Original Article

Treatment Of Bacterial Vaginosis To Prevent Infection Following Caesarean Delivery : A Randomized Control Study

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ABSTRACT

Background: There is shortage in clinical data determining significant benefit (i.e., decrease of severe infection outcomes) following screening and treatment of Bacterial vaginosis (BV) late in pregnancy. Due to this deficiency of data, there is controversy concerning whether ladies with BV should be screened and/or treated in late pregnancy to prevent peripartum infections. BV is a common lower genital tract infection with a global prevalence ranging between 23 and 29%.

Aim: To asses if treatment of BV positive women screened at cesarean delivery significantly reduces infection rate

Study Design: The trial was a randomized double-blinded, single center interventional study conducted at the Department of Obstetrics and Gynecology, Faculty of Medicine, Cairo University. The study population consisted of 150 eligible pregnant women who were admitted in the labour or obstetric ward and underwent elective or emergency CS from December 2019 to February 2021. The women were randomized into either of the two arms. The study arm "Group A" participants received 500gm MTZ twice daily for one week, starting 6hrs following CS, whereas the control arm "Group B" participants received one placebo tablet twice daily for one week, 6hrs following CS. Each group comprised 75 pregnant women.

Results: In total 150 patient, eight were excluded from statistical analysis for unknown infection morbidity status due to loss to follow up, leaving 142 women for analysis. Of those that were given treatment for BV, 66 women (91.7%) had a negative test for BV at one week. In this study, treatment of BV was found to be significantly associated with the reduction of post cesarean endometritis (*P value* = 0.0121) (cOR = 0.2834; 95%CI = [0.2228 to 0.8627]). However, the situation was different regarding wound infection incidence. No significant difference was recognized between the treatment and control groups (*P value* = 0.2048).

Conclusion: Given the results of our study, which is in agreement to same evidence associating BV with intrapartum chorioamnionitis and endometritis post CS, BV screening late in pregnancy, possibly at the 35-37 week and group B streptococcus culture visit, or immediately following CS, and treatment of those positively screened could be made. With none existence of guidelines from professional societies, preoperative screening and treatment of BV could cause more reduction in surgical site infections.

Key Words: Bacterial vaginosis, caesarean section, caesarean delivery, endometritis

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INTRODUCTION

Cesarean section (CS) rates have been on the rise all over the world[1]. Post CS infections are a large complication, which may cause women morbidities and financial burdens. The most frequent of these post cesarean infections include endometritis and wound infections[1]. The most common complications are endometritis then wound infection[2].

Endometritis is more prevalent post caesarean deliveries than post vaginal deliveries might be aggravated by peritonitis, pelvic abscess and septicemia[3,4]. Maternal mortalities from these complications are rare, but with a lengthy hospital stays[5,6].

Bacterial vaginosis (BV) is a common lower genital tract infection with a general prevalence between 23 and 29 percent. Greater dissimilarities in frequency is present between different ethnic groups[7,8] with BV being more common in women of low income households[9]. BV is related to a disturbance in ideal vaginal microbiota.

This is described by decreased proportions of healthy, hydrogen peroxide and lactic acidproducing Lactobacillus species, and increased proportions of a wide array of potentially pathogenic anaerobes including Gardenerella vaginalis, Mobiliuncus spp, and Prevotella spp[10-12].

Women who have BV have a greater possibility of infertility and pelvic inflammatory disease[11-16]. 84% of

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ladies who were screened positive for BV reported no symptoms[17], with other studies showing similar results[7,18].

There is no identifiable reason for BV , management of BV involves affordable powerful Antibiotics with anaerobic ability that donnot disturb lactobacilli[19-21]. The ability of oral metronidazole (MTZ) in recurring vaginal flora to normal is around 80-90 %[22-24].

Regarding gestation, BV rise the hazard of occurrence of intrapartum chorioamnionitis and postpartum endometritis[25,26]. A large cohort study linking BV with post cesarean delivery endometritis, reported an increased hazard of endometritis[27].

Surgical site infections comprise also spread of bacteria from lower genital organs to the uterus[28]. Surgical sites include the endomyometrium, incised at the time of CS, and BV microorganisms have commonly been isolated from these sites in women with surgical site infections[26,29].

First-generation cephalosporin is recently given prior to skin incision, however this may not provide optimal anaerobic coverage[30].

BV diagnosis is fast , cheap with using microscopy or available point-of-care testing. Vaginal discharge is a famous problem in gestation and could occur in around half of ladies[33].

Screening women for BV prior to CS may allow for its preoperative management by effective treatment options, reducing the prevalence of vaginal anaerobes, which could contribute to a substantial reduction of postoperative infections in a safe and cost-effective manner[31,32].

In order to decrease the possibility of vaginal cuff infection post hysterectomy , it is advised to do a screening and treatment for BV preoperatively[34,35] but guidelines do not currently advise routine screening or treatment of BV in females during pregnancy[36,37].

Many large studies to date focus on evaluating the hazard of preterm delivery in pregnant ladies with BV, though evidence is still unreliable with a shortage of data on the value of of screening and treating BV in gestation[38-44].

AIM OF THE STUDY

We aim in this study to asses if screening then subsequent treatment of BV at CS significantly reduces infection rate, with the intention to recommend or rebuke routine screening and treatment for all patients planning a CS late pregnancy or during cesarean delivery.

PATIENTS AND METHODS

Ethical committee approval was obtained before initiating women enrolment. The study was made at Obstetrics and Gynecology department, Cairo University. This hospital, one of the largest regional tertiary obstetric centers in Egypt, serves a largely high-risk, low income obstetric population. The study population consisted of 150 eligible pregnant women who were admitted in the labour or obstetric ward and underwent elective or emergency CS from December 2019 to February 2021.

Women were eligible for randomization if they were to undergo a cesarean delivery at or beyond 37 weeks' gestation with a singleton pregnancy and were tested positive to BV. BV was diagnosed from a Gram's stain-based evaluation of vaginal bacterial morphotypes using the Nugent score, where a score of seven to ten considered diagnostic (Table 1)[47].

Exclusion criteria were inability to give consent, obesity Type II or above, allergy to MTZ, eligibility for vaginal delivery, chorioamnionitis, other infections warranting postpartum antimicrobial use or fetal death. The exclusion criteria for our study population also included fever of ≥38°C within a week of CS, prolonged or obstructed labour, prolonged rupture of membranes (>18 hours), or any comorbid medical illness making the patient more susceptible to infections, i.e. during immunosuppressive therapy, heart disease, diabetes mellitus, retrovirus positive. All women fulfilling the study criteria were counselled to participate in our study after which an informed written consent was obtained from all participants.

Table 1: Nugent scoring criteria for the microscopic diagnosis of bacterial vaginitis

Number of Lactobacillus	Score	Number of Gardnerella/ Bacteroides	Score	Number of curved Gram-negative bacilli	Score	N score
≥30	0	0	0	0	0	0
5-20	1	<1	1	<1	1	3
1-4	2	1-4	2	1-4	1	5
<1	3	5-20	3	5-20	2	8
0	4	≥30	4	≥30	2	10

N score, sum of the scores for the presence/absence of Lactobacillus, Gardnerella/Bacteroides, and curved Gram-negative bacilli.

The clinically indistinguishable MTZ tablets and placebo tablets were prepared by the hospital pharmacy. The randomization order was generated through a computer program (Microsoft Excel 2016 program) and the medications maintained in serially numbered sealed bags in the labour and delivery area. The residents were available round the clock. Each envelope was opened, in sequential order, and were given to each candidate based on their respective allocation group. The identity of the study medication was concealed using uniformly packed opaque envelopes

The women were randomized into either of the two arms. The study arm "Group A" participants received 500gm MTZ twice daily for one week, starting 6hrs following CS, whereas the control arm "Group B" participants received one placebo tablet twice daily for one week, 6hrs following CS.

Each group comprised 75 pregnant women, meeting the selection criteria. Based on previously published data collected from the literature, we estimated that a clinically significant effect of 15% or more for reduction in postpartum endometritis would be of interest. Assuming postpartum endometritis rate in the control group and the intervention group of 15% and 7% respectively, with a two-sided significance of 0.05 and a power of 0.8, we calculated a sample size of 70 patients in each arm. Factoring loss to follow up, a total of 150 patients would be required, with 75 patients in each arm.

The CS was performed by an assistant lecturer / resident according to routine protocol. All patients received one prophylactic dose of cefazolin, a first-generation cephalosporin, immediately before skin incision. Both groups received similar postoperative care. On postoperative day 2, occlusive dressing applied at the time of surgery was changed, the wound was assessed, and the findings were recorded. All women were asked to return for stitch removal after one week where a test of cure for BV was also performed. The next follow-up was done on the fourth week.

The primary study outcome was post cesarean endometritis, defined as an oral temperature of 38C or greater on any two postoperative days (excluding the first 24 hours after delivery). In addition, the diagnosis required at least one of the following signs: uterine tenderness to palpation or persistent offensive lochia. The other maternal outcome assessed was the presence of wound infection. Wound infection was diagnosed when a wound drained purulent material or serosanguineous fluid, associated with induration, warmth, and tenderness. Nausea, a frequent adverse effect from treatment was documented. Neonatal outcomes including Apgar score less than seven at five minutes and the need for admission to the neonatal intensive care unit were obtained by reviewing each newborn's medical record.

STATISTICAL ANALYSIS

Data were statistically analysed in terms of mean and standard deviation, frequencies (number of cases) and percentages when appropriate. Comparison between groups was done using Chi- Square test in the cross tabulation. *P values* less than 0.05 were considered statistically significant. Statistical analysis was performed with the help of GraphPad prism, Version 9.1.2 (GraphPad Software, Inc. USA).

RESULTS

During the study period, 150 patients undergoing CS after 37 weeks' gestation and screened positive for BV were randomized. These represented 37.4% of a total of 401 patients screened for BV that were approached in this study that fit the inclusion criteria.

Of these, eight were excluded from statistical analysis for unknown infection morbidity status due to loss to follow up, leaving 142 women for analysis. Of those that were given treatment for BV, 66 women (91.7%) had a negative test for BV at one week.

Baseline maternal characteristics are shown in Table 2. The type of caesarean delivery, type of anesthesia and surgeon grade is shown in (Table 3).

In this study, treatment of BV was found to be significantly associated with the reduction of post cesarean endometritis (*P value = 0.0121, (cOR = 0.2834; 95% CI*=[0.2228 to 0.8627]). However, the situation was different regarding wound infection incidence. No significant difference was recognized between the treatment and control groups (*P value = 0.2048*). Patients were managed with broad spectrum antibiotics and wound dressing (Table 4 and Figure 1).

No statistically significant difference was observed between the two groups regarding previously known confounding factors such as age under 25 age, BMI over 30, emergency cesarean delivery and junior grade surgeon which could have otherwise altered the significance of the results (Table 5 and Figure 2).

Side-effects such as nausea were noticed among six (8%) of the 75 treated women. There were no significant differences between the two groups with respect to low Apgar scores or neonatal intensive care unit length of stay (Table 6).

Table 2: Demographic Characteristics

	Treatment group (n= 75)	Control group (n=75)	*P value*
Age (y)	27.8 ±5.6	27.3 ±6.1	0.7708
BMI	29,8 ±2.94	30.1 ±2.7	0.6815
Primigravida/Previous CS Previous 2 CS or more	48 (64) 27(36)	46(61.3) 29 (38.7)	0.8660
Gestational Age (wks)	38.7±0.90.9	38.8±0.9	

BMI = body mass index. wks = weeks. y = years

Data are presented as mean :± standard deviation or n (%). *P* > .05 for all comparisons

Table 3: Cesarean Delivery Characteristics

	Treatment group (n= 75)	Control group (n=75)	*P value*
Indication			
Malpresentation	14 (18.7)	12 (16)	
Arrest of descent/dilatation	14 (18.7)	10 (13.3)	
Elective repeat CS	32 (42.7)	36 (48)	
FHR abnormality	9 (12)	8 (10.7)	
Failed induction	2 (2.7)	4 (5.3)	
Placenta Previa	2 (2.7)	3 (4)	
Other	2 (2.7)	2 (2.7)	
Type of Anaesthesia			
General	9 (12)	13 (17.3)	0.4894
Spinal	66 (88)	62 (82.7)	
Type of CS			
Elective	45 (60)	44 (58.7)	>0.9999
Emergency	30 (40)	31 (41.3)	
Grade of surgeon			
Junior	54 (72)	57 (76)	0.7100
Senior	21 (28)	18 (24)	

FHR = fetal heart rate; Data are presented as n (%). P > .05 for all comparisons

Table 4: Primary Outcomes

	Treatment group (n= 73)	Control group (n=70)	*P value*
Endometritis	6 (8.2)	17 (24.3)	0.0121*
Wound infections	4 (5.5)	5 (7.1)	0.2048

Data are presented as n (%). *P* > .05 for all comparisons

Table 5: Confounding factors (factors that would likely increase outcome rates (endometritis/wound infection)

	Treatment group (n= 73)	Control group (n=70)	*P value*
Age <25	30 (40)	28 (37.3)	
BMI >30	42 (56)	41 (54.7)	
Parity 2 / more	27 (36)	29 (38.7)	0.9941
Emergency CS	30 (40)	31 (41.3)	
Junior grade urgeon	54 (72)	57 (76)	

Data are presented as n (%). *P* > .05 for all comparisons.

Table 6: Neonatal Characteristics

	Treatment group (n= 75)	Placebo group (n=75)	*P value*
Apgar score <7 at 5 min	3 (4)	5 (6.7)	0.4904
NICU	2 (2.7)	3 (4)	0.6786

NICU = neonatal intensive care unit.
Data are presented as n (%). $P > .05$ for all comparisons

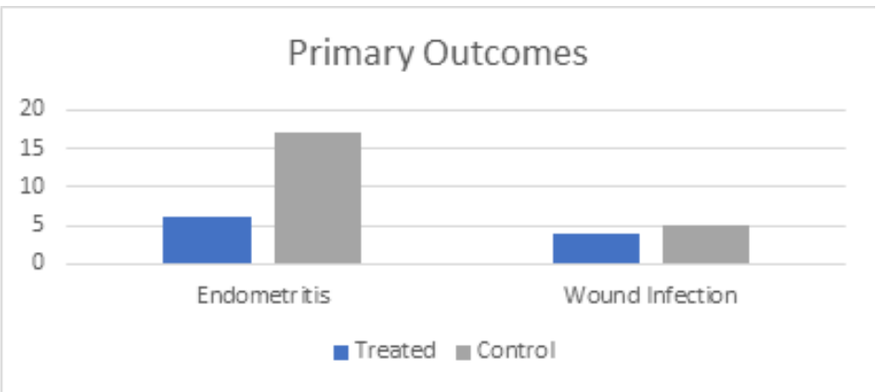

Fig. 1: Primary Outcomes

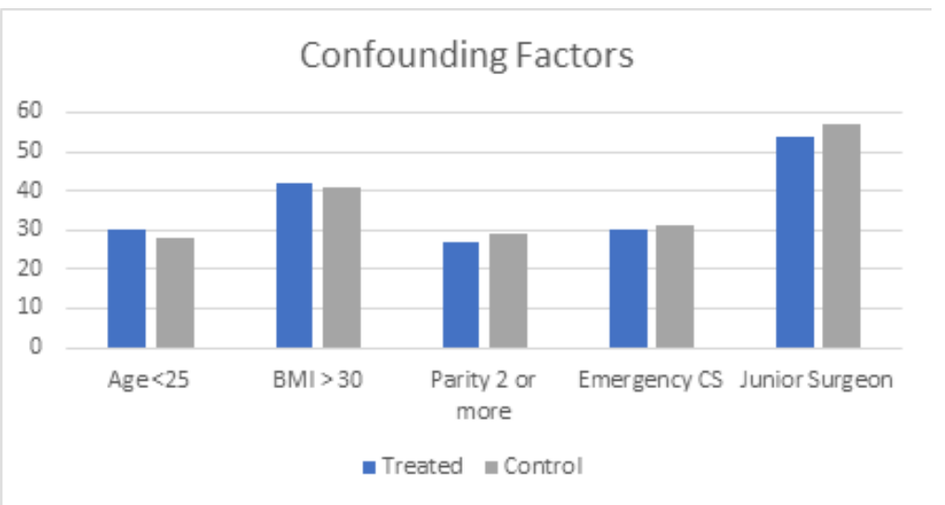

Fig. 2: Confounding Factors

DISCUSSION

To reach a cohort of 150 BV positive women, 401 pregnant women, who met the inclusion criteria, were tested, resulting in a 37.4% BV prevalence rate in our study. This prevalence rate is higher than the range found among women of reproductive age group worldwide (23 to 29%), though higher variations have been known to exist in women of low income households and among different races and ethnicities[1-3].

Treatment of BV was found, in this study, to be significantly associated with the reduction of post cesarean endometritis, but not with the reduction of wound infection incidence. A Various researches showed the relationship between BV and preterm labour[44-46]. Several have explored the relationship between MTZ, known to be effective against BV, and risk of post caesarean infection[30,48-53]. Only one to our knowledge has been focused on the relationship of BV positive women and the risk of endometritis and wound infection, prior to CS[26].

In accordance to our results, D H Watts *et al*., found BV to be an substantial risk for postpartum endometritis post CS[26].

In other studies, exploring the effect of MTZ on post caesarean infections, Pitt *et al* found the preoperative intake of intravaginal MTZ gel to reduce the hazard of post cesarean endometritis by 58%[30].

In another study, perioperative ampicillin plus MTZ reduced the percentage of infections for ladies undergoing CS (38% vs 15%) in comparison to perioperative benzylpenicillin in treating BV[47].

In two similar randomized clinical trials, Gerstner *et al.* and Ruiz-Moreno *et al.* showed that MTZ intravenously administered, significantly decreased post cesarean endometritis, wound infection, and overall postoperative febrile morbidity[49,50].

In contrast, Gummerus, in a randomized, placebo-controlled trial, was incapable to demonstrate a marked decrease in infectious morbidity following the perioperative intravenous infusion of 500-mg MTZ[51].

A single dose of MTZ (500 mg) does not provide adequate anaerobic protection in prevention of endometritis. Two researches studied the effectiveness of rectal MTZ in decreasing post cesarean endometritis, they showed a marked decrease in hospital stay, febrile morbidity, and wound infection[52].

In a study made by Rosler *et al.*, they reported that there was no decrease in post cesarean infectious morbidity after rectal MTZ[53].

In a larger research , antibiotics received preoperatively for BV decreased the incidence of severe postoperative infections by 73% in ladies with BV[54].

These studies are not consistent regarding the dose, frequency, route of administration or timing of administration of MTZ (preoperative versus postoperative). In addition, the results though most in agreement with the findings in our study regarding efficacy against post cesarean endometritis, still have mixed findings regarding the efficacy of MTZ against post cesarean wound infections.

Regarding the many studies demonstrating the association of BV with adverse obstetrical outcomes, the focus of the studies was the diagnosis of BV infection before 16 weeks gestation and its association with an increased risk for preterm birth. Of the secondary outcomes was the findings of an increased risk for postpartum endometritis[45, 55-58].

This study has several strengths, to the best of our knowledge, this is the first prospective randomized research, recently conducted, that aims at evaluating the influence of treatment of BV positive pregnant women, late in pregnancy, on post cesarean infections. We used the current gold standard Nugent score[47], for finding and diagnosis of BV, and followed latest guidelines to use agreed effective treatment against BV[59-64]. There was similar demographic and pregnancy characteristics among those, in both the treatment and control groups, who subsequently developed post cesarean infections. No statistically significant difference found between both groups regarding previously known confounders, that could otherwise significantly change the results of our analysis.

Our study has some limitations. This is a single-centre research that involved all ladies in a single Department of Gynecology and Obstetrics. Additionally, the study is conducted in a tertiary maternity care unit, serving mainly low socio-economic women or those with complicated pregnancies; therefore, the population represented may not be exhaustively representative. Our study has only evaluated the efficacy of the multidose administration of oral MTZ, six hours following caesarean delivery. More research is needed to study and compare the efficacy of different types, doses, routes, frequencies and timing of BV medication administration in relation to CS. A larger, multicentric study is recommended .

CONCLUSION

The majority of women with BV are asymptomatic[11] and are at increased risk of adverse infectious complications following cesarean delivery. The diagnosis of BV is quick, simple, and inexpensive. The ACOG guidelines for the avoidance of infection post gynecological operations,

have advised that screening and treatment for BV preoperatively could be made before hysterectomy[34].

Given the results of our study, which is in agreement to same evidence associating BV with intrapartum chorioamnionitis and endometritis post CS , BV screening late in pregnancy, possibly at the 35-37 week and group B streptococcus culture visit, or immediately following CS, and treatment of those positively screened could be made.

With none existence of guidelines from professional societies , preoperative screening and treatment of BV could cause more reduction in surgical site infections.

CONFLICT OF INTERESTS

There are no conflicts of interest

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