
Multimodal Pain Management for Cesarean Delivery: A randomized control trial

Study Protocol

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1. Introduction

1.1 Abstract:

Opioid use and abuse has become a major medical problem in the United States. Over prescription of opioid medications is a major contributor to this growing problem. Cesarean delivery (CD) is the most commonly performed surgery in the US and women are generally given opioid medications for postoperative pain management. This is not a common practice in other developed countries. We believe that a multimodal pain management strategy is superior to current practices for control of postoperative pain after CD and will lead to a decrease in the use of opioid medications. This will have beneficial effects on patients' recovery and bonding with their newborns, as well as societal effects in reducing the burden of opioid abuse in the US. Our objective is to investigate the use of a multimodal pain regimen in pregnant patients undergoing CD. This is a randomized double-blinded, placebo controlled trial. The multimodal intervention consists of a pre-operative dose of IV acetaminophen (Ofirmev), infiltration of subcutaneous bupivacaine prior to skin incision, and a dose of IM ketorolac at time of fascial closure. These study medications are currently used in our patient population but not in a standardized fashion, not in every patient, and not always in combination with each other. The control group will receive placebo IV infusion preoperatively and an IM injection at fascial closure, and subcutaneous infiltration with normal saline before skin incision. Both groups will receive spinal regional anesthesia as per anesthesia team and then postoperatively, both groups will receive the current standard of care, which consists postoperative hydrocodone/acetaminophen and ibuprofen as needed depending on pain score. Our primary outcome of interest will be the total opioid intake in the first 48 hours after surgery. Secondary outcomes include time to first opioid given, pain scores at 6-12, 24 and 48 hours post op and on POD#7 and at 3, 6 and 12 months after hospital discharge, and the total number of opioid tablets left after discharge on post op day number 7. We will also evaluate patient satisfaction scores and total length of hospital stay. Our hypothesis is that our multimodal pain regimen will decrease the total opioid requirement in the first 48 hours after surgery.

1.2 Specific Aims:

Specific aim 1: To determine if multimodal pain management decreases opioid intake in the first 48 hours postoperatively.

Specific aim 2: To evaluate patient's pain scores and satisfaction postoperatively in those receiving the multimodal regimen and standard regimen.

Specific aim 3: To determine if multimodal pain management increases the length of time to first request for opioid pain medication postoperatively.

Specific aim 4: To determine the number of remaining opioid tablets from outpatient prescriptions at 7 days post-op.

Specific aim 5: To determine if multimodal pain management decreases chronic pain incidence at 3, 6 and 12 months

2. Background

Opioid abuse and overdose has become a significant health problem in the United States in the last decade. Prescription drug overdose is now the leading cause of death in 17 states.¹ Even more shocking, deaths from opioid overdose in women has increased by 400% from 1999-2010, compared with a 265% increase in men. Prescription of opioids has increased 10 fold in the last 20 years.² A recent study by Bartels et al showed that the majority of patients discharged after cesarean delivery (CD) used either no or <5 of their prescribed opioid pills, leaving the rest to be stored in unsecure locations.³

Multimodal pain control is a pain control strategy that uses different types of pain medication with different mechanisms of action.⁴ Many studies have investigated the use of multimodal pain regimens for surgical pain control in gynecology, obstetrics, orthopedics and other areas of surgery. Multimodal pain control may include any combination of different pain medications such as acetaminophen, non-steroidal anti-inflammatory medications like ibuprofen, ketorolac and diclofenac, gabapentin, local anesthetics like bupivacaine, and opioids in various forms.

Studies evaluating pain control management after hysterectomy found improvement in various patient outcomes with multimodal strategies. A study by Santoso et al in 2014 found patients to have significantly decreased post-operative length of hospital stay after hysterectomy if they received a multimodal pain regimen vs. standard postop morphine PCA (1.6 days vs. 3.3 days).⁴ Several studies have also investigated subcutaneous bupivacaine at the time of hysterectomy, one study showed the pre-precision infiltration of bupivacaine significantly reduced opioid need in the first 72 hours post op⁵, while another study found no difference in morphine requirements when bupivacaine was infiltrated immediately after completion of the hysterectomy.⁶ This may indicate that there is an advantage to pre-incision infiltration prior to the initiation of tissue damage.

Studies of multimodal pain management in obstetrical literature have been promising. Several studies have shown improved postoperative pain control, improved bowel motility, and decreased opioid use when multimodal strategies are utilized.^{7,8,9,10,11,12,13} A study by Rosaeg et al in 1997 found that a multimodal strategy using intrathecal morphine, incisional bupivacaine and ibuprofen and acetaminophen was superior to morphine PCA and oral acetaminophen plus codeine in post op pain control in the first 24 hours and resulted in faster return of bowel function.⁷ A study by Ayatollahi in 2014 found that a pre-operative dose of intravenous (IV) Tylenol prior to CD resulted in lower pain scores, longer time until request for analgesic, and lower total dose of analgesic needed postoperatively. The aforementioned study also investigated neonatal outcomes and found no significant neonatal complications.¹⁰ A study by Munishankar et al in 2008 found that the combination of diclofenac and acetaminophen was superior to

acetaminophen alone in reducing total morphine intake.⁸ A study by Niklasson et al in 2012 found that intraoperative infiltration of bupivacaine prior to skin closure lead to decreased morphine requirement in the first 12 hours post op.¹¹

However, these were limited by their sample size, and none used a multimodal combination similar to the one we are proposing. Given the success with multimodal pain management in reducing opioid intake there is merit in further investigating these pain management strategies in our patient population.

3. Study Design

3.1 Primary Research Question:

Does a multimodal pain management approach decrease opioid use in the first 48 hours after cesarean delivery?

Hypothesis 1: Multimodal pain management in elective CD patients leads to decreased opioid (hydrocodone) intake in the first 48 hours post operatively compared to the current standard pain protocol.

3.2 Secondary Research Questions:

3.2.1 Does a multimodal pain regimen lead to pain control equal to or better than the current pain protocol?

Hypothesis 2: A multimodal pain regimen will result in lower pain scores and 6-12, 24 and 48 hours post CD compared with the current standard pain protocol.

3.2.2 Does a multimodal pain regimen lead to a longer time to first request for opioid pain medication compared to the current standard pain protocol?

Hypothesis 3: A multimodal pain regimen will result in a longer time to first request for opioid pain medication post-operatively.

3.2.3 Does a multimodal pain regimen result in less opioid pain pill use after discharge from the hospital on post op day 7?

Hypothesis 4: A multimodal pain regimen will result in less opioid pain pills used after discharge on post op day 7 compared to the current standard pain protocol.

3.2.4 Does a multimodal pain regimen result in less chronic pain incidence after discharge from the hospital at 3, 6 and 12 months?

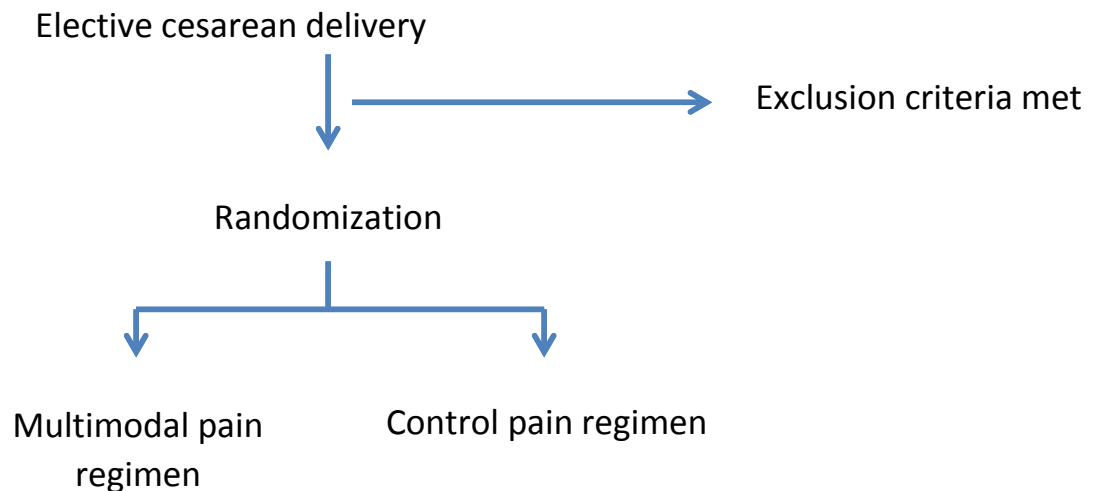
Hypothesis 5: A multimodal pain regimen will result in less chronic pain incidence after discharge from the hospital at 3, 6 and 12 months compared to the current standard pain protocol.

3.3 Design Summary

We are proposing a double-blinded, placebo controlled, randomized trial of patients undergoing elective cesarean delivery. Participants will be randomized to either a control group or study group. This is a double-blinded study, neither participants nor the obstetric or anesthesia team are aware of study assignment. The study group, aka

multimodal group, will receive 1 g of IV acetaminophen (ofirmev) within 30 minutes before starting the surgery, regional anesthesia (spinal anesthesia only) with fentanyl, duramorph (morphine) and bupivacaine will be performed as per anesthesia team, the anticipated sight of skin incision will be infiltrated with 20 mL of bupivacaine 0.25% in the subcutaneous space prior to skin incision, and 60 mg of intramuscular (IM) ketorolac (toradol) will be given at the time of fascial closure. The control group will receive a placebo drip within 30 minutes before starting the surgery, regional anesthesia (spinal anesthesia only) with fentanyl, duramorph (morphine) and bupivacaine will be performed as per anesthesia team, the anticipated sight of skin incision will be infiltrated with 20 mL of normal saline in the subcutaneous space prior to skin incision, and an IM dose of placebo at the time of fascial closure. Post-operatively both groups will be managed similarly; with pain medications to include ibuprofen 600 mg PO q 6 hours PRN pain 1-3 or 4-6 and oral hydrocodone/acetaminophen 5/325 mg 1-2 tabs PO q 4 hours PRN pain 7-10 or for pain not relieved by non-narcotic pain medication. The rest of the obstetrical care, including the need for breakthrough intravenous pain medications, will be similar in both arms and guided by center specific clinical guidelines. Total patient opioid use at 48 hours will be recorded along with timing of their first administration of opioid pain medication. At time of enrollment, patient will be asked to rate their pain on the numerical rating pain score (0-10) in the last week, last 24 hours and current pain. Pain scores on the numerical rating pain score at 6-12, 24 and 48 hours post operatively will be recorded. All patients will be given the same discharge pain medications consisting of Tylenol #3 30 tablets and ibuprofen 600 mg, 30 tablets (as is our current standard practice). Patients will be called on post op day #7 and asked to report how many Tylenol #3 pain tablets are left from their discharge prescription and to rate their satisfaction with their post-operative pain management. For chronic pain assessment, patients will be called and asked for numerical rating pain score (0-10) at 3, 6 and 12 months after hospital discharge or will be collected from patient's medical records if available.

Design



3.4 Eligibility Criteria

3.4.1 Inclusion Criteria:

- Women who are 18 – 45 years of age at the time of cesarean delivery with the ability to give informed consent
- Elective cesarean delivery
- Gestational age \geq 34 weeks
- Fluent in either English or Spanish
- Spinal anesthesia

3.4.1.1 Gestational Age Determination

Gestational age is determined in the following manner and is denoted as “project gestational age (GA).” The “project estimated date of confinement (EDC),” which is based on the project GA, cannot be revised once a determination has been made. Because the project EDC depends on information from the earliest dating ultrasound, if no ultrasound has been performed previously, one must be performed before the patient can be enrolled.

1. The first day of the last menstrual period (LMP) is determined and a judgment is made as to whether or not the patient has a “sure” LMP date.

2. If the LMP date is unsure, the ultrasound measurements obtained at the patient’s first ultrasound examination are used to determine the project GA by the standard method of ultrasound GA determination at that institution.

3. If the LMP date is sure and the ultrasound confirms this GA within the number of days specified in Table 3 1, then the LMP-derived GA is used to determine the project GA.

4. If the ultrasound-determined GA does not confirm the LMP-generated GA within the number of days specified in Table 3-1, then the ultrasound is used to determine the project GA.

Table 3-1. Cutoffs for Using LMP to Determine Gestational Age

Gestational age range at first ultrasound by LMP	Method of measurement	Ultrasound agreement with LMP
$\leq 8 \frac{6}{7}$ weeks	CRL	± 5 days
9 $\frac{0}{7}$ weeks to 13 $\frac{6}{7}$ weeks	CRL	± 7 days
14 $\frac{0}{7}$ weeks to 15 $\frac{6}{7}$ weeks	BPD, HC, AC, FL	± 7 days
16 $\frac{0}{7}$ weeks to 21 $\frac{6}{7}$ weeks	BPD, HC, AC, FL	± 10 days
22 $\frac{0}{7}$ weeks to 27 $\frac{6}{7}$ weeks	BPD, HC, AC, FL	± 14 days
28 $\frac{0}{7}$ weeks and beyond	BPD, HC, AC, FL	± 21 days

3.4.2 Exclusion Criteria:

- Urgent or emergent CD
- Active labor
- Epidural or combined spinal epidural anesthesia
- General anesthesia
- Patients with a contraindication for spinal anesthesia
- Acute or chronic hepatic disease
- Acute or chronic renal disease
- Active asthma
- Gastrointestinal ulceration
- Inflammatory bowel disease
- Allergy to ketorolac, acetaminophen, hydrocodone, codeine, ibuprofen or bupivacaine
- Opioid dependence
- Non reassuring fetal or maternal status requiring immediate delivery
- Placenta previa or accreta
- Acute or chronic pain disorder
- Maternal weight <50 kilograms
- Uncontrolled hypertension
- Ischemic cardiac disease
- Congestive heart failure
- Thrombocytopenia, platelet count <150,000/microliter
- Preeclampsia including Hemolysis Elevated Liver enzymes Low Platelets syndrome
- DIC or active hemorrhage before randomization
- Estimated blood loss > 2000 mL

3.5 Study Procedures

3.5.1 Informed consent

Written informed consent must be obtained from patients before they can be randomized into the study. Full disclosure of the nature and potential risks of participating in the trial are to be made. Women who are not fluent in English will be enrolled by a person fluent in their language. Both verbal and written informed consent and authorization will be obtained in that language; if this is not possible, the patient will not be included. A copy of the signed consent form will be provided to the patient.

3.5.2 Screening

Under the direction of the study team members, we will enroll patients at the time of admission to labor and delivery (L&D) for delivery by scheduled cesarean section. Medical records of all potential patients will be reviewed and those who satisfy inclusion and exclusion criteria will be approached for informed consent. A screening log will be used to track all patients approached for the study.

3.5.3 Randomization and Masking

After obtaining informed consent, women undergoing a scheduled cesarean delivery will be randomized to either control or study groups according to a randomization sequence

that is computer generated and maintained by investigational drug pharmacy. A study enrollment log with a study ID number will be used to track enrolled patients. The investigational pharmacy will be notified after randomization and study drugs or placebos will be sent as dictated by patient's randomization group.

3.5.4 Drug Administration

When the patient decides to participate in the study, they will be randomized to Group A or Group B (either the multimodal group or placebo group as known only to the investigational pharmacist). Patients will receive the pre-operative dose of either IV acetaminophen 1 g or IV normal saline placebo within 30 minutes of going to the OR for CD. The patient will receive the subcutaneous infiltration of either 20 mL of bupivacaine 0.25% or 20 mL of subcutaneous normal saline placebo after positioning and preparation but prior to skin incision. At the time of fascial closure, the patient will receive 60 mg of IM ketorolac or an IM dose of normal saline placebo. Group A and B will have the same post-operative pain control orders in the electronic medical record. These orders will include oral hydrocodone/acetaminophen 5/325 mg 1-2 tabs PO q 4 hours PRN pain 7-10 or for pain not relieved by non-narcotic pain medication and ibuprofen 600 mg PO q 6 hours PRN pain 1-3 or 4-6. All patients will be discharged with a prescription for Tylenol #3, 30 tabs and ibuprofen 600 mg, 30 tabs, as is the current standard of care at UTMB. Pre-, intra-, and post-operatively, the anesthesia team will be instructed not to give additional medications to patients enrolled in the study.

Study design and medications were reviewed with a faculty member in the Department of Anesthesiology. Will proceed with subcutaneous bupivacaine only in patients with spinal anesthesia (exclude epidural and intrathecal as the dose of bupivacaine would approach toxic levels). We will use IM ketorolac instead of IV given its longer duration of action.

3.5.5 Baseline Procedures

- Routine pre-, intra- and post-operative care will be provided to patients in both groups by their clinical providers.
- Pain scores will be obtained from the patient using a 0-10 scale at regular intervals post operatively.
- Providers will be given in-service training on the procedure to inject bupivacaine prior to skin incision
- Screening patients in L&D for eligibility will be performed by members of the research team daily during the study period.
- If a scheduled CD patient is deemed eligible for participation, the investigational pharmacy will be notified the day prior to CD to have the medications prepared in advance
- Data extraction from the chart will be performed by trained members of the research team.
- All data will be de-identified after collection and tracked only with a study ID number

- Total opioid use, time to first opioid use, and pain scores will be extracted from the medical record by members of the research team.

3.5.6 Data and Safety Monitoring Plan

- Data collected will include: a patient accrual log, patient demographic and medical information relevant to the study, and patient outcomes. A record of patients that have a protocol deviation or violation, any unanticipated problems, or adverse events will be kept as well.
- Data will be collected each time a patient is enrolled in the study. Their data will be collected throughout the hospital course. This includes pre-operative demographic and medical history information, peri-operative data with record of timing of study drug administration, peri-operative and intra-operative events (time of skin incision and drug administration and adverse events) will be recorded, postoperative data will be collected from the patient's chart (pain scores and adverse events), and the care team will be asked to notify the PI if an adverse event occurs in the postpartum period. Data will again be collected a 2 weeks post-op via a telephone call.
- Data will be collected by all members of the research team. The data will be monitored by the PI, Emily Hadley and the faculty sponsor, Maged Costantine.
- The data will be analyzed after the goal study accrual has been obtained (120 subjects)
- If adverse or unanticipated events occur they will be investigated by the PI and addressed appropriately.
- When an adverse or unanticipated event occurs the patient's course will be reviewed by the PI and faculty sponsor. If the event appears to be related to the study, a report will be made to the IRB as per IRB policies and procedures, serious events will be reported within 24 hours. Non-serious events and issues will be reported within 10 days as per IRB policy. These reports will be made by the PI, Emily Hadley.
- If an adverse event, that is believed to be related to the study medications occurs, the patient will be assumed to have received the study drugs and managed accordingly.
- If a trend of significant severe adverse events is identified, data will be evaluated closely and if the ongoing study is thought to be unsafe or pose undue risk to participants it will be stopped prior to accrual of the goal 120 participants.

3.5.7 Study Visits/Follow-up

- At time of enrollment, patients will be asked about demographic information and to rate their pain score for the last week, last 24 hours, and current pain.
- Maternal and delivery outcomes will be collected during hospital stay
- Patients will be discharged with a prescription for 30 tablets of Tylenol #3 as is the current standard of care

Patients will be called on postpartum day #7 and asked to report the number of remaining opioid tablets from their discharge prescription, to rate their satisfaction with postoperative pain management and rate their postoperative pain.

- Patients will be called at 3, 6, and 12 months after hospital discharge and asked for numerical rating pain score (0-10) or will be collected from patient's medical records if available

3.5.8 Procedures to Maintain Confidentiality

- Patients will be approached for participation in a private setting (their room in the labor and delivery unit). They will be given information about the study and allowed to ask questions in a private setting.
- Patient information collected will be only that which pertains to the study objectives. No unnecessary personal or medical information will be collected if not related to the study objectives.
- Data extraction from the medical chart will be performed by trained members of the research team.
- Each patient will be assigned a study ID number. This number will be used (instead of a medical record number or name) to identify the participant. All data will be de-identified after collection and tracked only with a study ID number. There will be a master list that connects the study ID with the medical record number, but only the research team will have access this information and will only use it if needed for clarification of data or a patient safety issue.
- Data will be stored on a password protected computer in a password protected network. Only the research team members listed on this IRB application will have access to the data during the collection period.

3.5.9 Study Benefits

- Improved postoperative pain control possible for those randomized to the multimodal pain control group.
- Improved pain control may decrease hospital admission times and allow for quicker ambulation post operatively
- Possibly less opioid pain requirement for those in the multimodal group
- Our findings may lead to an improved pain management strategy with less reliance on opioids for CD patients

3.5.10 Study Potential Risks

- There is a risk of loss of confidentiality of the patient's information, but as listed previously, every effort will be made to prevent this risk.
- The risks of this study are primarily associated with risks of the individual study drug. It is important to note that while these drugs have associated risks, all the study drugs included in this study are currently used (although not in a standardized fashion) on women undergoing CD in the perioperative period.
- Intramuscular ketorolac: serious but rare risks include GI bleeding, wound bleeding, anaphylaxis, bronchospasm, liver failure, kidney failure, myocardial infarction, congestive heart failure and Stevens-Johnson syndrome. More common but less serious side effects

include headache, nausea, dyspepsia, hypertension, abdominal pain, injection site irritation, and dizziness.

- Intravenous acetaminophen: serious but rare risks include anaphylaxis and liver failure. More common but less serious side effects include nausea and vomiting, headaches, insomnia, pyrexia, hypertension or hypotension and muscle spasm. Acetaminophen is a medication with excellent safety record in pregnancy with no known risk of fetal harm.
- Subcutaneous bupivacaine: Serious but rare risks include convulsions, anaphylaxis, heart block, arrhythmias, and hypotension. More common but less serious side effects include dizziness, nausea, injection site burning, skin tingling, severe skin itching, shivering, anxiety, and tinnitus. There is sparse data about the use of bupivacaine in pregnancy, but it is used regularly by anesthesia in their regional anesthesia. Animal studies have shown risks when given in the first trimester (during organogenesis), but there is not data of this kind for pregnancies at term. Given the small dose, mode of drug administration (subcutaneous injection), use only in spinal anesthesia patients, term pregnancy, and immediate delivery, the risks to the fetus and mother are minimal.
- All the study medication risks have been outlined for the patients on the consent form

4. Outcome Measures

4.1 Primary Outcome: The primary outcome of the study is the total opioid (hydrocodone) use in milligrams in the first 48 hours after cesarean delivery.

4.2 Secondary outcomes:

- 1- Time to first administration of opioid pain medication post operatively
- 2- Pain score at 6-12, 24 and 48 hours post operatively
- 3- Time to discharge from surgery
- 4- Maternal side-effects (nausea, vomiting, diarrhea, or any other unexpected adverse effect) and adverse events including any of the following:
 - a. Acute kidney injury: defined as an acute elevation of serum creatinine of ≥ 0.3 mg/dL above baseline during a period of 48 hours.
 - b. Acute liver injury: defined as an acute elevation in serum liver function tests $>$ twice baseline during a period of 48 hours.
 - c. Abnormal intraoperative bleeding: defined as estimated blood loss >1500 mL not explained by an intraoperative event such as adhesive disease or extension into uterine artery
- 5- Use of uterotonics other than routine use of oxytocin.
- 6- Administration of non-study protocol rescue pain medications intra- and post-operatively
- 7- Contributions of patient characteristics on efficacy of multimodal pain regimen.
- 8- Number of opioid pain tablets remaining on post-operative day #7 from the discharge prescription.
- 9- Hospital length of stay
- 10- Patient satisfaction score

11- Patient's numerical rating pain score at 3, 6, and 12 months after discharge

5. Statistical Considerations

5.1 Sample size calculation:

A chart review was performed on recent elective CD performed in the UTMB L&D and average total hydrocodone intake in the first 48 hours postop were recorded. The average hydrocodone intake was 48 mg (+/- 19). We aim to detect a 25% reduction in hydrocodone intake in the first 48 hours postop. We calculated a sample size of 53 subjects in each study arm to detect a 25% reduction with 90% power and an alpha of 0.05. If we assume approximately 10% loss to follow up, we will need approximately 60 subjects per study group, or 120 subjects total.

5.2 Interim Analysis

Interim statistical analyses will not be performed.

5.3 Unblinding Criteria

This is a double blinded study. Blinding will be maintained until completion of study procedures and data analysis. If a medical condition arises that requires unblinding, the patient will be treated assuming she received the active study drugs. If required by the medical team, and after discussion with the PI, the investigational drug pharmacy will be contacted to unblind the patient.

5.4 Feasibility: There are on average 1,845 cesarean deliveries at UTMB per year, if we assume that 1/3 of these are non-elective or non-scheduled, that would mean a total of 1,230 per year. Assuming 20% of women will be excluded, this leaves 984 eligible women per year to be approached for consent. With only 50% consent rate, almost 492 women may be randomized annually or 40 per month. Our conservative estimate suggests that this study can be completed in less than 6 months.

5.5 Data analysis: Analysis will be by intent-to-treat. Preliminary analyses will be conducted to test homogeneity of treatment groups for demographic data (gravidity, gestational age at randomization, race/ethnicity, BMI, number of prior cesarean) using the two-sample *t* test for continuous measurements and the Pearson chi-square test for categorical measurements. Primary and secondary outcomes will be analyzed between the two groups using univariable and multivariable analyses as needed.

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