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Research Article

THE OUTCOME OF CEFUROXIME VERSUS METRONIDAZOLE AS SURGICAL PROPHYLAXIS FOR HYSTERECTOMY - A RETROSPECTIVE STUDY IN A SOUTH INDIAN SETUP

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ABSTRACT

Objective: To evaluate the outcome of cefuroxime and metronidazole as surgical prophylactic measure for hysterectomy procedures in a South Indian setup.

Methods: A retrospective study was conducted in 60 women who underwent hysterectomy and was prescribed metronidazole and cefuroxime. The data regarding demographic details, presenting complaints, parity, obstetrics history, diagnosis, and need for hysterectomy were evaluated.

Results: A total of 148 women admitted with hysterectomies performed were taken into consideration of which 68 were prescribed cefuroxime and metronidazole alone but 8 patients did not respond to treatment and were given other antibiotics, hence 60 patients formed the study population. The mean age was 20±05.29 years. Patients above 51 years were mostly seen. Uterovaginal prolapse was very commonly observed, anemia (mild=7) was the main risk factor found, cefuroxime was commonly prescribed compared to metronidazole, and febrile episodes were commonly noticed. One-way ANOVA revealed the F ratio to be 6.04, p value calculated as 0.06 significant at p≤0.10.

Conclusion: In our study, cefuroxime appeared to be effective in prophylaxis against infections. Metronidazole appeared to be ineffective compared to cefuroxime.

Keywords: Antibiotic, Surgical prophylaxis, Hysterectomy, Infections.

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INTRODUCTION

During the last years, a significant decrease in the mortality was observed followed by intra-abdominal infections due to the improvement of surgical techniques and approach to new antibiotic treatments. The intra-abdominal infections can be differentiated in three different categories. Mild infections should be treated promptly with surgical drainage and a short-term therapy with a wide range antibiotic including anaerobes (ampicillin/sulbactam, cefoxitin). Mild-moderate infections which are treated with a single drug which include anaerobes in its spectrum and severe infections require a more aggressive therapeutic approach with a combination treatment covering anaerobes (clindamycin, metronidazole), Gram-negative rods (ciprofloxacin, aminoglycosides), and Gram-positive cocci (penicillin, cephalosporin) including methicillin-resistant *Staphylococcus aureus* (MRSA) (glycopeptides) and/or vancomycin-resistant enterococci (linezolid). From surgical point of view, the control of intra-abdominal infections requires different procedures such as laparotomy, relaparotomy, or less frequently laparostomy (totally or partially open abdomen).

Background/rationale

Hysterectomy is the surgical removal of the uterus. It may also involve removal of the cervix, ovaries, fallopian tubes, and other surrounding structures; surgery is normally recommended when other treatment options are not available or have failed [1]. Sometimes, women express a desire to undergo an elective hysterectomy for any reason other than the resolution of reproductive system.

- Radical hysterectomy: Complete removal of the uterus, cervix, upper vagina, and parametrium indicated for cancer. Lymph nodes, ovaries, and fallopian tubes are also usually removed in this situation, such as in Wertheim's hysterectomy [2].
- Total hysterectomy: Complete removal of the uterus and cervix, with or without oophorectomy.
- Subtotal hysterectomy: Removal of the uterus, leaving the cervix *in situ.*

Hysterectomy can be performed in different ways. The oldest known technique is abdominal incision followed by vaginal (performing the hysterectomy through the vaginal canal), laparoscopic vaginal (with additional instruments inserted through a small hole, frequently close to the navel) techniques were developed.

Abdominal hysterectomy (AH)

AH transverse (pfannenstiel) incision is made through the abdominal wall, similar to the incision made for a cesarean section. AH is mostly done in cases with post cesarean delivery, where indication is cancer and complications are expected and surgical exploration is required.

Vaginal hysterectomy (VH)

VH is performed through the vaginal canal and has clear advantages over abdominal surgery such as fewer complications, shorter hospital stays, and shorter healing time.

Laparoscopic-assisted VH (LAVH)

LAVH begins with laparoscopy and completed with the final removal of the uterus (with or without removing the ovaries) via the vaginal canal.

Laparoscopic-assisted supracervical hysterectomy (LASH)

The "LASH" removes the uterus from the abdominal cavity via the laparoscopic ports without removing the cervix using a morcellator which cuts the uterus into small pieces.

Total laparoscopic hysterectomy (TLH)
TLH is performed with laparoscopes, starting at the top of the uterus, with a uterine manipulator. The entire uterus is disconnected from its attachments using long thin instruments through the "ports" and all tissues to be removed are passed through small abdominal incisions [3].

Surgical site infection (SSI) can be defined as the presence or multiplication of pathogenic organisms in a wound giving rise to local signs and symptoms such as heat, redness, pain and swelling, and also systemic signs of fever or raised leukocyte count. Infection in a surgical wound prevents healing as the edges of wound separate leading to abscess in deeper tissues. Wound infection occurs approximately in 3% of AH cases due to obesity, diabetes, immunodeficiency disorder, use of systemic corticosteroids, smoking, wound hematoma, and preexisting infection such as chorioamnionitis and pelvic inflammatory disease. Taking the form of either incisional abscess or wound cellulites present with erythema, though incisional abscess confers purulent drainage. It is recommended to give an antibiotic active against staphylococci and streptococci if possible vancomycin when there is a risk of MRSA. However, if the infection is clear and healthy granulation tissue is visible at the base of the wound, the edges of the incision may be rejoined by using butterfly stitches, staples or sutures [5]. Sexual intercourse is attainable after hysterectomy. Reconstructive surgery remains an option for women who have experienced benign and malignant conditions [6].

Drugs play an important role in improving human health to promote well-being. Therefore, judicious use of drugs, adequate knowledge, positive approach, and awareness toward the drug use are mandatory prerequisites for good health [7].

Metronidazole is used to treat a wide variety of infections caused by anaerobic bacteria and micro-organisms; commonly recommended to treat bacterial vaginosis. It is also prescribed before gynecological surgery and surgery on the intestines, to prevent infections. Metronidazole can safely be taken by people who are allergic to penicillin. The usual dose is metronidazole 500 mg/100 ml. Intravenous Infusion should be infused intravenously at an approximate rate of 5 ml/minute (or one bag infused over 20-60 minutes). Primarily for abdominal (especially colorectal) and gynecological surgery. The duration of antibiotic prophylaxis should be short, limited to post-operative period (24 h not more than 48 h).

Adults	Intra-venous injection of single dose of 1000-1500 mg, 30-60 minutes preoperatively or alternatively 500 mg immediately before, during or after operation, then 500 mg 8 hourly

Anaerobic infections
Intravenous route is to be used initially if patient symptoms preclude oral therapy. Various schedules are possible.

Adults	1000-1500 mg daily as a single dose or alternatively 500 mg every 8 hrs

Treatment for 7-10 days should be adequate for most patients but the physician might opt to prolong treatment depending on clinical and bacteriological assessments as to eradicate infection from sites which cannot be drained or are prone to recontamination by anaerobic pathogens from the gut, oropharynx, or genital tract.

Cefuroxime is an enteral second-generation cephalosporin antibiotic, which crosses the blood-brain barrier less susceptible to beta-lactamase and greater activity against *Hemophilus influenza*, *Neisseria gonorrhea*, and Lyme disease.

Cefuroxime sodium for injection is implied to treat certain infections as obstetric and gynecological infections before any infecting organism has been identified.

Most of the infections will respond to 750 mg three times daily by intramuscular or intravenous injection where as in severe infections the dose is elevated to 1.5 g 3 times daily intravenously. The frequency of dosage may rise to 6-hourly injections, intramuscular or intravenous, rendering to total daily dose of 3-6 g.

METHODS

Study period
The study was conducted over a period of 3-month from November 2015 to February 2016.

Study design
Pharmacoepidemiological studies help in minimizing the intrinsic risk of drug use in by validating a profile of drug consumption, by assessing the existing health services, and by scrutinizing interventional measures [8]. The present retrospective study was conducted in Antenatal Out Patient Department of Obstetrics and Gynaecology of Owaisi Hospital and Research Centre to evaluate the outcome of cefuroxime and metronidazole when treated as antibiotic prophylaxis for hysterectomy procedures.

Ethics committee approval
The Institutional Ethics Committee permission was not required as retrospective study was conducted with no direct contact with the study population.

Patient data collection form
The demographic profile along with parity, present and past history of associated medical, surgical, gynecological and obstetrical illness, presenting complaints of the patient pertaining to main indications leading to hysterectomy procedures were recorded from the case sheets of the patients admitted in female ward for hysterectomy procedure. Advantages and disadvantages as shown in Fig 1 was considered to perform any hysterectomy procedure keeping in mind the condition of the patient.

Plan of work
A study form for each patient was completed at discharge by gynecological surgeon. Infections with subsequent discharge were documented on a separate form at the outpatient clinic of the same hospital. Contributing factor for wound infection was antibiotic usage and gushing being imperative, for urinary tract infection (UTI) was a single bacterial growth exceeding 10^5 bacteria/ml, and a febrile event was a clinically relevant fever for unknown reason with axillary temperature ≥38°C. Late-inceptive complications included pelvic infections, presented as an infected hematoma or abscess. The common dosages were intravenous cefuroxime 1.5 g and metronidazole 0.5 g at induction, administration on the previous evening was rare, most commonly with doses of 2 and 0.5 g, the separate and interactive effects of cefuroxime and metronidazole on total infections was analyzed.

Inclusion criteria
All hospitalized women in Obstetrics and Gynecology Department with the need for hysterectomy were enrolled via convenience sampling greater than or equal to 30 years of age, with or without comorbidities after screening and monitoring and treated with either cefuroxime or metronidazole were included in the study.

Exclusion criteria
Patients diagnosed with acute and chronic medical conditions other than requirement for hysterectomy procedure, patients prescribed with metronidazole in combination with cefuroxime and patients given other antibiotics or combination of other antibiotics were excluded from the study.

Statistical analysis
Statistical analysis was performed using descriptive statistics. Data were collected, tabulated, and graphs were designed in Excel-2007. Continuous variables were presented as mean values±standard

deviation (SD) and categorical variables were presented as percentages. One-way ANOVA was performed to obtain p value significant at p≤0.10. Chi-square test for two population proportions was performed at p≤0.10.

RESULTS

The majority of the patients belonged to above 51 years (43.3%) followed by 16 (26.6%), 18 (30%) patients in the age group 30-40 and 41-50, respectively.

The mean age was 20±05.29 years (mean age=20, SD=5.29, variance=28, age=mean±SD=20±5.29).

The main indication for admission to hysterectomy procedure was uterovaginal prolapse found in 12 (20%) patients.

The associated risk factors were anemia contributing to 23.3% in 14 patients, other risk factors observed were ischemic heart disease in 3 (5%), diabetes mellitus (DM) in 6 (10%), hypertension (HTN) in 7 (11.6%), hypothyroidism (HT) in 5 (8.33%), epilepsy in 3 (5%), hepatitis B surface antigen (HbsAg+) in 2 (3.33%), renal calculi in 4 (6.66%), and rheumatoid arthritis (RA) in 1 (1.66) patients, respectively.

Mild anemia was noted in 7 (11.6%) patients, whereas moderate in 5 (8.33%) and severe in 2 (3.33%) patients, respectively.

The use of metronidazole and cefuroxime was mostly seen in AH accounting for 12 (46.15%) and 14 (41.17%) prescriptions, respectively, cefuroxime was mostly prescribed in 34 (56.6%) and metronidazole in 26 (43.3%) patients as shown in Table 1; the Chi-square test for two population proportions was found to be 1.46, p value 0.07 significant at p≤0.10 (One-way ANOVA reveals, F ratio=6.04724 p=0.069758 significant at p<0.10).

The infection complications noted were febrile episodes followed by wound infection, pelvic infection, and wound dehiscence, UTI in abdominal, laparoscopic and vaginal hysterectomies respectively. Chi-square for 2 population proportions: Z=1.4606, p=0.07215 (p<0.10). The proportion of yes or no response for observation 1 (cefuroxime) is 0.567 whereas the proportion of observation 2 (metronidazole) is 0.433. One-way ANOVA revealed the F ratio to be 6.04, p value calculated as 0.06 significant at p≤0.10.

Drugs other than antibiotics are majority of them being multivitamins

A total of 148 women admitted with hysterectomies performed were taken into consideration of which 68 were prescribed cefuroxime and metronidazole alone, but 8 patients did not respond to treatment and were given other antibiotics, hence 60 patients formed the study population.

As the study was retrospective, the data were recorded from the case sheets of the patients admitted in female ward for hysterectomy procedure. The sociodemographic characteristics are shown in Table 2. The mean age was 20±05.29 years. The majority of the patients belonged to above 51 years (43.3%) followed by 16 (26.6%), 18 (30%) patients in the age group 30-40 and 41-50, respectively, as shown in Fig. 2. The main indication for admission to hysterectomy procedure was uterovaginal prolapse found in 12 (20%) patients followed by as depicted in Fig. 3. The associated risk factors were Anemia contributing to 23.3% in 14 patients, other risk factors observed were IHD in 3 (5%), DM in 6(10%), HTN in 7 (11.6%), HT in 5 (8.33%), Epilepsy in 3 (5%), HbsAg+ in 2 (3.33%), Renal Calculi in 4 (6.66%) and RA in 1 (1.66) patients, respectively, as illustrated in Fig. 4. Anemia was categorized into mild, moderate, severe and non-anemic patients. Anemia was classified according to WHO classification - severe anemia (<7 g/dl), moderate anemia (7-8.9 g/dl), and mild anemia (9-10.9 g/dl) [12].

Table 1: Infection complications by antibiotic prophylaxis

Hysterectomy procedures and use of antibiotics	Febrile episodes	Wound infection	Pelvic infection	Wound dehiscence	UTI	Total infections
Abdominal hysterectomy	6	3	2	1	2	14
Cefuroxime	40	20	15	7	14	96
Metronidazole	20	10	5	3	6	44
Laparoscopic hysterectomy	4	2	2	0	1	9
Cefuroxime	30	14	8	0	2	54
Metronidazole	10	6	12	0	8	36
Vaginal hysterectomy	3	2	3	0	2	10
Cefuroxime	20	16	15	0	12	63
Metronidazole	10	4	15	0	8	37

Technique	Benefits	Disadvantages
Abdominal hysterectomy	No limitation by the size of the uterus Combination with reduction and incontinence surgery possible	Longest duration of hospital treatment Highest rate of complications Longest recovery period
Vaginal hysterectomy	Shortest operation time Short recovery period Combination with reduction operations are possible	Limitation by the size of the uterus and previous surgery Highest blood loss Limited ability to evaluate the fallopian tubes and ovaries
Laparoscopic supracervical hysterectomy	Low risk of complication Less blood loss Short inpatient treatment duration	10-17% of patients continue to have minimal menstrual bleeding
Laparoscopic-assisted vaginal hysterectomy	Possible even with larger uterus and after previous surgery Combination with reduction operations are possible	Long operation time High instrumental costs by changing the access path
Total laparoscopic hysterectomy	Less blood loss Short inpatient treatment duration	None to date

Figure 1: Advantages and disadvantages of different hysterectomy techniques [4]

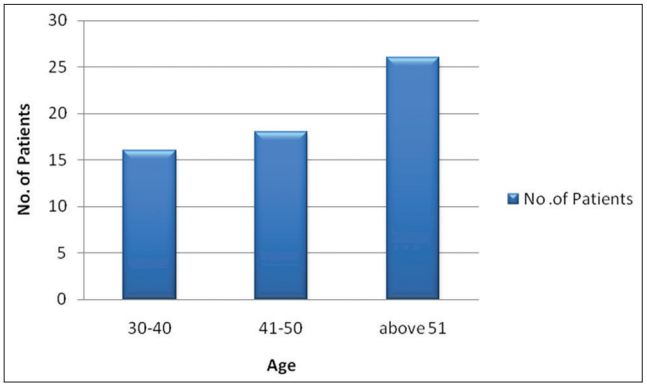

Fig. 2: Age

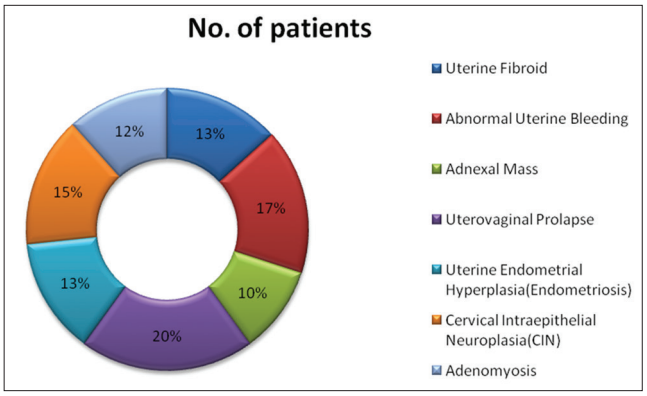

Fig. 3: Indications for hysterectomy

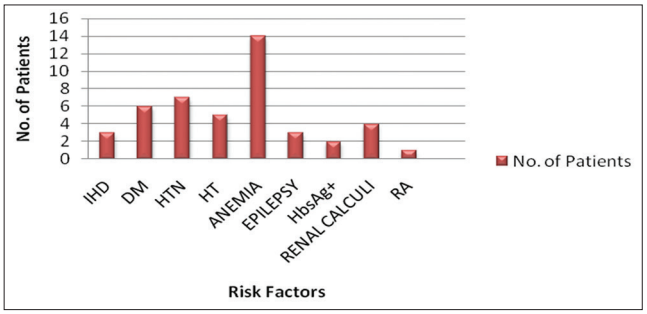

Fig. 4: Associated risk factors

Hemoglobin level more than 11 g/dl was classified as non-anemic. Mild anemia was noted in 7 (11.6%) patients, whereas moderate in 5 (8.33%) and severe in 2 (3.33%) patients, respectively, as shown in Fig. 5. Cefuroxime was prescribed in 34 (56.6%) patients compared to metronidazole which was prescribed in 26 (43.3%) patients. The use of metronidazole and cefuroxime was mostly seen in AH accounting for 12 (46.15%) and 14 (41.17%) prescriptions, respectively, cefuroxime was mostly prescribed in 34 (56.6%) and metronidazole in 26 (43.3%) patients as shown in Table 1; the Chi-square test for two population proportions was found to be 1.46, p value 0.07 significant at p≤0.10. The infection complications noted were febrile episodes followed by wound infection, pelvic infection, and wound dehiscence, UTI in abdominal, laparoscopic and vaginal hysterectomies respectively as shown in Table 3. One-way ANOVA revealed the F ratio to be 6.04, p value calculated as 0.06 significant at p≤0.10. Drugs other than antibiotics are illustrated in Table 4 majority of them being multivitamins.

Likewise taking hysterectomies (LH/AH/VH) into consideration, AH was most commonly preferred depending on the condition of the patients, age, indication and associated risk factors followed by laparoscopic hysterectomies (LH/LAVH), the least was VH performed in our hospital setup.

Table 2: Sociodemographic characteristics of patients

Characteristics	AH	LH/LAVH	VH	No. of patients
Age				
30-40	7	6	3	16
41-50	8	5	5	18
Above 51	11	9	6	26
Indications for hysterectomy				
Uterine fibroid	4	3	1	8
Abnormal uterine bleeding	3	3	4	10
Adnexal mass	2	2	2	6
Uterovaginal prolapsed	4	1	7	12
Uterine endometrial hyperplasia (endometriosis)	3	3	2	8
CIN	3	4	2	9
Adenomyosis	2	3	2	7
Associated risk factors				
IHD	3	0	0	3
DM	4	0	2	6
HTN	3	0	4	7
HT	3	0	2	5
Anemia	8	0	6	14
Epilepsy	2	0	1	3
HbsAg+	1	0	1	2
Renal calculi	2	0	2	4
RA	1	0	0	1
Antibiotics for prophylaxis				
Cefuroxime	14	8	12	34
Metronidazole	12	6	8	26
Infection complications				
Febrile episodes	6	4	3	13
Wound infection	3	2	2	7
Pelvic infection	2	2	3	7
Wound dehiscence	1	0	0	1
UTI	2	1	2	5

AH: Abdominal hysterectomy, LH: Laparoscopic hysterectomy, LAVH: Laparoscopic abdominal vaginal hysterectomy, VH: Vaginal hysterectomy, CIN: Cervical intraepithelial neuroplasia, IHD: Ischemic heart disease, DM: Diabetes mellitus, HTN: Hypertension, HT: Hypothyroidism, RA: Rheumatoid arthritis, UTI: Urinary tract infection, HbsAg: Hepatitis B surface antigen

Table 3: Independent effects of cefuroxime and metronidazole prophylaxis

Hysterectomies	Cefuroxime use in no. of patients (%)	Metronidazole use in no. of patients (%)
Abdominal	14 (41.17)	12 (46.15)
Laparoscopic	8 (23.52)	6 (23.07)
Vaginal	12 (35.29)	8 (30.76)

In our study, we recorded only patients treated with cefuroxime and metronidazole alone. Among which cefuroxime was most commonly prescribed in our hospital followed by less commonly recommended metronidazole even though it had wound healing activity besides acting as antimicrobial (antiprotozoal) antibiotic. Hence, our study revealed that cefuroxime was more effective than metronidazole.

DISCUSSION

Infections are responsible for a significant proportion of post-operative morbidity. Hysterectomy is a clean-contaminated operation, and post-operative infections are polymicrobial, as vaginal bacteria inoculate the surgical site and the majority of post-operative pelvic infections involve anaerobic bacteria [9]. The UK guidelines provide no recommendations separately for VH, and for AH they state, "There

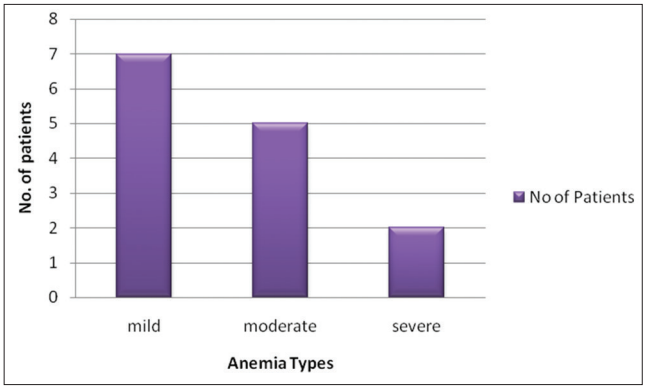

Fig. 5: Anemia classifications

Table 4: Drugs other than antibiotics

Drugs	Number of prescriptions
Alimentary tract drugs	
Pantoprazole	10
Rabeprazole	12
Lactulose	5
Bisacodyl	6
Ondansetron	12
Cardiovascular drugs	
Alphadopa	2
Atenolol	2
Telmisartan	3
Nervous system	
Paracetamol	18
Phenytoin sodium	3
Diclofenac sodium	26
Tramadol hydrochloride	24
Blood and blood forming agents	
Iron supplements	6
Iron dextrose/sucrose injectables	8
Multivitamins	60
Antithyroid drugs	
Levothyroxine	5
Drugs acting on uterus	
Isoxsuprine	24
Hypoglycemic agents	
Metformin	5
Insulin	2
Antimicrobial	
Metronidazole	26
Cefuroxime	34
Renal system	
SYP Citralka	8
Ciprofloxacin	12

is insufficient evidence that prophylactic administration of antibiotics results in fewer SSIs" [10].

Nevertheless, in the analysis, we controlled for many important factors affecting infection morbidity, such as age [11-14] obesity [11,14-16] and hemorrhage [17]. The reasons why drug choice for some patients was widened to cover the anti-aerobic spectrum, with a combination involving metronidazole in preference to cefuroxime alone, also remain unknown. A great deal of post-operative morbidity arises from the vaginal flora, which places hysterectomy in the category of clean-contaminated surgery. In most cases, regular clean-contaminated surgery was carried out: Only 7 of the 60 hysterectomy procedures performed caused pelvic infection, and could be categorized as contaminated.

Cefuroxime had an independent risk-reductive effect for total infections in all three types of hysterectomy compared with metronidazole alone as the independent effect of metronidazole in reducing the risk of total infections was insignificant.

Metronidazole has long been the drug of choice due to its low cost and positive results to cure infections but it can be more efficacious as few studies with other antimicrobial agents, does not support for the superiority of metronidazole compared to cephalosporins, cefuroxime, as a second-generation drug, has a wider spectrum than metronidazole, the classic antimicrobial agent against anaerobes. Hence, cefuroxime appears to be a sufficient prophylactic agent.

Limitation

A limitation of our evaluation is the lack of randomization. Therefore, unintentional bias may have occurred: A single-drug regime may have been chosen for the less challenging cases. The first-generation cephalosporins are as effective as cefuroxime in the prevention of infections with hysterectomy, arising from the anaerobic polymicrobial flora, remains uncertain. Our study, however, examined prophylactic use of antibiotics, either anaerobic bacteria resistant to cefuroxime are a minor issue or the eradication of other bacteria is sufficient to prevent infections: Anaerobic bacteria seem to require the presence of other pathogenic bacteria to initiate infection.

CONCLUSION

In our study, cefuroxime seemed to be effective in prophylaxis against postoperative infections, but metronidazole appeared inefficacious. The growing concern about long-term consequences of early life exposures to antibiotics requires new strategies for risk stratification after surgeries and the deployment of new approaches. Long-term studies of current prescribing practices of antibiotics need to be contrivanced so that the extent of the problem can be achieved. Hence, cefuroxime appears to be a sufficient prophylactic agent.

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