Effect of post-cesarean oral cephalexin and metronidazole on surgical site infections among obese women: a randomized clinical trial

Study Protocol

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a. Specific Aims:

Specific Aim 1: To evaluate if preoperative antibiotics, followed by 48 hour course of postpartum oral cephalexin plus metronidazole prevents wound infection complications in patients that are obese who undergo cesarean section. We hypothesize that a prolonged, 48 hour course of cephalexin-metronidazole, suited to prevent growth of normal vaginal flora, will decrease the rate of surgical site infection in obese patients that are at a greatly increased risk of postoperative infections complications.

- Primary outcome: frequency of surgical site infections (including cellulitis and endometritis) between cephalexin-metronidazole versus placebo among all obese women undergoing cesarean delivery.

Specific Aim 2: To determine if a 48 hour course of postpartum oral cephalexin plus metronidazole prevents wound infection complications and benefits obese women undergoing cesarean section depending on membrane status prior to delivery (intact vs. ruptured). A planned randomization scheme for both intact and rupture of membranes prior to delivery will be performed. We hypothesize that 48 hour course of cephalexin-metronidazole will decrease rates of surgical site infections in both cohorts – rupture of membranes and intact membranes prior to delivery.

- Secondary Outcomes: frequency of surgical site infections (including cellulitis and endometritis), any incisional morbidity, and individual outcomes (cellulitis, endometritis, wound separation, and febrile morbidity) between cephalexin-metronidazole versus placebo stratified by membrane status prior to delivery among obese women undergoing cesarean delivery.

b. Background:

It is well recognized that obesity is the foremost epidemic challenging the health of Americans. The rates of obesity are highly impacting our adolescent population and disproportionately reproductive age women. It is estimated that approximately one third of reproductive aged women are considered obese[1]. Multiple studies have demonstrated increased rates of complications such as miscarriage, gestational diabetes, preeclampsia, birth defects, abnormal labor patterns and increased cesarean section rates in obese women[6]. Maternal obesity further challenges cesarean sections, increasing complications rates such as hemorrhage and infection[7].

Multiple trials have consistently demonstrated a benefit for infection prevention with preoperative cephalosporin antibiotics in patients undergoing cesarean section[3]. A recent Cochrane Database review included 81 trials[2]. The reviewers found that “the use of prophylactic antibiotics in women undergoing cesarean section substantially reduced the incidence of episodes of fever, endometritis, wound infection, urinary tract infection and serious infection after cesarean section.” Specifically the risk of endometritis with antibiotics was 0.39 (95% CI 0.31 to 0.43) for all patients. The risk for wound infection was also reduced RR 0.41 (95% CI 0.29- 0.41). This risk reduction appeared to be similar in groups undergoing both elective and non-elective cesarean section. A small study of 160 patients randomized to cefazolin only versus cefazolin with one dose of metronidazole preoperatively demonstrated a significant reduction in the rate of postoperative infections.

No prior studies specifically addressed risk reduction in obese populations[4]. Rates of post-cesarean surgical site infection following cesarean delivery in obese patients are believe to be as high as 12% in studies, a 5 fold increase over normal weight rates of infection. In addition, endometritis risks are also substantially higher, and in total, postoperative infectious complications occur in 20-25% of these high risk patients. Studies evaluating the relationship between obesity and postoperative infections have demonstrated what appears to be a "dose-dependent" relationship between class of obesity and rate of infectious morbidity[5].

The surgical literature is inconclusive regarding optimal antibiotic regimens and duration to prevent surgical site infections (SSI) especially for the growing obese population. Strong data support that cefazolin pre-skin incision significantly decreases postoperative infectious morbidity, however obesity is an independent risk factor for postoperative infections despite this preoperative regimen. Metronidazole use for infection prevention has shown promise in high risk populations, but the obese population was not studied exclusively[8]. With the rising obese population and the significant morbidity associated with postoperative surgical site infections following cesarean deliveries, it is important to study promising antibiotic regimens that may help decrease infectious risks in this population.

c. Methods and Procedures:

We propose the conduction of a prospective, randomized, double-blind clinical trial to evaluate a prophylactic regimen for the prevention of surgical site infection. This study is to be conducted by the Department of Obstetrics and Gynecology at the University of Cincinnati Medical Center. The intervention being studied will be the continuation of prophylactic antibiotics in the postpartum period with 48 hours of cephalexin 500mg and metronidazole 500mg every 8 hours for a total of 6 doses per antibiotic. Forty-eight hours of postpartum prophylactic antibiotics was chosen for this study since it is an institutional standard for women to stay a minimum of 48-hours postoperatively and it is within the spectrum that has been studied. The primary outcome measure will be the development of surgical site infection (including cellulitis and endometritis) within the first 30 days following the delivery.

1. DESCRIPTION OF SUBJECTS (SAMPLE SIZE, PLAN SELECTION OF PATIENTS)

All patients to be considered for recruitment to this study will be undergoing delivery at The University of Cincinnati Medical Center. Patients with an elevated BMI ≥30 kg/m^2 who undergo cesarean section will be considered for randomization either prior to delivery or in the first 8 hours after delivery, to accommodate the need for the first dose of study medication or placebo 8 hours after surgery. Only patients who agree to inclusion after informed consent will be randomized per protocol.

For the purposes of our study, we define overweight at a BMI of 25-29.9 kg/m^2, Class I Obese as 30-34.9 kg/m^2, Class II Obese 35-39.9 kg/m^2 and Class III Obese as >40 kg/m^2. Women meeting the definition of obese, BMI ≥30 kg/m^2 who undergo

planned or non-elective cesarean delivery would be considered for randomization. To eliminate the variable of excessive weight gain in pregnancy, this study will use a pre-pregnancy body mass index of greater than or equal to 30.

2. SAMPLE SIZE

Assumptions:
95% confidence (p=0.05), 80% power (standard), 1:1 ratio of exposed to unexposed.

The rate of postoperative infectious morbidity in obese women is estimated to be 20-25% in the literature. Using a rate of disease of 20% and a 50% rate of reduced infectious complications:

RR = 0.50
Rate of disease in unexposed: 20%
217 in each group, total 438

Therefore, we would plan to randomize 450-475 patients for study inclusion.

3. INCLUSION AND EXCLUSION CRITERIA

Specific inclusion criteria would include all:

1. Age 13 or older
2. BMI ≥30 kg/m^2
1. Delivery via cesarean section
2. Consent to randomization.

Exclusion criteria would include any:

1. Patients with known immunodeficiency syndromes.
2. Patients receiving intravenous antibiotics for preexisting infections.
3. Patients with planned administration of antibiotics in the postpartum period for any indication.
4. Non-English speaking patients.
5. Known allergy to cephalosporins or metronidazole.

4. GENDER, AGE, RACE, POSSIBLE VULNERABLE SUBJECTS

By definition, in this study all participants with be reproductive aged, female, pregnant patients. Although this can be considered a vulnerable subject group, any study medications would be given after delivery in the postoperative time period.

5. SOURCE FROM WHICH STUDY POPULATION WILL BE RECRUITED

Any patient presenting to Labor and Delivery for delivery will be considered for inclusion. Patients will NOT be considered for study inclusion prior to admission for delivery.

6. PLANS FOR RECRUITMENT OF SUBJECTS

Only patients already under the care of the University of Cincinnati Medical Center providers for their labor and delivery care will be considered for eligibility and participation. Those who meet study criteria will be approached for informed consent. Because the first dose of postoperative antibiotics will be given approximately 8 hours after preoperative antibiotics are given for the cesarean delivery, potential study participants can be enrolled in the study up to 8 hours post-delivery. Consented study participants will be randomized to one of two potential study arms – cephalexin-metronidazole versus placebo. Randomization will be stratified by membrane status prior to delivery (intact membranes and rupture of membranes [ROM]). Separate randomization schemes will be prepared by Investigational Drug Services (Judy Houston, RPh) for study participants with intact membranes and ROM using the Wichmann-Hill random number generator using blocks of ten.

The placebo study arm will include the standard cefazolin prior to surgical incision followed by matched placebo pills for 48 hours post-delivery simulating the standard of care at this time. Placebo capsules were filled with lactose powder and snapped shut.

The study drug arm will also receive cefazolin prior to skin incision followed by a 48 hour course of cephalexin 500mg and metronidazole 500mg every 8 hours for six total doses. Physicians, staff, and patients will be blinded to the intervention administered, unless a break in blinding is required for medical intervention of adverse effects. All investigational drugs were over-encapsulated, blinded using size”00” dark green opaque capsules, and polished before placing in blister packaging by the investigational pharmacist.

7. SETTING

This study will take place on the Labor and Delivery unit at the University of Cincinnati Medical Center. All recruitment for study participation will occur after admission for women elective or non-elective undergoing cesarean delivery. Follow-up evaluation for postoperative evaluations typically takes place at either the Hoxworth Center for Obstetrics and Gynecology, The Medical Arts Building, or a Women’s Health Services outlying facility.

8. LABORATORY METHODS AND FACILITIES

Not applicable to this study.

9. OPERATING ROOM PROCEDURES

The study will continue to apply the current Cochrane and ACOG guidelines to administer cefazolin prior to skin incision. This is the current standard of care in which both arms will receive prior to skin incision.

To most effectively and accurately analyze our primary and secondary research outcomes, we will standardize our surgical operation techniques in all ways feasible. These recommendations will be in concordance with American College of Obstetrics and Gynecology recommendations and those generally accepted in the medical literature. All patients will undergo surgery in the same small group of HEPA filtration and positive air pressure operating rooms. Appropriate limitations on number of surgeons and assistants scrubbed for surgery as well as general OR traffic will be enforced. Patients will undergo hair clipping of the incision site when appropriate. Chlorhexidine skin decontamination will be the standard surgical site preparation. An antimicrobial, adhesive drape will be used with sterile technique. Prior to skin incision, 2 grams of cefazolin will be administered.

In general, use of excessive electrocautery will be discouraged as devitalization of tissue is a known risk factor for postsurgical infection. After delivery of the fetus, the uterus will be repaired in a standard technique. After hemostasis has been achieved, irrigation of the peritoneal cavity including the paracolic gutters will be performed with warmed saline in a standard fashion. The fascia will be reapproximated with a monofilament suture, preferable 0 Maxon suture, in a running stitch. Hemostasis will be achieved in the abdominal wall incision with sutures and electrocautery, again limiting excessive use of electrocautery as is surgically feasible. This potential subcutaneous adipose tissue dead space will then be reapproximated with 3-0 polyglacton in either a running or interrupted stitch. It will be encouraged to close the skin with a subcuticular stich. Subcutaneous surgical drains will not be used as they have been found to not decrease rate of wound infections.

There may be a relationship between type of incision and rate of postoperative infectious complications. However, the type of incision, Pfannenstiel versus a vertical skin incision, is very dependent upon individual body habitus, prior incisions, and surgeon preferences. Given the complexity involved in determining the optimal method of skin incision for a particular clinical situation, this will be left to the discretion of the primary surgeon.

All patients will be followed after delivery in a routine fashion. The surgical dressing will be removed 24-36 hours post operation. The staples, if used, will be removed on postoperative day 3-4 for Pfannenstiel skin incisions day 5-6 for vertical skin incisions. The incision will be daily and final examination on day of discharge for signs of infection in all study patients. In addition, patients will be asked to return in two weeks for a postoperative check. Any signs of infection will be noted at that time. Finally, six weeks after surgery at the traditional postpartum check, the incision will be inspected for evidence of a wound infection. Study participants will be encouraged to notify research staff if concerns for an infection arise outside of these postpartum visits. If participants are noncompliant with the scheduled follow-up examinations, the research staff will attempt to reach the participant and encourage her return for examination and assess for any concerning signs of infection. If the participant refuses or is unable to come in for clinical evaluation, she will be questioned regarding: pain at incision site, drainage from incision, fever, separation of the incision, or any unexpected evaluation at an urgent or emergency care facility.

Study deviations will include study drug administration beyond 12 hours from preoperative antibiotics, any missed dosage of study drug, administration of study

medication more than one hour before or after the scheduled time of administration, or patient refusal to continue to participate. Investigators will remain blinded to the intervention until all data analysis is complete, but will be integral to the determination of the presence of postoperative infectious complications.

We will define infections as follows, according to the National Nosocomial Infectious Surveillance System of the Center for Disease Control:

- Surgical site infections can be defined as incisional, organ or space infections and incisional infections can be subcategorized as superficial or deep tissue (muscle and/or fascia) infections **(see below).**
- Endometritis would be considered a postsurgical organ infection **(see below).**
- Fever will defined as a temperature of greater than 38.3^{o}C, or two fevers greater than 38.0^{o} C. The combination of significant temperature elevation, increased incisional tenderness, increased pelvic organ tenderness, out of the ordinary operative site tenderness, or purulent incisional or vaginal drainage, with or without a leukocytosis will indicate the presence of a surgical site infection **(see below).**

Infections will be determined using the following criteria:

1) Surgical site infection
    a. Infection within 30 days after operation
    b. Partial or total wound dehiscence
    c. Presence of purulent or serous wound discharge with induration
    d. Warmth/erythema
    e. Tenderness
    f. *Blue top wound culture* to be used perform wound sampling to ensure appropriate bacteria covered with antibiotics
2) Febrile morbidity
    a. Persistent fever ≥38°C (100.5°F) for ≥24 hours or temperature >38°C on two occasions 4 hours apart
    b. Not associated with lower abdominal or pelvic tenderness on bimanual exam
    c. No signs of infection elsewhere
3) Urinary tract infection
    a. >10^5 bacteria per mL urine
    b. Urinalysis & *Urine culture* to be obtained for sensitivities
4) Endometritis
    a. Temperature ≥38°C (100.5°F) on 2 separate occasions
    b. Clinical diagnosis: (≥ one clinical observation)
        i. Abnormal uterine tenderness on bimanual exam in absence of other clinical or laboratory findings suggestive of another source of infection.
        ii. Concomitant foul-smelling discharge. *Blue top wound culture* to be performed if present.
        iii. Tachycardia (>100bpm)
        iv. Leukocytosis (<12,000 per mm^3)

c. Postpartum antibiotics given

d. Data Analysis and Monitoring:

Data will be collected prospectively in a blinded fashion as to study drugs or placebo arm. At randomization and throughout the hospital stay for the delivery, data regarding maternal demographic information, medical history, physical exam, and delivery information will be collected by research staff. These sheets will remain in the sole position of either Dr. Amy Valent, or the PI. During this time, any information regarding patient presentation to the clinic or hospital regarding wound infection or incisional issues will be relayed by the resident team to the two primary investigators (Valent and Warshak). Further information regarding wound complications will be collected on the data collection sheet. Once the patient has reached six weeks out, this sheet will be reviewed for completion. If the study participant has not followed up, the patient will be called as described above.

Once the data collection sheet is completed, it will be stored in a locked cabinet in the secured office of the PI. The data will be entered in to the REDCap database, which is secure, web based application designed to support data capture for research studies. After data is entered into REDCap, the datasheets will be discarded in appropriate secure confidential document receptacles per the University of Cincinnati Medical Center protocols. The data will remain blinded until all analyses are completed by Emily DeFranco who will blinded to study group designation and not involved in study recruitment or data collection. At this time, all data will be unblinded, entered into SPSS software package spreadsheets for evaluation and analyzed. Statistical analysis will be performed using STATA software (STATA, release 12; Stata-Corp, College Station, TX USA).

Demographic characteristics will be compared between women who received cephalexin-metronidazole and placebo using one-way ANOVA for continuous variables and Chi square tests for categorical variables. Logistic regression will be used to determine the relative risk of SSI between women who received cephalexin-metronidazole compared to placebo, and the number needed to treat to prevent one SSI will be calculated. The analysis will be performed with an intention to treat principle. Comparisons with a probability value <0.05 or 95% confidence interval without inclusion of the null were considered statistically significant.

e. Data Storage and Confidentiality:

All data will be deidentified for the purposes of protecting of study participant confidentiality. Data collection sheets and subsequent spreadsheets will therefore be removed of any identifying information. These hard paper copies and electronic spreadsheets will remain on the University of Cincinnati Medical Center and College of Medicine property throughout the duration of the study. Access will be limited to the two primary investigators (Valent and Warshak) and Srini Reddy who will have limited access to enter data in to REDCap and follow up with study participant providers regarding postpartum outcomes.

f. Risk/benefit Assessment:

1. LEVEL OF RISK

There are minimal, but present sources of risk for participants of this study. All patients in the study will receive the standard 2 grams of cefazolin prior skin incision. The additional exposure to cephalexin is unlikely in induce an allergic reaction after receiving a cephalosporin preoperatively without adverse events. Potentially, subjects could have allergic reactions to metronidazole, however this is a widely used antibiotic in obstetrics and gynecology and allergic reactions are very uncommon. Respecting inappropriate use of antibiotics and the risks of microbial resistance, obese women are at very high risk for infection after a cesarean delivery with postoperative infectious complications that approach 25% and we believe the use of additional antibiotic prophylaxis can be justified.

The AAP takes a conservative approach to the majority of medications consumed by the breastfeeding mothers in the postpartum period. Metronidazole does cross into breast milk but no adverse neonatal effects have be reported[9]. The medication would be used in the first 48 hours were there is negligible milk formation and effects on colostrum composition are unknown. However, in light of this concern, it would be reasonable to have study participants consider pumping and discard for these 2 days if participants are concerned of the overall low risk and unknown data.

2. HOW ANTICIPATED BENEFIT JUSTIFIES THE RISK

Because obese women have a significant risk for post-cesarean infection, broad spectrum postpartum antibiotics may decrease their risk for significant morbidity and costs associated with treatment of these uterine and wound infections. Often patients are admitted for many extra days, readmitted and require extensive use of home health care resources because of these common complications. This impacts not only mother-baby bonding but breastfeeding and overall recovery. If we are correct in our predictions regarding the substantial reduction in these complications there will be no question as to the benefit to patient care in this high risk population. Given the current rates of obesity in our country this will undoubtedly prove to be both a beneficial and cost-effective prevention strategy.

In comparison to the minimal risks stated above, the potential benefit far outweighs these risks. We must begin to understand how to treat our obese population better. This is especially true in the obstetrical population that has traditionally been considered low risk for medical complications given the perception women reproducing are healthy. While fortunately this is true in many instances, obese women are far from healthy and we know how obesity increases many significant complications of pregnancy. Obese women have much higher rates of cesarean delivery and postoperative infectious complications. Research to figure out how to ideally manage and prevent these complications is needed.

Payment: Study participants will not be paid for their participation in this project.

Study costs: There will be no cost to the subject. The cost of the additional antibiotic per patient: six 500 mg cephalexin capsules are $23.40 and six 500 mg metronidazole capsules are $34.20. There will also be a cost associated with development of the matched placebo pills. These medication costs will be covered by the internal study funds. All other care, demands on nursing staff and resident staff, medical visits, etc. are part of standard care.

g. **References**:

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Effect of post-cesarean oral cephalexin and metronidazole on surgical site infections among obese women: a randomized clinical trial

Patient Study Consent

UNIVERSITY OF CINCINNATI - Medical

CONSENT TO PARTICIPATE IN A RESEARCH STUDY

Study Title: Use of 48 Hour Course of Antibiotics to Prevent Surgical Site Infection in Obese Patients Undergoing Cesarean Delivery

UC IRB Study #: 2013-3717 Sponsor Name: Investigator-Initiated

Investigator Information:

Carri Warshak, MD (513) 558-6130 (619) 208-9966
Principal Investigator Name Telephone Number 24 hr Emergency Contact

Subject Name: _____ Date of Birth: _____/_____/____

INTRODUCTION:

A biomedical or health-related research study is performed to answer specific questions about a disease.

Before you agree to participate in this research study, it is important that you be told the purpose, procedures, benefits, risks, discomforts, and precautions of the research. You should also be told what alternative procedures are available to you if you do not participate in the research study. The informed consent document is a written summary of this information. Be sure to ask questions while you read this consent document and ask questions if there is anything that you do not understand.

Your participation in this research study is entirely voluntary.

You may choose either to take part or not to take part in this research study. If you decide to take part, you may decide to leave the study at any time. Leaving the study will not result in any penalty or loss of benefits to you. The researcher and sponsor of this study do not promise that you will receive any benefits from this study.

WHY IS THIS RESEARCH BEING DONE?

The purpose of this research study is to find out if the addition of a 48 hour course of antibiotics to the standard antibiotic treatment before cesarean section reduces post-surgical infection compared to the standard antibiotic treatment alone.

Currently, patients who are going to have a cesarean section have an antibiotic given by IV (a tube placed in the vein) before the surgery to reduce infection. However, in obese women, infection rates are 5 times higher than infection rates in non-obese women even though everyone receives the antibiotic before surgery. Obese women are more likely to have risk factors that increase the chance of infection. These include having diabetes, thickening fat layers where bacteria can grow, breathing problems, sleep apnea and low oxygen supply to the body or to the organs. In addition, the rate of infection is higher in women with high body mass index (a measure of how heavy you are related to how tall you are).

This study will look at the effect (good or bad) of the standard pre-surgery antibiotic given by IV followed by antibiotic pills taken for 48 hours after surgery compared to the standard pre-surgery antibiotic given by IV followed by placebo pills (an inactive pill) taken for 48 hours after surgery.

WHY HAVE YOU BEEN ASKED TO TAKE PART IN THIS RESEARCH STUDY?

You are being asked to take part in this research study because you are 13 years old or older, have a body mass index (BMI) ≥ 30, and you are going to have or recently had a cesarean section.

HOW LONG WILL YOU BE IN THE RESEARCH STUDY?

You will be in the research study for approximately 6 weeks after your cesarean section.

The researcher may decide to take you off this research study at any time. This may happen if you do not follow the researcher's instructions or the study requirements. The researcher may also take you off the study if it is in your best interest to stop participating. This may happen if your condition worsens, you are unable to tolerate side effects, or new information becomes available about the study medication or other medication options.

You may withdraw from the study at any time. If you decide to stop participating in the study, we encourage you to talk to the researcher and your regular doctor first so that stopping can be done safely. Another reason to tell your doctor that you are thinking about stopping is to discuss what follow-up care and testing could be most helpful to you.

You may be contacted in the future by representatives of the University of Cincinnati who are interested in asking you survey questions about your participation in this research study. If you choose to participate in the survey, your responses will be used for quality assurance purposes only.

WHO IS CONDUCTING THE RESEARCH STUDY?

This study is Investigator-Initiated.

The study is directed by Dr. Carri Warshak, the researcher at the University of Cincinnati. Medical supervision for the study is provided by Dr. Warshak.

HOW MANY PEOPLE WILL TAKE PART IN THE RESEARCH STUDY?

About 475 people will take part in this study at the University of Cincinnati.

WHAT IS INVOLVED IN THE RESEARCH STUDY?

If you choose to participate in this study, you will be "randomized" into one of the study groups described below. Randomization means that you are put into a group completely by chance. It is like flipping a coin.

Group 1 will receive the standard antibiotic treatment, cefazolin given by IV (through a tube in your vein) before surgery (during surgery when the umbilical cord is clamped) followed by a 48 hour course of antibiotic pills, cephalexin pill (500 mg three times a day) and metronidazole pill (500 mg three times a day).

Group 2 will receive the standard antibiotic treatment, cefazolin given by IV (through a tube in your vein) before surgery (during surgery when the umbilical cord is clamped) followed by a 48 hour course of 2 placebo pills (an inactive substance) three times a day.

Neither you nor the researcher conducting this study will know what group you will be in. You will have an equal chance of being placed in either group. However, in the event of an emergency, the researcher will be able to find out which treatment you are receiving.

The researchers will also record information about your medical history, medications you are on while in the hospital, information about your delivery, information about your health after delivery, whether or not you have an infection, fever, pain, or other health changes.

After you are released from the hospital, you will come back to the outpatient clinic in 2 weeks to have your incision checked for signs of infection. You will return again after 6 weeks from your surgery for another check of the incision site. If you are unable to come to the clinic, the researchers may call you to see how you are doing.

WHAT ARE YOUR RESPONSIBILITIES IF YOU PARTICIPATE IN THIS STUDY?

You will be responsible for coming to the researcher's office or hospital throughout the treatment period and follow-up period of the study.

You will be asked not to participate in any other clinical research studies taking another investigational medicine (study drug).

WHAT ARE THE RISKS AND DISCOMFORTS OF THE RESEARCH STUDY?

Risks associated with cephalexin (Keflex):

Likely:

- **Diarrhea**
- **Oral (mouth) or vaginal yeast infection**
- **Stomach cramps**

Unlikely:

- **Loss of appetite**
- **Fever**
- **Genital or anal itching**
- **Itching**
- **Increase in liver function tests**
- **Increase in kidney function tests**

Rare:

- **Allergic reaction**
- **Increased in eosinophils, a type of white blood cell**
- **Hepatitis (inflammation of the liver)**
- **Decrease in leukocytes, a type of white blood cell**
- **Nausea**
- **Vomiting**
- **Decrease in neutrophils, a type of white blood cell**
- **Phlebitis (inflammation of veins)**
- **Pseudomembranous colitis, an infection of the intestines**
- **Seizure**
- **Decrease in platelets in the blood**
- **Increase in platelets in the blood**
- **Vaginitis, inflammation of the vagina**

Very Rare:

- **Stevens-Johnsons syndrome, a serious skin condition**

Risks associated with metronidazole (Flagyl):

Likely:

- **Abdominal discomfort, abdominal pressure or bloating**
- **Diarrhea**
- **Nausea**

- **Vomiting**
- **Oral (mouth) or vaginal yeast infection**

<u>Unlikely:</u>

- **Painful urination**
- **Rash with redness of the skin**
- **Flushing, sudden redness of the face, neck, or chest**
- **Headache**
- **Incontinence, urinary leaking and/or frequent urges to urinate**
- **Decrease in neutrophils, a type of white blood cell**
- **Increase in urination or amount of urine**
- **Itching**
- **Unpleasant metallic taste**
- **Hives**
- **Development of microbial resistance, bacteria that becomes resistant to antibiotics**

<u>Rare:</u>

- **Aseptic meningitis, swelling of the covering of the brain and spinal cord that is not caused by a bacteria**
- **Convulsive seizures**
- **Inflammation of the bladder**
- **Darkened urine**
- **Encephalopathy, a brain condition with the following symptoms: subtle personality changes, inability to concentrate, lethargy, progressive loss of memory and thinking abilities, progressive loss of consciousness, and abnormal involuntary movements.**

- **Inflammation and redness of the tongue• Flattening of the T-wave on EKG, which may be a sign that there isn't enough blood getting to the heart muscle or a sign that the heart muscle is thickening**
- **Damage to the optic (eye) nerves and to damage to the nerves outside the spinal cord and brain**
- **Inflammation of the pancreas**
- **Sense of pelvic pressure**
- **Inflammation of the mucous lining of the mouth**
- **Decrease in the platelets in the blood**
- **Inflammation of the veins**

<u>Very Rare:</u>

- **Stevens-Johnsons syndrome, a serious skin condition**

You should not drink alcohol while taking metronidazole, and for several days

after you stop taking it. Common side effects from drinking alcohol while taking metronidazole include fast heartbeat, warmth or redness under the skin, tingly feeling, nausea, and vomiting.

The use of an intravenous catheter (IV) may cause pain, bruising, and possibly infection at the site of the intravenous catheter placement.

There may be unknown or unforeseen risks associated with study participation.

WHAT ARE THE REPRODUCTION RISKS?

Cephalexin is excreted into breast milk in low concentrations. Although not specifically listing cephalexin, the American Academy of Pediatrics classifies other cephalosporin antibiotics as compatible with breast feeding.

Metronidazole is excreted into breast milk. Because of the unknown consequences of exposure in the nursing infant, the American Academy of Pediatrics recommends using metronidazole with caution during lactation. However, metronidazole has been used during lactation for a variety of post-partum and gynecologic infections with no demonstrated or consistent side effects for infants.

ARE THERE BENEFITS TO TAKING PART IN THE RESEARCH STUDY?

If you agree to take part in this research study, there may or may not be a direct medical benefit to you. We hope the information learned from this research study will benefit other patients who are obese and will have a cesarean section in the future. Potential benefits to you may include: having no post-surgical infection or having a less severe infection.

WHAT OTHER CHOICES FOR CARE ARE THERE?

Instead of being in this research study, you will receive the standard antibiotic treatment, cefazolin given by IV (through a tube in your vein) before surgery and at 'cord clamp' (during surgery when the umbilical cord is clamped).

HOW WILL INFORMATION ABOUT YOU BE KEPT PRIVATE AND CONFIDENTIAL?

Every effort will be made to maintain the confidentiality of your medical and research records related to this study. Agents of the University of Cincinnati, members of the research team in the Department of Obstetrics and Gynecology, and the Institutional Review Board (IRB) will be granted direct access to your original medical and research records for verification of clinical trial (research study) procedures or study data without violating your confidentiality, to the extent permitted by the applicable laws and regulations. By signing this consent form, you or your legally authorized representative is authorizing such access.

The data from the study may be published; however, you will not be identified by name. Your identity will remain confidential unless disclosure is required by law.

AVAILABILITY OF INFORMATION

You will receive a copy of this signed and dated consent form.

You will be told about any new information from this or other studies that may affect your health, welfare, or willingness to stay in this study.

WHAT ARE YOUR COSTS TO BE IN THIS STUDY?

There are no additional costs to you by participating in this study. The study-related medications will be provided at no cost.

You and/or your insurance company will be responsible for your hospital stay and delivery charges because these are part of your regular care. You and/or your insurance will be responsible to cover any costs related to treating infections that may occur while on this study.

WILL YOU BE PAID TO PARTICIPATE IN THIS RESEARCH STUDY?

You will not be paid for your participation in this study.

WHAT COMPENSATION IS AVAILABLE IN CASE OF INJURY?

In the event that you become ill or injured from participating in this research study, emergency medical care will be provided to you. The University of Cincinnati will decide on a case by case basis whether to reimburse you for your out of pocket health care expenses.

WHAT ARE YOUR RIGHTS AS A PARTICIPANT?

You may choose either to take part or not to take part in this research study. If you decide to take part, you may decide to leave the study at any time. Leaving the study will not result in any penalty or loss of benefits to you. The investigators will tell you about new information that may affect your health, welfare, or willingness to stay in this study.

If you have questions about the study, you will have a chance to talk to one of the study staff or your regular doctor. Do not sign this form unless you have had the chance to ask questions and have received satisfactory answers.

Nothing in this consent form waives any legal rights you may have nor does it release the investigator, the sponsor, the institution, or its agents from liability for negligence.

WHO DO YOU CALL IF YOU HAVE QUESTIONS OR PROBLEMS?

If you have questions, concerns or complaints about this research study or to report a research-related injury, please contact the researcher Dr. Warshak at (513) 558-6130.

Please call the University of Cincinnati Medical Institutional Review Board at 513-558-5259 (Monday – Friday 8 am to 5 pm) if you:

- **Think the research has hurt you.**
- **Have general questions about giving consent or your rights as a research participant in this research study.**
- **Have questions, concerns, or complaints about the research.**
- **Cannot reach the research team or you want to talk to someone else.**

To report complaints or concerns to an independent agency in an anonymous and confidential manner, please call the Research Compliance Hotline at 1-800-889-1547.

PRIMARY CARE PHYSICIAN NOTIFICATION

****Please indicate below whether you want us to notify your primary care physician or your specialist of your participation in this study.**

_____ **Yes, I want the researcher to inform my primary care physician/specialist of my participation in this study.**

_____ **No, I do not want the researcher to inform my primary care physician/specialist of my participation in this study.**

_____ **I do not have a primary care physician/specialist.**

_____ **The researcher is my primary care physician/specialist.****

UNIVERSITY OF CINCINNATI - Medical

CONSENT TO PARTICIPATE IN A RESEARCH STUDY

Study Title: Use of 48 Hour Course of Antibiotics to Prevent Surgical Site Infection in Obese Patients Undergoing Cesarean Delivery

UC IRB Study #: 10-08-05-02 Sponsor Name: Investigator-Initiated

Investigator Information:

Carri Warshak, MD (513) 558-6130 (619) 208-9966
Principal Investigator Name Telephone Number 24 hr Emergency Contact

SIGNATURES

I have read or someone has read to me, this Informed Consent/Assent Document which describes the purpose and nature of this research. I have had time to review this information and have been encouraged to ask questions. I have received answers to my questions. If I do not participate or if I discontinue my participation, I will not lose any benefits. I will not lose any legal rights if I discontinue. My participation in this research is completely voluntary. I give my consent/assent to participate in this study. I have received (or will receive) a copy of this form for my records and future reference.

_____
Name of Participant (if under 18 years of age)

_____ _____
Signature of Participant if 18 years of age or older Date

_____ _____
Signature/Assent of Participant if under 18 years of age Date

_____ _____

Parent/Legal Guardian Signature **Date**
for participants under 18 years of age

_____ _____

WITNESS TO THE CONSENT/ASSENT PROCESS **Date**
{To be signed if the subject is unable to read the consent/assent document and it has been read to the subject instead}

<u>PERSON OBTAINING CONSENT/ASSENT:</u>

I have reviewed this form with the participant and/or representative. An explanation of the research was given and questions from the subject were solicited and answered to the subject's satisfaction. In my judgment, the subject has demonstrated comprehension of the information.

_____

_____

Signature and Title of Person Obtaining Consent/Assent Date and Identification of Role in the Study