healthcare research and Quality. Making Health Care Safer: A Critical Analysis of Patient Safety Practices. Evidence report/technology assessment No, 43 AHRQ Publication No.01-E058. 1-15-2010. Atlanta, GA:CD , 2001
20. Shapiro M, Shimon D, Freund U, Sacks T; A decisive period in antibiotic prophylaxis of cutaneous lesions caused by Bacteroides fragilis in guinea pigs. J Infect Dis 1980;141:532
21. Classen D, Evans R, Pestotnik S, Horn S, Menlove R, Burke J; The timing of prophylactic administration of antibiotics and the risk of surgical wound infection. N Engl J Med 1992; 326:281–6.
22. Bratzler DW, Houck PM; Antimicrobial prophylaxis for surgery; an advisory statement from the National Surgical Infection Prevention Project. Clin Infect Dis 2004; 38:1706-15.
23. Thigpen BD, Hood WA, Chauhan S, Bufkin L, Bofill J, Magann E, *et al.;* Timing of prophylactic antibiotic administration in the uninfected laboring gravida: a randomized control trial. Am J Obstet Gynecol 2005;192: 1864-8
24. Sullivan SA, Smith T, Chang E, Hulsey T, Vandorsten JP, Soper D; Administration of cefazolin prior to skin incision is superior to cefazolin at cord clamping in preventing post cesarean infectious morbidity: a randomized, controlled trial. Am J Obstet Gynecol 2007; 196:455.e1–5.
25. Yildirim G, Gungorduk K, Guven HZ, et al.; When should we perform prophylactic antibiotics in elective cesarean cases? Arch Gynecol Obstet 2009; 280:13–18.
26. Kaimal AJ, Zlatnik MG, Cheng YW, Thiet MP, Connatty E, Creedy P, *et al.;* Effect of a change in policy regarding the timing of prophylactic antibiotics on the rate of post cesarean delivery surgical site infections. Am J Obstet Gynecoln2008;199:310-5
27. Owens SM, Brozanski BS, Meyn LA, et al.; Antimicrobial prophylaxis for cesarean delivery before skin incision. Obstet Gynecol 2009; 114:573–9.
28. Wax JR, Hersey K, Philput C, Wright MS, Nichols KV, Eggleston MK, *et al.;* Single dose cefazolin prophylaxis for post cesarean infections: before vs. after cord clamping. J Matern Fetal Med 1997;6:61-5
29. Witt A, Doner M, Petricevic L, Berger A, Germann P, Heinze G, Tempfer C; Antibiotic prophylaxis before surgery vs after cord clamping in elective cesarean delivery: a double-blind, prospective, randomized, placebo-controlled trial. Arch Surg 2011;146:1404–9
30. Macones GA, Cleary KL, Parry S, Stamilio DM, Cahill AG, Odibo AO, *et al.;* The Timing of antibiotics at cesarean: a randomized controlled trial. Am J Perinatal 2012; 29:273–6.

31. J. Brown; pre-incision antibiotic prophylaxis reduces the incidence of post-caesarean surgical site infection; I Journal of Hospital Infection 83 (2013) 68-70.
32. Gibbs RS, Blanco JD, Bernstein S; role of aerobic gram negative bacilli in endometritis after caesarean section. Rev Infect Dis 1985 Nov-Dec; 7 Suppl 4:S690-5.
33. Gordon HR, Phelps D, Blanchard K; Prophylactic cesarean section antibiotics: maternal and neonatal morbidity before or after cord clamping. Obstet Gynecol 1979; 53:151-6.
34. Steinberg JP, Braun BI, Hellinger WC; Timing of antimicrobial prophylaxis and risk of surgical site infections; Ann Surg 2009; 250: 10-16.
35. Kaplan NM, Smadi AA; Microbiology of wound infection after caesarean section in a Jordanian hospital. Eastern Mediterranean Health Journal, Vol.9, Nos 5/6, 2003.
36. Smail F, Hofmeyr GJ; Antibiotic prophylaxis for cesarean section. Cochrane Database Syst Rev 2002;(3):CD000933.