

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

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Study Protocol

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26 **a. Specific Aims:**

27
28 **Specific Aim 1:** To evaluate if preoperative antibiotics, followed by 48 hour course of
29 postpartum oral cephalexin plus metronidazole prevents wound infection complications
30 in patients that are obese who undergo cesarean section. We hypothesize that a
31 prolonged, 48 hour course of cephalexin-metronidazole, suited to prevent growth of
32 normal vaginal flora, will decrease the rate of surgical site infection in obese patients
33 that are at a greatly increased risk of postoperative infections complications.

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

37
38 **Specific Aim 2:** To determine if a 48 hour course of postpartum oral cephalexin plus
39 metronidazole prevents wound infection complications and benefits obese women
40 undergoing cesarean section depending on membrane status prior to delivery (intact vs.
41 ruptured). A planned randomization scheme for both intact and rupture of membranes
42 prior to delivery will be performed. We hypothesize that 48 hour course of cephalexin-
43 metronidazole will decrease rates of surgical site infections in both cohorts – rupture of
44 membranes and intact membranes prior to delivery.

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

50
51 **b. Background:**

52 It is well recognized that obesity is the foremost epidemic challenging the health of
53 Americans. The rates of obesity are highly impacting our adolescent population and
54 disproportionately reproductive age women. It is estimated that approximately one third
55 of reproductive aged women are considered obese¹. Multiple studies have
56 demonstrated increased rates of complications such as miscarriage, gestational
57 diabetes, preeclampsia, birth defects, abnormal labor patterns and increased cesarean
58 section rates in obese women⁶. Maternal obesity further challenges cesarean sections,
59 increasing complications rates such as hemorrhage and infection⁷.

60 Multiple trials have consistently demonstrated a benefit for infection prevention
61 with preoperative cephalosporin antibiotics in patients undergoing cesarean section³. A
62 recent Cochrane Database review included 81 trials². The reviewers found that “the
63 use of prophylactic antibiotics in women undergoing cesarean section substantially
64 reduced the incidence of episodes of fever, endometritis, wound infection, urinary tract
65 infection and serious infection after cesarean section.” Specifically the risk of
66 endometritis with antibiotics was 0.39 (95% CI 0.31 to 0.43) for all patients. The risk for
67 wound infection was also reduced RR 0.41 (95% CI 0.29- 0.41). This risk reduction
68 appeared to be similar in groups undergoing both elective and non-elective cesarean
69 section. A small study of 160 patients randomized to cefazolin only versus cefazolin
70 with one dose of metronidazole preoperatively demonstrated a significant reduction in
71 the rate of postoperative infections.

72 No prior studies specifically addressed risk reduction in obese populations⁴.
73 Rates of post-cesarean surgical site infection following cesarean delivery in obese
74 patients are believe to be as high as 12% in studies, a 5 fold increase over normal
75 weight rates of infection. In addition, endometritis risks are also substantially higher,
76 and in total, postoperative infectious complications occur in 20-25% of these high risk
77 patients. Studies evaluating the relationship between obesity and postoperative
78 infections have demonstrated what appears to be a “dose-dependent” relationship
79 between class of obesity and rate of infectious morbidity⁵.

80 The surgical literature is inconclusive regarding optimal antibiotic regimens and
81 duration to prevent surgical site infections (SSI) especially for the growing obese
82 population. Strong data support that cefazolin pre-skin incision significantly decreases
83 postoperative infectious morbidity, however obesity is an independent risk factor for
84 postoperative infections despite this preoperative regimen. Metronidazole use for
85 infection prevention has shown promise in high risk populations, but the obese
86 population was not studied exclusively⁸. With the rising obese population and the
87 significant morbidity associated with postoperative surgical site infections following
88 cesarean deliveries, it is important to study promising antibiotic regimens that may help
89 decrease infectious risks in this population.

90 91 **c. Methods and Procedures:**

92
93 We propose the conduction of a prospective, randomized, double-blind clinical trial to
94 evaluate a prophylactic regimen for the prevention of surgical site infection. This study
95 is to be conducted by the Department of Obstetrics and Gynecology at the University of
96 Cincinnati Medical Center. The intervention being studied will be the continuation of
97 prophylactic antibiotics in the postpartum period with 48 hours of cephalexin 500mg and
98 metronidazole 500mg every 8 hours for a total of 6 doses per antibiotic. Forty-eight
99 hours of postpartum prophylactic antibiotics was chosen for this study since it is an
100 institutional standard for women to stay a minimum of 48-hours postoperatively and it is
101 within the spectrum that has been studied. The primary outcome measure will be the
102 development of surgical site infection (including cellulitis and endometritis) within the
103 first 30 days following the delivery.

104 105 106 **1. DESCRIPTION OF SUBJECTS (SAMPLE SIZE, PLAN SELECTION OF** 107 **PATIENTS)**

108
109 All patients to be considered for recruitment to this study will be undergoing delivery at
110 The University of Cincinnati Medical Center. Patients with an elevated BMI ≥ 30 kg/m²
111 who undergo cesarean section will be considered for randomization either prior to
112 delivery or in the first 8 hours after delivery, to accommodate the need for the first dose
113 of study medication or placebo 8 hours after surgery. Only patients who agree to
114 inclusion after informed consent will be randomized per protocol.

115 For the purposes of our study, we define overweight at a BMI of 25-29.9 kg/m²,
116 Class I Obese as 30-34.9 kg/m², Class II Obese 35-39.9 kg/m² and Class III Obese as
117 >40 kg/m². Women meeting the definition of obese, BMI ≥ 30 kg/m² who undergo

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

121 122 2. SAMPLE SIZE

123
124 Assumptions:

125 95% confidence ($p=0.05$), 80% power (standard), 1:1 ratio of exposed to unexposed.

126
127 The rate of postoperative infectious morbidity in obese women is estimated to be 20-
128 25% in the literature. Using a rate of disease of 20% and a 50% rate of reduced
129 infectious complications:

130
131 $RR = 0.50$

132 Rate of disease in unexposed: 20%

133 217 in each group, total 438

134
135 Therefore, we would plan to randomize 450-475 patients for study inclusion.

136 137 3. INCLUSION AND EXCLUSION CRITERIA

138
139 Specific inclusion criteria would include all:

- 140 1. Age 13 or older
- 141 2. $BMI \geq 30 \text{ kg/m}^2$
- 142 1. Delivery via cesarean section
- 143 2. Consent to randomization.

144
145 Exclusion criteria would include any:

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

152 153 4. GENDER, AGE, RACE, POSSIBLE VULNERABLE SUBJECTS

154
155 By definition, in this study all participants will be reproductive aged, female, pregnant
156 patients. Although this can be considered a vulnerable subject group, any study
157 medications would be given after delivery in the postoperative time period.

158 159 5. SOURCE FROM WHICH STUDY POPULATION WILL BE RECRUITED

160
161 Any patient presenting to Labor and Delivery for delivery will be considered for
162 inclusion. Patients will NOT be considered for study inclusion prior to admission for
163 delivery.

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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.

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

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

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

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

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

255 medication more than one hour before or after the scheduled time of administration, or
256 patient refusal to continue to participate. Investigators will remain blinded to the
257 intervention until all data analysis is complete, but will be integral to the determination of
258 the presence of postoperative infectious complications.
259

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

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

272
273 Infections will be determined using the following criteria:

- 274 1) Surgical site infection
 - 275 a. Infection within 30 days after operation
 - 276 b. Partial or total wound dehiscence
 - 277 c. Presence of purulent or serous wound discharge with induration
 - 278 d. Warmth/erythema
 - 279 e. Tenderness
 - 280 f. *Blue top wound culture* to be used perform wound sampling to ensure
281 appropriate bacteria covered with antibiotics
- 282 2) Febrile morbidity
 - 283 a. Persistent fever $\geq 38^{\circ}\text{C}$ (100.5°F) for ≥ 24 hours or temperature $>38^{\circ}\text{C}$ on
284 two occasions 4 hours apart
 - 285 b. Not associated with lower abdominal or pelvic tenderness on bimanual
286 exam
 - 287 c. No signs of infection elsewhere
- 288 3) Urinary tract infection
 - 289 a. $>10^5$ bacteria per mL urine
 - 290 b. Urinalysis & *Urine culture* to be obtained for sensitivities
- 291 4) Endometritis
 - 292 a. Temperature $\geq 38^{\circ}\text{C}$ (100.5°F) on 2 separate occasions
 - 293 b. Clinical diagnosis: (\geq one clinical observation)
 - 294 i. Abnormal uterine tenderness on bimanual exam in absence of
295 other clinical or laboratory findings suggestive of another source of
296 infection.
 - 297 ii. Concomitant foul-smelling discharge. *Blue top wound culture* to be
298 performed if present.
 - 299 iii. Tachycardia ($>100\text{bpm}$)
 - 300 iv. Leukocytosis ($<12,000$ per mm^3)

301 c. Postpartum antibiotics given

302
303 **d. Data Analysis and Monitoring:**

304
305 Data will be collected prospectively in a blinded fashion as to study drugs or placebo
306 arm. At randomization and throughout the hospital stay for the delivery, data regarding
307 maternal demographic information, medical history, physical exam, and delivery
308 information will be collected by research staff. These sheets will remain in the sole
309 position of either Dr. Amy Valent, or the PI. During this time, any information regarding
310 patient presentation to the clinic or hospital regarding wound infection or incisional
311 issues will be relayed by the resident team to the two primary investigators (Valent and
312 Warshak). Further information regarding wound complications will be collected on the
313 data collection sheet. Once the patient has reached six weeks out, this sheet will be
314 reviewed for completion. If the study participant has not followed up, the patient will be
315 called as described above.

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

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

335
336 **e. Data Storage and Confidentiality:**

337
338 All data will be deidentified for the purposes of protecting of study participant
339 confidentiality. Data collection sheets and subsequent spreadsheets will therefore be
340 removed of any identifying information. These hard paper copies and electronic
341 spreadsheets will remain on the University of Cincinnati Medical Center and College of
342 Medicine property throughout the duration of the study. Access will be limited to the two
343 primary investigators (Valent and Warshak) and Srinu Reddy who will have limited
344 access to enter data in to REDCap and follow up with study participant providers
345 regarding postpartum outcomes.

346

347 **f. Risk/benefit Assessment:**

348
349 1. LEVEL OF RISK

350
351 There are minimal, but present sources of risk for participants of this study. All patients
352 in the study will receive the standard 2 grams of cefazolin prior skin incision. The
353 additional exposure to cephalexin is unlikely to induce an allergic reaction after receiving
354 a cephalosporin preoperatively without adverse events. Potentially, subjects could have
355 allergic reactions to metronidazole, however this is a widely used antibiotic in obstetrics
356 and gynecology and allergic reactions are very uncommon. Respecting inappropriate
357 use of antibiotics and the risks of microbial resistance, obese women are at very high
358 risk for infection after a cesarean delivery with postoperative infectious complications
359 that approach 25% and we believe the use of additional antibiotic prophylaxis can be
360 justified.

361 The AAP takes a conservative approach to the majority of medications
362 consumed by the breastfeeding mothers in the postpartum period. Metronidazole does
363 cross into breast milk but no adverse neonatal effects have been reported⁹. The
364 medication would be used in the first 48 hours were there is negligible milk formation
365 and effects on colostrum composition are unknown. However, in light of this concern, it
366 would be reasonable to have study participants consider pumping and discard for these
367 2 days if participants are concerned of the overall low risk and unknown data.

368
369 2. HOW ANTICIPATED BENEFIT JUSTIFIES THE RISK

370
371 Because obese women have a significant risk for post-cesarean infection, broad
372 spectrum postpartum antibiotics may decrease their risk for significant morbidity and
373 costs associated with treatment of these uterine and wound infections. Often patients
374 are admitted for many extra days, readmitted and require extensive use of home health
375 care resources because of these common complications. This impacts not only mother-
376 baby bonding but breastfeeding and overall recovery. If we are correct in our
377 predictions regarding the substantial reduction in these complications there will be no
378 question as to the benefit to patient care in this high risk population. Given the current
379 rates of obesity in our country this will undoubtedly prove to be both a beneficial and
380 cost-effective prevention strategy.

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

390
391 *Payment:* Study participants will not be paid for their participation in this project.
392

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

399

400 **g. References:**

- 401 1. Prevalence of overweight and obesity among adults 1999-2000. 2010, at
402 <http://www.cdc.gov/nchs/products/pubs/pubd/hestats/obese/obese99.htm>.)
- 403 2. Hofmeyr GJ, Smaill FM. WITHDRAWN. Antibiotic prophylaxis for cesarean
404 section. Cochrane Database Syst Rev 2010:CD000933.
- 405 3. Tita AT, Rouse DJ, Blackwell S, Saade GR, Spong CY, Andrews WW. Emerging
406 concepts in antibiotic prophylaxis for cesarean delivery: a systematic review. *Obstet*
407 *Gynecol* 2009;113:675-82.
- 408 4. Meyer NL, Hosier KV, Scott K, Lipscomb GH. Cefazolin versus cefazolin plus
409 metronidazole for antibiotic prophylaxis at cesarean section. *South Med J* 2003;96:992-
410 5.
- 411 5. Robinson HE, O'Connell CM, Joseph KS, McLeod NL. Maternal outcomes in
412 pregnancies complicated by obesity. *Obstet Gynecol* 2005;106:1357-64.
- 413 6. Weiss JL, Malone FD, Emig D, et al. Obesity, obstetric complications and
414 cesarean delivery rate--a population-based screening study. *Am J Obstet Gynecol*
415 2004;190:1091-7.
- 416 7. Alanis MC, Villers MS, Law TL, Steadman EM, Robinson CJ. Complications of
417 cesarean delivery in the massively obese parturient. *Am J Obstet Gynecol*
418 2010;203:271 e1-7.
- 419 8. Elyan A, Mahran M, el-Maraghy M, Abou-Seeda M. Prophylactic intravenous
420 metronidazole in cesarean section. *Chemioterapia* 1984;3:67-70.
- 421 9. Passmore CM, McElroy JC, Rainey EA, D'Arcy PF. Metronidazole excretion in
422 human milk and its effect on the suckling neonate. *Br J Clin Pharmacol* 1988;26:45-51.

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

428

429 **Patient Study Consent**

430

431 UNIVERSITY OF CINCINNATI - Medical

432 CONSENT TO PARTICIPATE IN A RESEARCH STUDY

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

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

436 Investigator Information:

437 Carri Warshak, MD (513) 558-6130 (619) 208-9966
438 Principal Investigator Name Telephone Number 24 hr Emergency
439 Contact
440

441 Subject Name: _____ Date of Birth: ____ / ____ / ____
442

443 INTRODUCTION:

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

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

453 Your participation in this research study is entirely voluntary.

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

459 WHY IS THIS RESEARCH BEING DONE?

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

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

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

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

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

482 **HOW LONG WILL YOU BE IN THE RESEARCH STUDY?**

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

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

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

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

500 **WHO IS CONDUCTING THE RESEARCH STUDY?**

501 This study is Investigator-Initiated.

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

504 **HOW MANY PEOPLE WILL TAKE PART IN THE RESEARCH STUDY?**

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

506 **WHAT IS INVOLVED IN THE RESEARCH STUDY?**

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

510 Group 1 will receive the standard antibiotic treatment, cefazolin given by IV
511 (through a tube in your vein) before surgery (during surgery when the umbilical
512 cord is clamped) followed by a 48 hour course of antibiotic pills, cephalexin pill
513 (500 mg three times a day) and metronidazole pill (500 mg three times a day).

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

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

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

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

531 **WHAT ARE YOUR RESPONSIBILITIES IF YOU PARTICIPATE IN THIS STUDY?**

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

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

536 **WHAT ARE THE RISKS AND DISCOMFORTS OF THE RESEARCH STUDY?**

537 Risks associated with cephalexin (Keflex):

538 **Likely:**

- 539 • Diarrhea
- 540 • Oral (mouth) or vaginal yeast infection
- 541 • Stomach cramps

542 **Unlikely:**

- 543 • Loss of appetite
- 544 • Fever
- 545 • Genital or anal itching
- 546 • Itching
- 547 • Increase in liver function tests
- 548 • Increase in kidney function tests

549 **Rare:**

- 550 • Allergic reaction
- 551 • Increased in eosinophils, a type of white blood cell
- 552 • Hepatitis (inflammation of the liver)
- 553 • Decrease in leukocytes, a type of white blood cell
- 554 • Nausea
- 555 • Vomiting
- 556 • Decrease in neutrophils, a type of white blood cell
- 557 • Phlebitis (inflammation of veins)
- 558 • Pseudomembranous colitis, an infection of the intestines
- 559 • Seizure
- 560 • Decrease in platelets in the blood
- 561 • Increase in platelets in the blood
- 562 • Vaginitis, inflammation of the vagina

563

564 **Very Rare:**

- 565 • Stevens-Johnsons syndrome, a serious skin condition

566

567 Risks associated with metronidazole (Flagyl):

568 **Likely:**

- 569 • Abdominal discomfort, abdominal pressure or bloating
- 570 • Diarrhea
- 571 • Nausea

- 572 • Vomiting
- 573 • Oral (mouth) or vaginal yeast infection

574 **Unlikely:**

- 575 • Painful urination
- 576 • Rash with redness of the skin
- 577 • Flushing, sudden redness of the face, neck, or chest
- 578 • Headache
- 579 • Incontinence, urinary leaking and/or frequent urges to urinate
- 580 • Decrease in neutrophils, a type of white blood cell
- 581 • Increase in urination or amount of urine
- 582 • Itching
- 583 • Unpleasant metallic taste
- 584 • Hives
- 585 • Development of microbial resistance, bacteria that becomes resistant to
- 586 antibiotics

587

588 **Rare:**

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

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

608

609 **Very Rare:**

- 610 • Stevens-Johnsons syndrome, a serious skin condition

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

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

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

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

618 **WHAT ARE THE REPRODUCTION RISKS?**

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

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

628 **ARE THERE BENEFITS TO TAKING PART IN THE RESEARCH STUDY?**

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

634 **WHAT OTHER CHOICES FOR CARE ARE THERE?**

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

638 **HOW WILL INFORMATION ABOUT YOU BE KEPT PRIVATE AND CONFIDENTIAL?**

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

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

649 **AVAILABILITY OF INFORMATION**

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

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

653 **WHAT ARE YOUR COSTS TO BE IN THIS STUDY?**

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

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

660 **WILL YOU BE PAID TO PARTICIPATE IN THIS RESEARCH STUDY?**

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

662 **WHAT COMPENSATION IS AVAILABLE IN CASE OF INJURY?**

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

667 **WHAT ARE YOUR RIGHTS AS A PARTICIPANT?**

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

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

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

679 **WHO DO YOU CALL IF YOU HAVE QUESTIONS OR PROBLEMS?**

680 **If you have questions, concerns or complaints about this research study or to**
681 **report a research-related injury, please contact the researcher Dr. Warshak at**
682 **(513) 558-6130.**

683 **Please call the University of Cincinnati Medical Institutional Review Board at 513-**
684 **558-5259 (Monday – Friday 8 am to 5 pm) if you:**

- 685 • **Think the research has hurt you.**
686 • **Have general questions about giving consent or your rights as a research**
687 **participant in this research study.**
688 • **Have questions, concerns, or complaints about the research.**
689 • **Cannot reach the research team or you want to talk to someone else.**
690 **To report complaints or concerns to an independent agency in an anonymous**
691 **and confidential manner, please call the Research Compliance Hotline at 1-800-**
692 **889-1547.**

693 **PRIMARY CARE PHYSICIAN NOTIFICATION**

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

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

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

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

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

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709 UNIVERSITY OF CINCINNATI - Medical

710 CONSENT TO PARTICIPATE IN A RESEARCH STUDY

711

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

714

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

716 Investigator Information:

717 Carri Warshak, MD (513) 558-6130 (619) 208-9966

718 Principal Investigator Name Telephone Number 24 hr Emergency

719 Contact

720

721 SIGNATURES

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

730

731

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

734

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

737

738

739 _____
740 Signature/Assent of Participant Date

741 if under 18 years of age

742

743

744
745 _____
746 **Parent/Legal Guardian Signature** **Date**
747 **for participants under 18 years of age**

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

752

753 **PERSON OBTAINING CONSENT/ASSENT:**

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

758 _____
759 _____
760 **Signature and Title of Person Obtaining Consent/Assent Date and Identification of**
761 **Role in the Study**
762

763

764

765

766