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PROJECT PREVENT: a randomized controlled trial of preoperative vaginal metronidazole to decrease patient issues and infections after hysterectomy

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ABSTRACT

Objectives To evaluate if vaginal metronidazole for 5 days before hysterectomy decreases postoperative infections and patient issues.

Design This randomized trial compared vaginal metronidazole for 5 days before a scheduled hysterectomy to no intervention. Sample size calculation was based on a 20% difference in issues and infection (30% incidence and 10% in the intervention arm) with 80% power and an alpha error of 0.05 and indicated 62 subjects needed in each arm.

Setting Outpatient gynecology clinics at a single academic institution.

Participants 154 subjects were screened for eligibility between July 2020 and September 2022. 133 underwent hysterectomy including 68 subjects (51.1%) randomized to the metronidazole and 65 (48.9%) controls. Overall, the population was racially and ethnically diverse. There was no significant difference in characteristics between the two groups.

Interventions Vaginal metronidazole for 5 days before hysterectomy.

Main outcome measures Postoperative patient issues and documented postoperative infections at 4–8 weeks after surgery.

Results There was no difference in the composite rate of patient-reported issues and/or documented postoperative infection (53/133 (39.8%) with no difference between groups (29/68 (42.6%) vs 24/65 (36.9%), p=0.50). There was no difference in patient-reported issues which was 51/133 (38.3%) with no difference between groups (28/68 (41.2%) vs 23/65 (33.8%), p=0.49) or in documented infections with a rate of 25/133 (18.8%) with no significant difference between groups (15/68 (22.0%) vs 10/65 (15.4%), p=0.33). In the intervention arm, the compliance rate was 73.5% for all 5 days of vaginal metronidazole, and a per-protocol analysis was performed which resulted in no significant difference between groups.

Conclusions There is insufficient evidence to suggest a significant benefit of preoperative vaginal metronidazole to prevent surgical site infections and postoperative patient issues in patients undergoing hysterectomy.

Trial registration number ClinicalTrials.gov, NCT04478617.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Infection or patient-reported issues of infection with a subsequent use of healthcare resources can become an economic burden to our healthcare system and negatively affect patient satisfaction. Metronidazole vaginal gel is an inexpensive and well-tolerated antibiotic that covers much of the polymicrobial flora in the vagina.

WHAT THIS STUDY ADDS

⇒ This study evaluates the efficacy of a preoperative course of vaginal metronidazole in decreasing postoperative issues and/or infections in patients undergoing scheduled hysterectomy.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ While well tolerated, preoperative vaginal metronidazole gel was not effective at reducing postoperative infection or associated patient issues compared with cephalosporin alone. The study findings underscore the importance of continued research into interventions that improve both objective postoperative infection rates as well as patient-reported symptoms.

INTRODUCTION

Although surgical site infection rates for hysterectomy range from 1% to 10% depending on the patient population, route of hysterectomy and risk factors, the frequency of reported issues of presumed infection post hysterectomy may be higher.[1] Patient-reported issues whether they represent verified infection or not are still worrisome for the patient and may cause additional testing and office visits. These medical interventions consume resources in our constrained healthcare system. Despite accepted standards of chlorhexidine wipes, standard intravenous prophylaxis with a cephalosporin, and frequent use of incisional, skin, and vaginal preparation with chlorhexidine or betadine, additional

prophylactic strategies to improve patient issues or infection rates would be beneficial.[2] Post-hysterectomy infections including pelvic abscess formation can cause significant patient morbidity including hospitalization for intravenous antibiotics, cuff dehiscence, delayed wound healing, and interventions such as interventional radiology drainage or return to the operating room.

Most pelvic and vaginal infections post-hysterectomy are polymicrobial including anaerobic bacteria which would presume that the addition of metronidazole may be beneficial. Vaginal metronidazole is a standard-of-care antibiotic often used to treat infections such as bacterial vaginosis typically for a 5 day course.[3] To our knowledge, current data evaluating the efficacy of metronidazole as an adjunct to hysterectomy antibiotic prophylaxis stems mainly from non-randomized studies.[4–6]

Infection or patient-reported issues of infection with a subsequent use of healthcare resources can become an economic burden to our healthcare system and negatively affects patient satisfaction. Therefore, the primary aim of this study was to evaluate if vaginal metronidazole use for 5 days prior to scheduled hysterectomy, decreased postoperative issues and/or infections.

METHODS

This randomized, open-label clinical trial consisted of a treatment group using metronidazole 0.75% gel (MetroGel or Vandazole) per vagina for five nights prior to the scheduled hysterectomy along with standard of care prophylactic intravenous antibiotics at the start of the procedure compared with a control group which underwent standard of care alone. Vaginal metronidazole, rather than intravenous antibiotic, was used due to the fact that vaginal dosing would allow for local administration to a surgical site and perhaps treat asymptomatic bacterial vaginosis and/or vaginitis prior to hysterectomy. We selected a 5-day treatment duration based on a study by Avila *et al*.[4] The control group did not receive metronidazole and was followed for data collection. All subjects were followed for 8 weeks postoperatively. Additionally, this trial was registered with www.clinicaltrials.gov prior to enrollment of the first subject. Consolidated Standards of Reporting Trials reporting guidelines were used.[7] The lead author (TP) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as originally planned and registered have been explained.

Participants were recruited from gynecological oncology, urogynecology, minimally invasive gynecologic surgery, and general gynecology outpatient clinics at the time that they were evaluated for a hysterectomy procedure for benign and malignant indications. Eligible participants included candidates who were 18 years or older scheduled for subtotal or total hysterectomy. The approach to hysterectomy included laparoscopic, robotic, open, and vaginal. Participants were excluded based on known hypersensitivity to metronidazole, active bacterial vaginosis at the time of consent, or if a hysterectomy was scheduled within 5 days from the date of consent.

The randomization sequence was created using an online platform and consisted of 25 blocks with a 1:1 distribution.[8] The randomization scheme was maintained by the research team in an electronic spreadsheet with subsequent randomizations concealed. On the day of the hysterectomy, the study team confirmed the use of the vaginal antibiotic and the total number of doses used. All office visits, imaging, and testing were conducted as standard perioperative procedures as per their gynecologic surgeon. There were no additional study visits or procedures required.

The primary outcome was the composite variable of patient issues related to possible infection and/or documented postoperative infection up to the 8-week postoperative visit. Patient-reported issues were defined as dysuria, vaginal discharge with or without pelvic pain, subjective fever and wound-related issues as documented in the postoperative visit, and any issue that generated an additional postoperative visit for evaluation. Documented postoperative infections requiring antibiotic use included urinary tract infection either empirically treated or culture-proven infection, vaginal cuff cellulitis or vaginitis and pelvic abscess confirmed by pelvic ultrasound or CT scan with or without vaginal cultures. Secondary outcomes were individual rates of patient-reported issues and documented postoperative infections. Adverse events were assessed through the postoperative follow-up visits. In the intervention group, patient-reported drug adverse events were collected. Both groups were reviewed for new documented infections in the 5 days before surgery.

Continuous variables were described with mean and SD and compared with Student's t-test or Mann-Whitney depending on the distribution of data. Categorical variables were described as counts (percentages) and compared with χ^2 or Fisher exact test. Correlations were conducted using Spearman's rho. A p value of <0.05 was defined as statistically significant. Analyses were first performed in an intent-to-treat fashion with patients analyzed in the groups to which they were randomized and secondary per-protocol analyses were conducted taking into account those subjects who received all or some of the metronidazole doses. Statistical analysis was performed with IBM SPSS Statistics for Windows, V.25.0. Armonk, New York, USA: IBM Corp.

Based on institutional data estimating 30% incidence in the primary outcome (documented infection and/or patient-reported issues), our sample size calculation determined that to demonstrate an effect size of 20% difference between the control and intervention arms with 80% power and an alpha error of 0.05, we needed 62 subjects in each arm. Thus, to account for a 10% dropout rate we aimed to recruit at least 136 subjects.

Patient and public involvement

The study was purposefully designed to be patient-centered rather than disease-centered. By focusing on a primary outcome that is a composite of the most commonly elicited patient symptoms rather than documented lab or radiology-proven infections, we were able to assess subjective issues that may not have objective findings but are nonetheless distressing for the postoperative patient. Patients were involved in the execution of this clinical trial both in their participation in their assigned intervention groups and in their reporting of postoperative issues. We carefully assessed the burden of the trial intervention on our patients. Patients in the intervention group who were unable to complete the full 5-day course of vaginal metronidazole were queried. Their responses were essential to assessing the feasibility of the intervention as we received a wide variety of responses such as undue financial burden, inability to

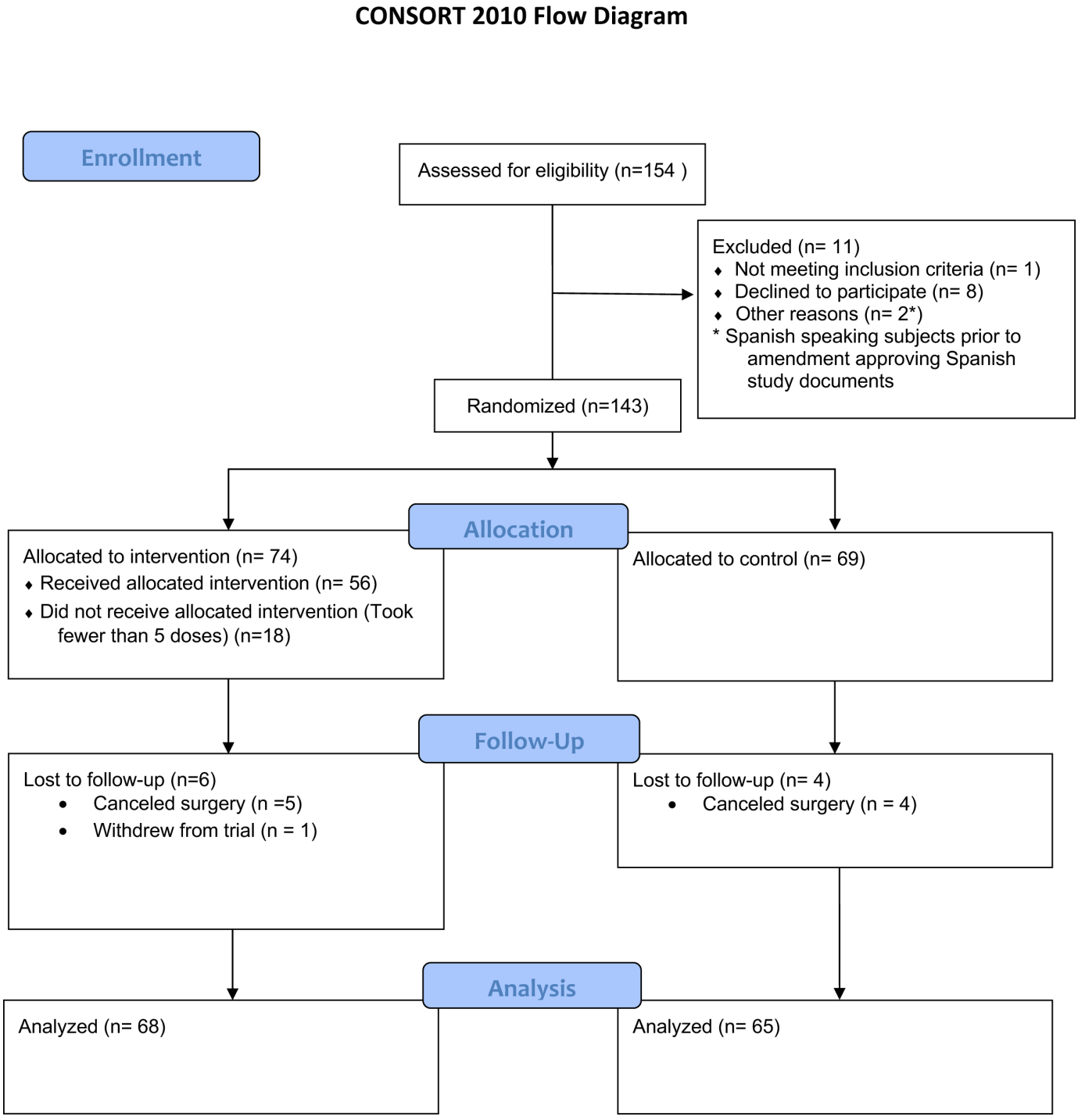

Figure 1 Randomization and follow-up of study participants. Figure 1 depicts the flow of enrollment, allocation and follow-up of subjects as per the CONSORT guidelines for randomized controlled trials. CONSORT, Consolidated Standards of Reporting Trials.

Table 1 Subject characteristics

Characteristic	Vaginal metronidazole* N=68	Control arm* N=65
Age (years), mean (SD)	55.5±12.2	52.4±12.9
BMI (kg/m^2), mean (SD)	31.8±6.2	31.9±9.4
Race/ethnicity, number (%)		
Asian	2 (2.9)	1 (1.5)
Black	11 (16.2)	12 (18.5)
Hispanic	24 (35.3)	21 (32.3)
White, non-Hispanic	29 (35.3)	27 (41.5)
None of the above	2 (2.9)	4 (6.2)
Indication for surgery, number (%)		
Abnormal bleeding/fibroids/adenomyosis/pelvic pain/endometriosis	26 (38.2)	25 (38.5)
Prolapse	6 (8.8)	3 (4.6)
Cancer/suspected cancer	33 (48.5)	35 (53.8)
Cervical dysplasia	3 (4.4)	2 (3.1)
Medical history, number (%)		
Diabetes	13 (19.1)	11 (16.9)
Smoking	2 (2.9)	7 (2.9)
Chronic steroid use	1 (1.5)	0
Pertinent medications, number (%)		
Steroids/prednisone	3 (4.4)	2 (3.1)
Anti-inflammatories	0	2 (3.1)
Methotrexate	0	2 (3.1)
Chemotherapy within 30 days	5 (7.4)	2 (3.1)
Doses of metronidazole, number (%)		
0 doses taken	15 (22.1)	65 (100)
1 doses taken	0	
2 doses taken	3 (4.4)	
3 doses taken	0	
4 doses taken	0	
5 doses taken	50 (73.5)	

*Groups compared with Student's t-test and χ^2.
BMI, body mass index.

place the vaginal gel due to body habitus, and adverse side effects.

RESULTS

A total of 154 people were screened for eligibility and 143 subjects were randomized between July 2020 and September 2022 (figure 1). Enrollment occurred during the COVID-19 pandemic during a time of decreased surgical volume. 10 patients were randomized but canceled surgery or withdrew from the study and did not receive the intervention or control. In total, 133 hysterectomies were performed during this study, with 68 subjects (51.1%) randomized to the metronidazole gel group and 65 (48.9%) subjects serving as controls.

Overall, the population was diverse in race and ethnicity as well as route and indication for surgery (table 1). There was no significant difference in age, body mass index (BMI), race/ethnicity, indication for surgery, or route of surgery between the two groups. The mean age was 54.0 years (±12.6). Our population was 42% white, 34% Hispanic, 17% black, 2% Asian, and 4% self-identified as "Other". Most (78%) subjects had no medical history, while 14 (11%) had diabetes, 4 (3%) smoked, and 0 had chronic steroid use. Surgical characteristics were not different between groups (table 2). The most common indication for surgery was cancer or suspected cancer including complex pelvic masses 51 (38%), followed by abnormal bleeding/fibroids/adenomyosis/pelvic pain/

Table 2 Surgery characteristics

Surgery characteristics	Vaginal metronidazole* N=68	Control arm* N=65
Hysterectomy, number (%)		
RA-TLH	22 (32.4)	24 (36.9)
RA-LSH	7 (10.3)	3 (4.6)
TLH	18 (26.5)	10 (15.4)
LSH	2 (2.9)	1 (1.5)
TAH	17 (25.0)	23 (35.4)
SCH	1 (1.5)	1 (1.5)
TVH	7 (10.3)	3 (4.6)
LAVH	1 (1.5)	3 (4.6)
Additional procedures (n=116), number (%)		
Urogynecology procedure with mesh	6 (8.8)	5 (7.7)
Gynecologic oncology lymphadenectomy	15 (22.1)	16 (2.5)
Gynecologic oncology tumor debulking	4 (5.9)	3 (4.6)
Small bowel procedure (including appendectomy)	1 (1.5)	0
Large bowel procedure	0	0
Intraoperative adverse events, number (%)	4 (5.9)	4 (6.2)
Transfusion	1 (1.5)	3 (4.6)
Bowel injury	1 (1.5)	0
Urinary injury	0	0
Conversion to laparotomy	2 (2.9)	1 (1.5)
Mean Estimated Blood Loss (SD)	182.3 (±189.8)	183.2 (±215.6)
Median EBL (range)	100 (20–900)	100 (10–1000)
Intraoperative antibiotic prophylaxis, number (%)		
Cefazolin	30 (44.1)	20 (30.8)
Cefoxitin	31 (45.6)	39 (60.0)
Other	7 (10.3)	6 (9.2)

*Groups compared with Mann-Whitney and χ^2.
LAVH, laparoscopic assisted vaginal hysterectomy; LSH, laparoscopic supracervical hysterectomy; RA, robotic assisted; SCH, supracervical abdominal hysterectomy; TAH, total abdominal hysterectomy; TLH, total laparoscopic hysterectomy; TVH, total vaginal hysterectomy.

endometriosis 38 (29%), prolapse 7 (5%), and cervical dysplasia 4 (3%). There were no differences in demographic variables in subjects who received the intervention or control compared with 10 subjects who withdrew as they did not have surgery. An intent-to-treat analysis was performed.

Of the subjects in the metronidazole gel group, 50/68 (73.5%) received all five doses of the medication, while 15/68 (22%) took no doses (table 1). No subjects in the control arm took metronidazole. All subjects were followed through 8 weeks postoperatively with no difference in the mean follow-up time between groups (43±11 days vs 42±12 days, p=0.65). No subjects who underwent hysterectomies were lost to follow- up.

Overall, for the composite primary outcome of patient-reported issues and/or postoperative infection there was no difference between groups (42.6% vs 36.9%, p=0.50) (table 3). We also looked at patient-reported issues and documented postoperative infections separately and found no difference between groups (41.2% vs 33.8%, p=0.49; 22.0% vs 15.4%, p=0.33, respectively) (table 4).

Table 3 Primary outcome measure

Primary outcome number (%)	Vaginal metronidazole N=68	Control arm N=65	P value*
Patient-reported symptom or documented postoperative infection	29/68 (42.6)	24/65 (36.9)	0.50

*Groups compared with χ^2.

Table 4 Secondary outcome measures

Secondary outcome number (%)	Vaginal metronidazole N=68	Control arm N=65	P value*
Patient-reported symptoms	28/68 (41.2)	23/65 (33.8)	0.49
Dysuria	8/68 (11.8)	7/65 (10.8)	0.86
Vaginal discharge	8/68 (11.8)	5/65 (7.7)	0.43
Subjective fever	3/68 (4.4)	4/65 (6.2)	0.65
Wound redness/erythema/drainage documented in postoperative visit	7/68 (10.3)	7/65 (10.8)	0.93
Issue that generates additional postoperative visit for evaluation	12/68 (17.6)	6/65 (9.2)	0.16
Documented postoperative infections	15/68 (22.0)	10/65 (15.4)	0.33
Urinary tract infection	6 (8.8)	5/65 (7.7)	0.81
Vaginal discharge that warrants treatment with antibiotics including vaginal cuff cellulitis or vaginitis	9/68 (13.2)	5/65 (7.7)	0.30
Pelvic cuff abscess confirmed by imaging that results in antibiotic use	1/68 (1.5)	1/65 (1.5)	0.97

*Groups compared with χ^2.

Individual issues and postoperative infections are listed in table 4.

Patients in the intervention group were queried regarding adverse events in the preoperative period attributed to the metronidazole insert but these issues were not assessed in the control group (table 5). During the preoperative period, the control group was not specifically asked about any adverse events however none were self-reported. Drug adverse events included vaginal discharge (n=2), vulvovaginal irritation (n=1), and Gastrointestinal distress (n=1). Both groups were reviewed for new documented infections in the 5 days before surgery and no preoperative infections occurred.

The compliance rate for the use of all five doses of metronidazole was 72.5% in our study population, however in order to account for the lack of completion of all doses, a per-protocol analysis was performed to investigate differences in those 50 subjects who took all five doses versus control group participants. No significant difference was observed in this per-protocol analysis (p=0.92) (online supplemental appendix A). We also analyzed those who took any dose (50 subjects took five doses and 3 took two doses) versus no doses in the control arm with no significant difference (data not shown).

Dysuria was included in patient-reported symptoms, however, if a urinary tract infection was diagnosed

Table 5 Patient-reported adverse events and documented infections

Intervention characteristics number (%)	Vaginal metronidazole N=68	Control arm N=65 *
Drug adverse events reported by patient on day of surgery	4 (5.9)	
Vaginal discharge	2 (2.9)	
Pruritus	0	
Gastrointestinal distress	1 (1.5)	
Abdominal pain	0	
Vulvovaginal irritation	1 (1.5)	
Headache	0	
Drug adverse events diagnosed during intervention and prior to surgery	0	0
Fungal infection	0	0
Vaginitis	0	0

*Patients in the intervention group were asked about adverse events in the preoperative period attributed to the metronidazole insert but these issues were not assessed in the control group. Both groups were reviewed for new documented infections in the 5 days before surgery.
GI, Gastrointestinal.

Table 6 Prior studies on use of metronidazole in hysterectomy

Author	Type of study	Groups	Infection rates
Avila *et al*[4]	Retrospective cohort. **Vaginal**, single dose.	n=46 control. n=50 metronidazole.	Pelvic infection 0% v 13% p=0.02. Urinary infection 20% v 2.2% p=0.02.
Larsson *et al*[6]	Randomized controlled trial. **Rectal**, night before surgery, then nightly before discharge.	n=75 control. n=67 metronidazole.	Wound infection 9% v 5.3%, ns. Cuff infection 1.5% v 17.3% p=0.016. Cuff infection in abnormal flora subjects 0% v 27% p=0.003. Urinary tract infection 17.9% v 17.3% ns.
Okamura *et al*[5]	Retrospective cohort. **Vaginal**, tablets inserted day before surgery, day after surgery, and then postoperative day 3.	n=95 control. n=425 metronidazole.	Vaginal bacterial-related postoperative complications 6.3% v 2.35%, OR 0.36, p<0.05.
Till *et al*[9]	Retrospective cohort. **Intravenous.**	n=14,971 cefazolin or n=2,365 second-generation cephalosporin. n=919 cefazolin and metronidazole intravenous.	Unadjusted rate of surgical site infection: cefazolin 1.8%, 2.1% second generation cephalosporin and 1.4% cefazolin plus intravenous metronidazole.
Cochrane systematic review[12]	Systematic review 37 randomized controlled trials. **Various** routes and types of antibiotics.	N=6,079 subjects total.	Unclear which antibiotic and dose has the highest efficacy for prevention of infection after hysterectomy.

postoperatively by a clinical provider, this infection may not have any association with preoperative metronidazole use. Whether vaginal metronidazole use alters bacterial flora with either association or prevention of Urinary tract infection postoperatively is unclear from current data. Therefore, an analysis was performed to remove documented urinary tract infection from the primary and secondary outcomes and still, there was no significance between groups (p=0.62) (online supplemental appendix B). Patient-reported symptoms and documented postoperative infections were moderately correlated (r=0.53, p<0.001). When UTIs were removed from the postoperative infections, a high correlation was detected (r=0.78, p<0.001).

DISCUSSION

Based on the results of this randomized controlled trial, there is insufficient evidence to recommend preoperative vaginal metronidazole prophylaxis in asymptomatic patients undergoing elective hysterectomy. The primary outcome of patient-reported issues and/or documented postoperative infection up to 8 weeks after surgery did not demonstrate a significant difference. Secondary outcomes of individual rates of issues of postoperative infection similarly showed no differences. Vaginal metronidazole was well tolerated by the study group with minimal drug adverse events. In addressing rates of compliance in the antibiotic arm, a per-protocol analysis comparing the use of all five doses to the control group and also any dose of metronidazole to the control groups did not reveal any significant differences.

Prior research on the use of local metronidazole in the preoperative period has consistently demonstrated benefit. In a recent non-randomized retrospective study, Okamura *et al* reported that vaginal metronidazole 250 mg tablets before and immediately after total laparoscopic hysterectomy resulted in a greater than 50% reduction in complications related to vaginal bacteria.[5] In another retrospective study of a gynecologic oncology population, Avila *et al* found that a single dose of preoperative vaginal metronidazole reduced the risk of pelvic (13%, 0%) and urinary infection (20%, 2.2%) after robotic radical hysterectomy.[4] In our analysis, we included urinary tract infections and then did a post hoc analysis removing these infections and still, there was no difference between groups. Larsson *et al* demonstrated that preoperative and postoperative 1 g rectal metronidazole significantly reduced rates of vaginal cuff infections in premenopausal women with asymptomatic abnormal vaginal flora undergoing total abdominal hysterectomy for benign indications.[6]

Prophylactic use of intravenous metronidazole has been studied with conflicting results. In a retrospective review by Till *et al* of 18,255 subjects in the Michigan Surgical Quality Collaborative undergoing all routes of hysterectomy for benign and malignant indications, lower surgical site infection rates were demonstrated with the use of prophylactic intraoperative cefazolin plus intraoperative intravenous metronidazole compared with cephalosporin alone.[9] Conversely, a large observational prospective cohort study comparing prophylactic intravenous metronidazole to cefuroxime at the time of hysterectomy found that metronidazole alone was inferior for infection prevention.[10] A 2017 Cochrane review on antibiotic prophylaxis for hysterectomy reports unclear differences in outcomes for women receiving metronidazole as part of the prophylactic regimen.[11] Studies summarizing the use of prophylactic metronidazole in hysterectomy patients are listed in table 6.

In contrast to previous work, our study did not demonstrate reduced genitourinary or surgical site infections. We selected a preoperative regimen of vaginal metronidazole commonly used to treat bacterial vaginosis. Five g of 0.75% vaginal metronidazole contains 37.5 mg of metronidazole compared with much higher doses of metronidazole in tablets used previously. The mean bioavailability of intravaginal metronidazole gel is 56%.[12] Furthermore, our intervention ended the day before surgery in contrast to those studies where metronidazole continued postoperatively. Serum levels of metronidazole may not have been sufficient to prevent infection at the time of incision.

This study addressed both patient-reported issues and documented postoperative infections. Patient satisfaction with a reduction in reportable issues in the postoperative period would be beneficial for both the patient and the provider. Interestingly, in our study population we did find a significant correlation between patient-reported symptoms and documented postoperative infection. With increasing emphasis on value-based care, global improvement of the postoperative period includes not just reducing surgical site infection but the use of resources to rule out infection due to associated patient issues. The use of novel, low-cost, high-yield strategies will be imperative to positively impact the quality of gynecologic care.

Our study has several limitations. First, we did not use a placebo (eg, inert vaginal suppository). However, with randomization despite the placebo effect, our patient-related reports of infection did not differ between groups. Second, 22% of the study group did not comply with the prescribed vaginal antibiotic regimen and all patients were analyzed using the intent-to-treat principle. However, the per-protocol analysis did not reveal differences in groups.

Additional limitations include the inability to blind subjects or providers to the assigned study group. This may have contributed to a symptom reporting bias. It should also be noted that this trial took place in the midst of the COVID-19 pandemic, during which many elective surgeries were not performed. For this reason, our surgical indications leaned heavily towards malignancy. However, both groups were balanced with respect to the type of gynecologic surgeries performed. Finally, patients in the intervention group were asked about adverse events in the preoperative period attributed to the metronidazole insert (eg, vaginal discharge, diagnosed fungal infection, and headache) but these issues were not assessed in the control group.

Compared with existing literature, the strengths of the study include its prospective randomized design and the diversity of study subjects. Our population for a single-institution randomized control trial was more than 50% non-white. Many patients were obese with a mean BMI of 31, a risk factor for postoperative infection. We also recruited subjects with both benign and malignant indications and all routes of hysterectomy. Despite recruiting during the COVID-19 pandemic, we were able to achieve target enrollment.

Vaginal metronidazole given for 5 days prior to scheduled hysterectomy for benign and malignant indications is well tolerated but not effective at reducing postoperative infection or associated patient issues compared with cephalosporin alone. Future investigations on perioperative interventions should continue to emphasize both outcomes and patient experiences.

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Contributors TP and CG designed the present study, performed statistical analysis, and provided all supervision. HZ and AK were involved in carrying out the experiment including recruiting subjects, managing participants, and collecting data. AB, SP, SM, and TR were involved in participant recruitment. All authors took part in writing and editing the present manuscript. TP is the primary author responsible for the overall content and accepts full responsibility for the work and conduct of the research.

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Competing interests None declared.

Patient consent for publication Not applicable.

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