Antibiotic **P**rophylaxis to **P**revent **O**besity-Related **I**nduction Complications in **N**ulliparae at **T**erm (APPOINT): A Pilot Randomized Controlled Trial

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Abstract

Obesity increases the risk of pregnancy complications, including among others puerperal infections and cesarean delivery, and risk rises with increasing body mass index (BMI). Since obese women are more likely to have comorbidities that would necessitate delivery prior to their due date (i.e. prior to 40 weeks gestation), and class III obesity specifically is an indication for delivery by 39 weeks, these patients have a high rate of labor induction. In nulliparous women from the general population (obese and non-obese), labor induction at 39 weeks (compared to expectant management) is associated with less morbidity and a lower cesarean rate. Antibiotic prophylaxis, standard before cesarean delivery, is associated with less post-cesarean infection if azithromycin is added to the standard cefazolin. In this placebo-controlled pilot trial, we will estimate the parameters necessary to calculate the sample size for a planned multicenter clinical trial of prophylactic antibiotics administered at the start of labor inductions of obese nulliparous women at term.

Specific Aims

The aim of this study is to estimate the parameters necessary to calculate the sample size for a clinical trial of prophylactic antibiotics administered at the start of labor inductions of obese nulliparous women at term.

Background and Significance

More than one-third of American adults are obese (1). Obesity, defined as a body mass index (BMI) ≥30 kg/m^2, increases the risk of pregnancy complications including hypertensive disorders, gestational diabetes, macrosomia, puerperal infection, cesarean delivery, and stillbirth (2-6). Risk of complications rises with increasing BMI (7), and women with class III obesity (BMI ≥40) have a risk of stillbirth that increases more sharply with advancing gestational age compared to women with lesser obesity (8).

Consequently, since June 2014, the Section of Maternal-Fetal Medicine at the University of Oklahoma Health Sciences Center has had a policy of delivering women at 39 weeks for the indication of class III obesity. We recently evaluated this practice change in a before-and-after cohort study and found that the policy did not affect the overall cesarean rate among women with class III obesity or rates of maternal or neonatal morbidity (9). In addition, a large (n >6000) randomized controlled trial of labor induction at 39 weeks versus expectant management (until 41 weeks) in low-risk nulliparous (including both lean and obese) women demonstrated that labor induction did not adversely affect neonatal morbidity but reduced the cesarean delivery and maternal morbidity rates (10). Therefore, we anticipate an increase in the rate of labor inductions.

Nulliparous women with class III obesity undergoing induction of labor at our center have a rate of puerperal infection (chorioamnionitis, endometritis, and/or cesarean wound infection) of 20% (9). In addition, chorioamnionitis is associated with an increased likelihood of cesarean delivery due to labor dystocia (11). In our population of class III obese nulliparous women undergoing labor induction, the cesarean delivery rate is 52% (9). Women with lesser degrees of obesity also have increased rates of infection and cesarean delivery than lean women.

Antibiotic prophylaxis is standard practice before cesarean delivery, since it results in lower rates of post-cesarean infection (endometritis and wound infection). A recent multicenter randomized controlled trial compared standard prophylaxis with intravenous cefazolin prior to the procedure to cefazolin and azithromycin; women in the trial were from the general obstetric population and were undergoing cesarean after labor and without the diagnosis of chorioamnionitis (12). The primary outcome (composite of endometritis and/or wound infection) was less likely with the expanded spectrum prophylaxis—12.0% compared to 6.1%, relative risk 0.51 (95% confidence interval 0.38-0.68). Both endometritis and wound infection, individually, also were significantly less likely with expanded spectrum prophylaxis. There are also data regarding antibiotic prophylaxis during the postpartum period. One trial showed that giving antibiotic prophylaxis for 48 hours postpartum in women with obesity (class I, II and III) who underwent cesarean delivery was associated with a decreased risk of surgical site infection – 15.4% in the placebo group vs 6.4% in the group receiving antibiotics, relative risk 0.41 (95% confidence interval 0.22-0.71) (13).

Antibiotic prophylaxis is not standard during labor inductions except as it relates to prevention of early-onset neonatal infection with group B streptococci (GBS) (14). That prophylaxis is with a narrow spectrum agent (penicillin or ampicillin). As mentioned above, there is a clear benefit of giving pre-operative antibiotic prophylaxis for patients undergoing cesarean delivery and also evidence for a reduction in surgical site infection in obese women receiving post-operative antibiotic prophylaxis. Therefore it is plausible that giving prophylactic antibiotics during labor induction to obese women, who are at higher risk for infection complications during and after labor and delivery, may decrease their risk for complications. We hypothesize that antibiotic prophylaxis given at the start of a labor induction in nulliparous women with obesity may reduce the rates of cesarean delivery and puerperal infection in this high-risk group. We propose to undertake a pilot randomized controlled trial to estimate the parameters necessary to calculate the sample size for a large, multicenter trial to test this hypothesis.

Experimental Design and Methods

Trial Design

We will enroll consenting women delivering at The Children's Hospital at OU Medical Center who meet enrollment criteria. Patients may be given information about the study during a third trimester prenatal care visit. However, they will be enrolled in the hospital before their labor induction is started.

The study will be registered with clinicaltrials.gov.

Inclusion criteria

- BMI ≥30
- No prior deliveries at or beyond 20 weeks gestation
- Undergoing induction of labor
- Gestational age 37 weeks or more
- Age 15-45

Exclusion criteria

- Fetal death prior to labor induction
- Known fetal anomaly
- Multiple gestation
- Ruptured membranes for more than 12 hours
- Chorioamnionitis or other infection requiring antibiotics at the start of the labor induction
- Previous myometrial surgery
- Allergy to azithromycin or beta-lactam antibiotics

Intervention

Women will be randomized 1:1 to receive either cefazolin 2 grams intravenously at the start of the labor induction and every 8 hours thereafter for a maximum of three doses and azithromycin 500 mg intravenously once at the start of the labor induction or like placebos of each drug. We will enroll 300 patients total: 100 with class I obesity (BMI 30-34), 100 with class II obesity (BMI = 35-39), and 100 with class III obesity (BMI = 40 or above). There will be a separate randomization scheme for each obesity class. The allocation tables for the randomization sequences will be computer-generated in randomly chosen blocks of size 4 and 6 and provided to the research pharmacist, who will prepare and deliver the treatment packets in the randomly assigned order.. Investigators, clinical personnel and patients will be blinded to allocation. The research pharmacist will not be blinded to allocation.

- Patients undergoing intrapartum cesarean delivery:
    - Per our institutional guideline, patients in whom intrapartum cesarean delivery is indicated will receive cefazolin 2 grams intravenously and azithromycin 500 mg intravenously within 60 minutes prior to skin incision, regardless of their assigned study group
- Patients with chorioamnionitis diagnosed intrapartum:
    - Per our institutional guideline, patients with an intrapartum diagnosis of chorioamnionitis will be treated with ampicillin 2 grams intravenously every 6 hours and gentamicin (dose based on weight) every 8 hours. If they deliver vaginally, both of those drugs will be discontinued after the first postpartum dose. If they undergo cesarean delivery, clindamycin 900 mg intravenously every 8 hours will be started, and all three drugs will be continued for 24-48 hours postpartum. These antibiotic drugs (used to treat chorioamnionitis) will be in addition to receiving the assigned study drugs or placebo. Patients with chorioamnionitis who undergo cesarean delivery will also receive prophylactic azithromycin 500mg intravenously at the time of cesarean.

Primary outcomes (there will be two)

- Cesarean delivery rate
- Puerperal infection rate (chorioamnionitis, endometritis and/or cesarean wound infection)

Secondary outcomes

- Other maternal complications
    - Individual infections above
    - Postpartum hemorrhage
    - Blood transfusion
    - Intensive care unit admission
    - Indications for cesarean delivery
    - Length of maternal hospital stay
    - Length of neonatal hospital stay
    - Maternal hospital readmission within 30 days after delivery
- Neonatal complications (established composite of neonatal morbidities)

Definitions

- Chorioamnionitis will be defined clinically by 1) a maternal temperature of 38.0 degrees Celsius or higher plus one or more of a) maternal heart rate over 100, b) baseline fetal heart rate over 160, c) fundal tenderness, d) purulent amniotic fluid, or 2) antibiotics administered for that indication.
- Endometritis will be defined clinically by 1) a maternal temperature of 38.0 degrees Celsius or higher plus uterine tenderness and/or foul-smelling lochia; or 2) antibiotics administered for that indication within 30 days after delivery.
- Cesarean wound infection will be defined according to the Centers for Disease Control and Prevention's National Healthcare Safety Network definitions for surgical site infections if occurring within 30 days after delivery and classified accordingly as superficial, deep and/or organ space (15).

Gender/Minority/Pediatric Inclusion for Research

Since only women become pregnant and undergo labor induction, all subjects in this study will be pregnant woman and fetus/infant dyads. The inclusion of minorities is anticipated in keeping with the racial/ethnic distribution of our obstetric population. Therefore, we anticipate including about 15% African-Americans, 45% Caucasians, 29% Hispanics, and 11% of other ethnicities.

Human Participants

Women with scheduled labor inductions will be screened by study personnel for eligibility. They will be approached about participation when they present for their scheduled induction. Since these women will not be in labor and it will be emphasized that participation is not required, coercion should not be an issue. Those women agreeing to participate will be consented by trained study personnel in their preferred language. We will have both English and Spanish consent forms.

Because we will have consent forms in both English and Spanish, and since our patient population is 29% Hispanic, we anticipate enrolling non-English speaking participants. In

addition to the Spanish consent form, hospital translation services will be utilized.

This study will include 300 female patients ages 15-45 who will meet the above enrollment criteria. We will recruit 100 women with class I obesity, 100 women with class II obesity, and 100 women with class III obesity. No specimens will be collected. Clinical data will be recorded at the time of enrollment. Clinical data will also be abstracted later from the medical record. A data collection form is attached.

The patient's treating physician will discuss the treatment options and the risks and benefits of participating in this clinical trial. The patient will have the opportunity to review the consent and ask questions, and these questions will be answered to the patient's satisfaction. Patients will be given adequate time to consider participation in the study and will in no way be coerced into participating.

Participants will be contacted via phone by a member of the research team at 30 days after delivery to assess for occurrence of any of the primary or secondary outcomes at a location outside of our institution.

Risks/Benefits

Risks to participants are largely those that would occur during the labor induction that the patient would be undergoing if not enrolled in the study. These risks will be similar in women with each class of obesity (I, II, and III) and include risk of prolonged labor or cesarean delivery; these risks would be present during the labor induction whether or not the patient is enrolled in the study. There is a risk of allergic or other adverse reaction to the prophylactic antibiotics that are the study intervention, however known allergy to either study drug will be an exclusion criteria for participation in the study. The likelihood of allergic reaction should be on the order of 1 in 100,000 to 1 in 1,000,000.

The potential benefits of enrolling in the study would result from being randomized to the active drug group if our hypothesis turns out to be true related to one or both of the primary outcomes. The above risks are reasonable in relation to benefits, since the likelihood of adverse events is low and since most similar patients not included in the study will be exposed to the same antibiotics during the delivery admission.

To protect the privacy and confidentiality of research subjects, we will assign each participant a study ID number in REDCap. This ID number will be linked to the patient's name and medical record number only via a key that will be maintained in a locked file drawer in the research coordinator's locked office. Once data collection is complete, the key will be destroyed, and the de-identified data will not be able to be linked to participants. Researchers will protect against loss of confidentiality by keeping all data containing PHI in a locked cabinet or on a password-protected, encrypted computer. Only key personnel will have access to PHI. Interactions and data analysis will be held in a private area.

Data and Safety Monitoring Plan

All adverse events will be reviewed by the PI and co-investigators and reported to the IRB according to institutional guidelines. All research data will be stored on a password-protected computer in the administrative offices of the Section of Maternal-Fetal Medicine. Any paper records and CRFs will be stored in a locked file drawer in the locked office of the research coordinator that is also located in the administrative offices of the Section of Maternal-Fetal Medicine. Since this study is a pilot which initially included only 100 participants, we did not

assemble a Data and Safety Monitoring Board. With the inclusion of an additional 200 patients, we will convene a Data and Safety Monitoring Board. The DSMB will consist of three participants: two Obstetrics and Gynecology physicians and one statistician. No members of the DSMB will be co-investigators or key personnel on this study. The DSMB has met prior to this submission and has established a charter document (see attached). The DSMB will convene every six months to review data and assess risk-benefit ratio of the study intervention, and will also meet as needed to review any study-related adverse events. Prior to each DSMB meeting, the PI will provide information regarding protocol adherence, outcome variables, adverse events, recruitment, and data quality. At the twice yearly review, the DSMB may vote to modify the protocol or terminate study.

Statistical Analysis

We will enroll 300 women total: 100 women with class I obesity, 100 women with class II obesity, and 100 women with class III obesity. As previously mentioned, no sample size calculation has been performed since this is a pilot trial designed to estimate the parameters necessary to calculate the sample size for a large, multicenter trial. The enrollment numbers for the class I and II groups were chosen to match that of the original class III obese group. Since the sample sizes in each of the obesity classes will be 50 (n=50 in the placebo groups and n=50 in the active drug groups), the confidence limit around the proportions will be less than or equal to ±13%. In addition, practically speaking we have chosen a small enough number so as to limit the number of patients exposed to the potential study-related risks, but substantial enough to allow meaningful estimation of study parameters. This plan for sample size and analysis has been created with the collaboration of our statistician. We will not stratify the randomization by whether or not prophylaxis against early-onset neonatal infection with GBS is indicated at the beginning of the labor induction (due to known colonization). However, we will perform a secondary analysis stratified by whether GBS prophylaxis was received.

In total there will be 150 each in the placebo and active drug groups (for each of the three obesity classes, there will be 50 each in the placebo and active drug groups). We anticipate the rate of GBS prophylaxis to be 25-30%. Even if it is as high as 40%, there will be 90 women each in the placebo and active drug groups who were not also exposed to GBS prophylaxis.

For each of the three obesity classes separately, we will estimate the frequency of the primary outcomes in the placebo and active drug groups. Proportions and ninety-five percent confidence limits will be calculated for each of these outcomes. We will perform within-group comparisons of outcomes in the placebo and active drug groups for each of the three obesity classes individually. We will also perform a comparison of outcomes in the placebo and active drug groups using BMI as a continuous variable in order to determine whether there is a BMI cut point at which the antibiotic intervention significantly reduces infection complications. In addition to the co-primary outcome variables, this BMI evaluation will inform design of the next-step, larger multicenter trial.

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