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# Antibiotic Prophylaxis in Gynecologic Laparoscopy: Study Protocol for a Randomized Controlled Trial

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## Abstract

**Background:** Laparoscopy is a surgical procedure indicated for most gynecological pathologies. It presents numerous advantages over laparotomy; among these are lower rates of surgical site infection and less febrile comorbidity. Despite this, the use of antibiotic prophylaxis is widely accepted and performed by most gynecologists. However, no evidence exists in the literature to support the routine use of antibiotics in the prophylaxis of wound infection in laparoscopic pelvic surgery.

**Objective:** This study aims to assess the surgical site infection rates for gynecological laparoscopies, not involving the opening of hollow viscera, among patients receiving or not antibiotic prophylaxis.

**Methods:** This is a clinical, prospective, double-blind, randomized study. A total of 216 women with gynecological pathologies, undergoing laparoscopic surgical approach, will be consecutively selected. The patients will be randomly allocated to either the placebo group (n=108), to receive 10 mL of intravenous sterile saline, or to the antibiotic group (n=108), to receive 1 g of intravenous cefazolin 30 minutes before the surgery. To evaluate the incidence of surgical site infection, criteria of the Centers for Disease Control and Prevention (CDC) will be used. The patients will be evaluated weekly for 30 days.

**Discussion:** The CDC "Guideline for Prevention of Surgical Site Infection" provides recommendations for the prevention of surgical site infections. However, for some practices, no recommendations are offered, due to a lack of consensus or insufficient evidence on the effectiveness of preventative measures. Interventions to reduce the incidence of surgical site infections are essential to reduce not only morbidity, but also costs to patients and society.

**Trial registration:** ClinicalTrials.gov identifier: NCT01991834.

**Keywords:** Gynecologic diseases; Gynecologic surgical procedures; Minimally invasive surgical procedures; Laparoscopy; Antibiotic prophylaxis; Postoperative care; Surgical wound infection

## Introduction

Laparoscopy is a surgical technique in which operations are performed through small incisions using a laparoscope [1]. The development of laparoscopy is one of the most important advances in the field of surgery over the last 20 years [2]. After initially being recommended for the investigation of female infertility, gynecologic laparoscopy has become a surgical discipline in its own right [2]. Currently, most gynecologic operations are within reach of laparoscopy and, where the results are similar to a conventional surgery, the surgeon should adopt a laparoscopic approach [3].

A procedure to be performed by laparoscopy must be precise, and the patient must be properly prepared, with adherence to a routine for avoiding complications [4]. In this context, antibiotic prophylaxis for gynecologic surgery practice is widely used to reduce post-surgical complications, such as wound infection, cellulitis of the vaginal vault, endometritis, urinary tract infections, and foreign body infections. Intravenous antibiotics applied minutes before surgery are recommended for many hospitals. Although prophylaxis is generally performed with the goal of increasing patient safety, the administration of unnecessary antibiotics is undesirable because it can result in the development of antibiotic-resistant bacteria, unnecessary cost, adverse reactions, and changes in the normal microbiota [5].

Surgical site infections (SSIs) are defined as wound infections that occur after invasive procedures [6]. SSIs correspond to 14–16% of all nosocomial infections in hospitalized patients, and are most common among surgical patients [7]. The umbilical incision, used in laparoscopies, is associated with infection rates of approximately 8% [8]. In gynecologic laparoscopic procedures, not including hysterectomies, SSI rates vary from 0% to 5.5% [9].

Despite the low SSI rates, over 50% of gynecologists use antibiotic prophylaxis in their laparoscopy operations [10]. In a study conducted in Campinas, Brazil, to evaluate the microbial load of reprocessable trocars after gynecological laparoscopy, 93.9% of gynecologists performed antibiotic prophylaxis [11].

As with any accepted practice, antibiotic prophylaxis has indications for periodic reviews. The collective orientation available from the Guidelines Project (antibiotic prophylaxis recommendations for

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selected surgical procedures) of the Brazilian Medical Association and the Brazilian Council of Medicine does not provide uniform guidance regarding laparoscopy for gynecologic surgeons. While recommending antibiotic prophylaxis for surgeries such as myomectomy and oophorectomy, the Project does not consider the approach employed. However, the laparoscopic approach does not require prophylaxis for surgeries of the digestive tract due to a low risk of surgical site infection [12].

Litta et al. in a prospective study of 300 women undergoing laparoscopy, compared the use of antibiotic prophylaxis to placebo and found no significant differences in infectious complications and febrile morbidity [13]. Also, according to Department of Health and Human Services of the United States, the use of antibiotic prophylaxis is not recommended for laparoscopic procedures that do not involve direct access to the abdominal cavity through the endometrial cavity or the vagina [14]. Given the differences among the gynecological practice, guidelines, and Brazilian literature data, this randomized clinical trial was designed to evaluate the need for antibiotic prophylaxis in laparoscopic gynecological surgeries.

## Methods

### Study aims

To assess the SSI rates for gynecological laparoscopies, not involving the opening of hollow viscera, among patients receiving or not antibiotic prophylaxis.

Our primary hypothesis is that antibiotic prophylaxis for this kind of procedure does not provide benefit for patients, since it does not significantly decrease SSI rates.

### Ethical issues

The Universidade do Vale do Sapucaí Ethical Committee approved the study protocol (CAAE: 1979691.8.0000.5102). Only participants providing written informed consent will be included in the study.

### Study design and setting

This is a two-arm, parallel group, randomized, controlled trial, to be conducted in a university-affiliated hospital (Hospital das Clínicas Samuel Libânio – Universidade do Vale do Sapucaí) and a private hospital (Hospital e Maternidade Santa Paula). Patients will be recruited from the outpatient gynecology clinics. This trial was registered in ClinicalTrials.gov as NCT01991834.

### Sample size

SSI rates following gynecological operations vary from 0% to 5.5% in published literature [9]. Considering a Type 1 error of 5% as acceptable, Type 2 errors of 20% and clinically relevant a 5.5% difference in SSI rate, the estimated sample size was 108 patients per arm.

### Eligibility criteria

**Inclusion criteria:** Female patients, aged between 18 and 65 years old, with gynecologic disease, scheduled for a laparoscopic operation that does not involve the opening of hollow viscera, will be considered eligible for participation.

**Exclusion criteria:** Patients with a body mass index (BMI) above 30 kg/m$^2$, with usual contraindications for gynecological laparoscopic procedures, such as diabetes with glycated hemoglobin exceeding 6.5% [15], a heavy smoker status (≥ 10 cigarettes per day or an equivalent quantity of cigar or pipe smoke) [16], a physical status (risk) classification by American Society of Anesthesiologists (ASA) [17] of level III or higher, patients contraindicated to cefazolin and those who used antibiotics less than 15 days prior to operation will be excluded. Patients in which antibiotic therapy was used after the surgery for other diseases, such as urinary tract infection, will also be excluded.

### Group assignment, randomization and allocation concealment

Two hundred and sixteen patients will be prospectively enrolled, after giving informed consent. Patients will be randomly assigned either to group I (placebo; n=108), to receive intravenous saline sterile before the surgery, or to group II (antibiotic; n=108), to receive 1g of intravenous cefazolin 30 minutes before the operation. Cefazolin was selected because it is the drug recommended by the Guidelines of the Brazilian Medical Association for gynecological surgery [12].

The allocation will be determined by a computer-generated sequence (Bioestat 5.0, Instituto de Desenvolvimento Sustentável Mamirauá, Belém, PA, Brazil).

A sealed opaque envelope with patient's group allocation in the study will be opened by the anesthesiologist at the time of anesthesia induction.

The patients, the surgical team, the gynecologists who perform the follow-up regarding the occurrence of SSI and the statistician will be blinded. Only the anesthesiologists, who administer the placebo or antibiotics, will know the allocation of patients into the groups.

### Baseline procedures and interventions

In both hospitals the same anesthesiology and surgical teams will perform all the procedures, using the same techniques of anesthesia, medications, surgical techniques and postoperative follow-up protocol.

Each patient will be transported to the operating room. Immediately after the induction of general anesthesia, the anesthesiologist will administer either sterile saline or cefazolin according to the patient's group allocation. Only the anesthesiologist will be aware of the group allocation of each patient.

An alcoholic solution of chlorhexidine (0.5%) will be used for antisepsis of the surgical site in the operating room, after skin preparation with 4% chlorhexidine degermante [7,18,19]; A laparoscope will be inserted through a small (1 cm) incision in the umbilicus by the open-entry technique or by Veress Needle/trocar entry [20,21]. After identifying the epigastric vessels by transillumination and intraperitoneal observation, one to three secondary trocars will be placed, depending on the procedure and the number of trocars required for the operation [22]. At the end of surgery, a conventional dressing with gauze will be placed over the sutured wound and removed 24 hours after the procedure, as recommended by the CDC (category 1B – *evidence based on individual randomized controlled trial with narrow confidence interval*) [7].

### Monitoring and evaluation of surgical site infection

The CDC defines SSI as an infection that occurs within 30 days after the operation, when implants are not used [6]. Thus, these patients will be systematically followed by a single and blinded surgeon to assess postoperative infection in the first postoperative day, throughout the duration of the hospital stay, and once a week for 30 days. The CDC definitions and classifications of SSI will be considered (Table 1) [6]. As with all CDC definitions of nosocomial infections, a surgeon's diagnosis of infection will be considered an acceptable criterion for an SSI. In

| Superficial Incisional SSI | Deep Incisional SSI | Organ/Space SSI |
|---|---|---|
| • Involves only skin or subcutaneous tissue and meets at least one of the following:<br>• Purulent drainage from the superficial incision;<br>• Organisms isolated from an aseptically obtained culture of fluid or tissue from the superficial incision;<br>• At least one of the following signs or symptoms of infection: pain or tenderness, localized swelling, redness or heat, and the superficial incision is deliberately opened by surgeon unless the incision is culture-negative;<br>• Diagnosis of superficial incisional SSI by the surgeon or attending physician. | • Involves deep soft tissues (fascial and muscle layers) and meets at least one of the following:<br>• Purulent drainage from the deep incision but not from the organ/space component of the surgical site;<br>• A deep incision that spontaneously dehisces or is deliberately opened by a surgeon when the patient has at least one of the following signs or symptoms: fever (>38°C), localized pain or tenderness, unless the incision is culture-negative;<br>• An abscess or other evidence of infection involving the deep incision is found on direct examination, during reoperation, or by histopathologic or radiologic examination;<br>• Diagnosis of deep incisional SSI by the surgeon or attending physician. | • Involves any part of the anatomy (organs or spaces) and meets at least one of the following:<br>• Purulent drainage from a drain that is placed through a stab wound into the organ/space;<br>• Organisms isolated from an aseptically obtained culture of fluid or tissue in the organ/space;<br>• An abscess or other evidence of infection involving the organ/space that is found on direct examination, during reoperation, or by histopathologic or radiologic examination;<br>• Diagnosis of an organ/space SSI by the surgeon or attending physician. |

**Table 1:** CDC definitions of Surgical Site Infections (SSI) [6].

this follow-up period, information concerning the evolution of patients will be noted according to the protocol for data collection. The protocol includes information such as axillary temperature, wound appearance (presence of purulent drainage, pain or tenderness, localized swelling, redness or heat), and clinical condition of the patient. Whenever a deep incisional or organ/space SSI is suspected, laboratory and radiological investigation will be promptly performed.

In the event a patient is identified as having an SSI, she will be treated with third generation cephalosporin, due to its potential for action against gram-negative bacteria [11], including those resistant to Oxacillin [23]. In cases of deep SSI, a surgical procedure for cleaning and removal of infectious focus will be associated and patient will remain hospitalized until complete 48 hours without fever.

### Outcomes measures

The primary outcome of this study is the incidence of SSI, which is defined on the basis of the CDC's definitions [6].

### Statistical analysis

The rejection level for the null hypothesis will be fixed at 5% ($\alpha \pounds 0.05$). Fisher's test will be used to compare groups I and II regarding SSI occurrence. Multivariate logistic regressions will be applied to detect significant associations between variables such as age, BMI and duration of operation, number of incisions, incision size, and the incidence of SSI. Statistical analysis will be performed using SPSS, version 18 (Statistical Package for Social Sciences, IBM Inc., Chicago, USA), and Bioestat 5.0 (Instituto de Desenvolvimento Sustentável Mamirauá, Belém, PA, Brazil).

## Discussion

Interventions to reduce the incidence of surgical site infection are essential to reduce not only morbidity, but also costs to patients and society [24]. However, the collective guidelines available from the American College of Obstetricians and Gynecologists [5], the Surgical Infection Prevention Project [25], the Brazilian Federal Medical Council, and the Brazilian Medical Association [12] do not provide uniform guidance to gynecologic surgeons regarding gynecologic laparoscopies.

A recent study indicated that compliance with prophylaxis is incomplete and that local hospital-based guidelines may supersede national guidelines [10]. Furthermore, with the advent of many new surgeries, including minimally invasive procedures such as laparoscopy, data regarding prophylaxis for these procedures are not well-known [9].

As protocols and guidelines should be evidence-based, well-designed clinical trials are essential to justify or to adjust clinical practice. This trial aims to clarify the need of antibiotic prophylaxis in gynecologic laparoscopy. We will test the hypothesis that antibiotic prophylaxis for this kind of procedure does not significantly decrease SSI rates; thus, it is not beneficial for patients.

A recent review of literature found a SSI rate following gynecologic laparoscopy ranging from 0 to 5.5% [9]. Thus, for our sample size calculation, it was considered that clinically relevant a 5.5% difference in SSI rate. In this review, Morrill et al. [9] found only two randomized clinical trials that evaluated antibiotic use in benign gynecologic laparoscopic procedures, excluding hysterectomy [26,27]. Kocak et al. randomized 450 women to either a single preoperative dose of a first-generation cephalosporin (n=200) or no antibiotics (n=250) [26]. However, in their study, the technique of randomization was not described, and the physicians caring for the women postoperatively were not blinded. Cormio et al. randomized 356 patients undergoing laparoscopy to amoxicillin–clavulanate or cefazolin at anesthesia induction; the study did not involve a placebo control group [27]. The present study will use a randomized, double-blind design to assess SSI rates, and includes a placebo group.

Minas et al. in another recent review of literature concluded that there is a paucity of evidence to address the use of antibiotic prophylaxis in gynecologic hysteroscopy, laparoscopy and robotic surgery [28]. Morrill et al. concluded that antibiotic prophylaxis for laparoscopic surgery does not provide a significant benefit and questioned the applicability of studies that were published some time ago [9]. This is because certain practices are now obsolete, such as prolonged hospitalization after short laparoscopic procedures. Therefore, these authors recommended further clinical studies on prophylactic antibiotics for procedures such as vaginal surgery without hysterectomy, advanced laparoscopic surgery, and robotic surgery [9].

Thus, the results of this trial may support standard recommendations regarding the use of antibiotic prophylaxis in gynecologic laparoscopy.

### Author's Contributions

FSMC conceived the study and participated in study design, surgical procedures, patient follow-up, and generating the manuscript draft. RPFL is responsible for anesthesia and patient allocation into groups. SCVA and AMCF are involved in surgical procedures and patient follow-up. YJ participates in the analysis and interpretation of data. DFV and LMF participated in the design and coordinates the study. All authors contributed to the development of the study protocol and all authors have read and approved the final version of the manuscript.

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