A Randomized Controlled Trial to Assess the Effectiveness of Multimodal Prophylactic Uterotonics in Patients Undergoing Non-Elective Cesarean Sections after a Trial of Labor

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Nicole Masse, MD

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PI: Nicole Masse
IRB ID #: 201904756

Form Content

I. Project Introduction

I.1 ***Project to be reviewed by:***
IRB-01

I.2 ***Project Title:***
A Randomized Controlled Trial to Assess the Effectiveness of Multimodal Prophylactic Uterotonics in Patients Undergoing Non-Elective Cesarean Sections after a Trial of Labor

I.3 ***Short Title (optional):***

I.4 ***Provide a short summary of the purpose and procedures of the study proposed in this IRB application.***

- ***DO NOT include information on studies not proposed in this application.***
- ***Use LAY terminology only. This must be easily understandable by IRB community members and nonscientists.***
- ***DO NOT cut and paste technical abstracts from funding applications that may not be understood by a general audience.***

Postpartum hemorrhage remains a leading cause of maternal morbidity and mortality worldwide, even in high income countries. Uterine atony is estimated to cause 70-80% of postpartum hemorrhage. Prolonged labor and augmented labor are known risk factors for postpartum hemorrhage. In attempts to reduce the incidence of postpartum hemorrhage, particularly in patients with known risks factors, it is essential to optimize preventative practices in order to reduce the rates postpartum hemorrhage.

Although oxytocin is considered the first line therapy for preventing and treating uterine atony, early consideration of additional prophylactic uterotonic agents may be indicated in women with prior oxytocin exposure given oxytocin receptor desensitization and down regulation.

As such, we sought to examine whether multimodal prophylactic uterotonics (standard oxytocin + methylergonovine), in patients who are increased risk of developing postpartum hemorrhage (specifically laboring patients who ultimately require a cesarean section) would benefit from the addition of prophylactic uterotonics. The clinical rational for administration of multimodal prophylactic uterotonics at the time of cesarean delivery in laboring patients is three-fold: to decrease the incidence of uterine atony, to decrease the incidence of postpartum hemorrhage, decrease the number of uterotonics required at the time of cesarean section.

Our primary outcome will evaluate the need for additional uterotonic agents (Methylergonovine, Carboprost, Misoprostol).
Secondary outcomes will include the incidence of postpartum hemorrhage (quantitative blood loss >1 liter), surgical assessment of uterine tone four minutes following delivery of the placenta, preoperative and postoperative hemoglobin, the need for a blood transfusion, intensive care unit admission, uterine infection (endometritis)

Procedures of the Study:
Written informed consent will be obtained from all study participants. Patients will be consented at the time of their clinic visit or upon admission to labor delivery. Nicole Masse MD (or designated members of the research team) will be responsible for enrolling study participants. If patients ultimately require a cesarean section and meet study criteria, participants will receive routine oxytocin infusion at the time of cesarean section and will be randomly allocated to receive 200 mcg of intramuscular methylergonovine or placebo (1

ml of intramuscular saline) immediately after delivery of the newborn.

As prophylactic methylergonovine at the time of delivery is not currently the standard of care, the investigators (Maternal Fetal Medicine Department) will cover the cost of both the study drug (prophylactic methylergonovine) and the placebo drug (normal saline).

To detect a 2 fold decrease in the need for additional uterotonics (42% vs 21%) with a 2 sided type 1 error of 5% and power of 80%, a sample size of 76 patients per group will be necessary. To recruit this number of patients, an 18 month inclusion period is anticipated.

Inclusion criteria: patients who are least 18 years of age, laboring patients requiring a cesarean section. Reasons for cesarean section would include failure to progress in labor and nonreassuring fetal well-being.

Exclusion criteria: Known placenta or uterine anomalies. Patients with a history of chronic hypertension, gestational hypertension or preeclampsia will be excluded as these conditions are contraindications to the administration of methergine. HIV/AIDS patients on protease inhibitors (PIs) will be excluded as the concomitant use of methergine with PIs have been associated with exaggerated vasoconstrictive responses.

The randomization process will include:
--1:1 allocation using a randomized block design with mixed block sizes. A computer generated list of random numbers will be used to generate the allocation sequence - NQuery Advisor will be used to generate allocation sequence.
--Sealed envelopes will be prepared using the allocation concealment mechanism described above. Once a patient has met study criteria, the anesthesiologist will open the envelope to assess whether patient will be given study drug (methylergonovine vs placebo).

The allocation sequence and group assignment will be concealed from Nicole Masse (NM) who will be enrolling study participants.

The obstetrician (delivery provider) will be blinded to the group assignment. The treatment will be drawn up and administered by the anesthesiologist. The delivering provider will be responsible for determining and relaying to the anesthesiologist whether additional uterotonics are needed. Additional uterotonics will be given in accordance to the dose/routine/frequency recommended by the American College of Obstetricians and Gynecologists. The delivery provider will assess uterine tone at 4 minutes (satisfactory versus unsatisfactory). As routinely done at the time of cesarean delivery, the registered nurse will be responsible for measuring and documenting the quantitative blood loss. As routinely performed on all are patients who undergo a vaginal or cesarean delivery, preoperative hemoglobin and postoperative day one hemoglobin levels will be collected.

In the event a delayed postpartum hemorrhage was to occur, the obstetrician will be unblinded at the conclusion of the cesarean delivery as management of a delayed hemorrhage will be driven by the uterotonics received in the operating room. Although this will be a limitation of the study, the majority of our outcomes will be assessed at the time of cesarean section while providers are blinded.

I.5 ***Specify your research question(s), study aims or hypotheses (do not indicate "see protocol")***
The aim of this study is to test the hypothesis that multimodal prophylactic uterotonic administration at the time of cesarean delivery in laboring patients will be more effective in improving uterine tone, thus reducing the incidence of postpartum hemorrhage and reducing the need for additional uterotonic agents.

I.6 ***Background and significance and/or Preliminary studies related to this project. (do not indicate "see protocol")***
Postpartum hemorrhage remains a significant maternal morbidity at the University of Iowa. From December 2017 to February 2019, one fourth of our patients (26%) undergoing a cesarean section at the University of Iowa had a procedure complicated by a postpartum hemorrhage (blood loss greater than 1 liter).

Laboring patients who ultimately require a cesarean delivery are at increased risk for uterine atony which can result in a significant increase in intraoperative blood loss. Within the past twelve months at the University of Iowa, 42% of our laboring patients required additional uterotonics agents (methylergonovine, carboprost, misoprostol) at the time of cesarean section in addition to the standard oxytocin infusion. At the University of Iowa, first line uterotonics agents are given in accordance to recommendations outlined by the American College of Obstetricians and Gynecologists: Methergine 0.2 mg is administered as an intramuscular injection every 2-4 hours; Hemabate 0.25 mg is given as an intramuscular injection every 15 minutes for a maximum of 8 doses; misoprostol 600-1000 mcg if typically given rectally as a single dose.

Significant Studies Related to Project:
Senturk et al demonstrated that routine use of oxytocin with prophylactic methergine during the intraoperative and postoperative period to patients undergoing cesarean delivery considerably reduced the level of postpartum hemorrhage. No adverse effects were observed in the patients who received prophylactic methergine. Although not specifically looked at, Senturk et al believed prophylactic methylergonovine would

likely reduce the risk of uterine atony. One of our study outcomes will be looking at uterine tone following administration of the study drug to determine whether prophylactic methylergonovine decreased the incidence of uterine atony.

Lavioe et al demonstrated that women with prior exposure to exogenous oxytocin required a higher initial infusion rate of oxytocin to prevent uterine atony after cesarean delivery than women without prior exposure. Their group also found that laboring patients requiring a cesarean section required additional uterotonic agents compared to a scheduled cesarean/nonlaboring patients (34% vs 8%). This is likely secondary to oxytocin desensitization and down regulation in patients exposed to oxytocin prior to their cesarean delivery. Our study intends on administering multimodal prophylactic uterotonic agents in laboring patients undergoing a cesarean section as this may be more effective in improving uterine tone by using different medications which mechanisms are not affected by potential oxytocin desensitization and down regulation.

I.7 ***Literature cited / references (if attaching a grant or protocol enter N/A).***

References:

1. The American College of Obstetricians and Gynecologists. “Postpartum Hemorrhage.” Practice Bulletin, Number 183. October 2017.

2. Lavoie A, McCarthy RJ, Wong C. The ED90 of Prophylactic Oxytocin Infusion After Delivery of the Placenta During Cesarean Delivery in Laboring Compared with Nonlaboring Women: An Up-Down Sequential Allocation Dose-Response Study. Anesth Analg. 2015; 121:159-64.

3. Khan KS, Wojdyla D, Say L et al. WHO analysis causes of maternal death: a systemic review. Lancet 2006; 367:1066-74.

4. Senturk S, Kagitci M, Baluk G et al. The Effect of the Combined Use of Methylergonovine and Oxytocin during Cesarean Section in the Prevention of Post-partum Hemorrhage. Basin Clin Pharmacol Toxicol. 2016; 118(5)338-43.

5. U.S. Department of Health and Human Services (2018, December 7). Recommendations for the Use of Antiretroviral Drugs in Pregnant Women with HIV Infection and Interventions to Reduce Perinatal HIV Transmission in the United States. Retrieved from https://aidsinfo.nih.gov/guidelines/html/3/perinatal/183/other-intrapartum-management-considerations

II. Research Team

II.2 ***Team Members***

UI Team Members

Name	E-mail	College	Contact	Key Prsn	UI COI	VAMC COI	Consent Process Involvement	Deactivated
Nicole Masse, MD	nicole-masse@uiowa.edu	Carver College of Medicine	Yes	Yes	No		Yes	Yes
Mildrede Bonglack, MD	mildrede-bonglack@uiowa.edu	Carver College of Medicine	No	No	No		Yes	No
Rebecca Chung, BS	rebecca-chung@uiowa.edu	University Hospitals	No	No	No		Yes	Yes
Colette Gnade, MD	colette-gnade@uiowa.edu	Carver College of Medicine	No	No	No		Yes	Yes
Shelby Green, MD	shelby-r-green@uiowa.edu	Carver College of Medicine	No	No	No		Yes	No

Name	E-mail	College	Contact	Key Prsn	UI COI	VAMC COI	Consent Process Involvement	Deactivated
Leigh Hess, MD	leigh-hess@uiowa.edu	Carver College of Medicine	No	No	No		Yes	Yes
Danielle Ikoma, MD	danielle-ikoma@uiowa.edu	Carver College of Medicine	No	No	No		Yes	No
Emily Jacobs, MD, MS	emily-jacobs@uiowa.edu	Carver College of Medicine	No	No	No		Yes	No
Jordan Mattson, MD	jordan-mattson@uiowa.edu	Carver College of Medicine	No	No	No		Yes	Yes
Laura Rasmussen, MD	laura-rasmussen@uiowa.edu	Carver College of Medicine	No	No	No		Yes	No
Hope Richards, MD	hope-richards@uiowa.edu	Carver College of Medicine	No	No	No		Yes	Yes
Keely Ulmer, MD	keely-ulmer@uiowa.edu	Carver College of Medicine	No	No	No		Yes	No
Vincent Wagner, MD	vincent-wagner@uiowa.edu	Carver College of Medicine	No	No	No		Yes	Yes
Noelle Waldschmidt, BS	noelle-waldschmidt@uiowa.edu	Carver College of Medicine	No	No	No		Yes	No
Heather Winn, MD	heather-winn@uiowa.edu	Carver College of Medicine	No	No	No		Yes	Yes
Cynthia Wong, MD	cynthia-wong@uiowa.edu	Carver College of Medicine	Yes	Yes	No		No	No

Non-UI Team Members

Name	Institution	Location	FWA	Role	DHHS	Contact	Key Prsn	UI COI	VAMC COI	Consent Process Involvement	Email
Nothing found to display.											

II.3 ***The Principal Investigator of this study is:***
Fellow or Research Scholar

II.3.a ***Select the mentor or faculty advisor:***
Cynthia Wong

II.6 ***Identify the key personnel. The system will automatically designate the PI and all faculty members on the project as "key personnel." For information about other team members who should be designated as "key personnel" please click on the help information.***

Name	Is Key Personnel
Nicole Masse, MD	Yes
Mildrede Bonglack, MD	No
Rebecca Chung, BS	No
Colette Gnade, MD	No
Shelby Green, MD	No
Leigh Hess, MD	No
Danielle Ikoma, MD	No
Emily Jacobs, MD, MS	No

Name	Is Key Personnel
Jordan Mattson, MD	No
Laura Rasmussen, MD	No
Hope Richards, MD	No
Keely Ulmer, MD	No
Vincent Wagner, MD	No
Noelle Waldschmidt, BS	No
Heather Winn, MD	No
Cynthia Wong, MD	Yes

II.5 ***Select research team member who is the primary contact for study participants.***
Nicole Masse

III. Funding/Other Support

III.1 ***Funding Sources***

Source Entered as Text	DSP Link	Type	Source Grant Title	Name of PI on Grant
Source is entered as text * new source name	no	Departmental / PI Discretionary		

III.3 ***Does any member of the research team have a financial conflict of interest related to this project according to the Conflict of Interest in Research policy? If yes, please indicate which members below.***

Name	Has Conflict of Interest
Nicole Masse, MD	No
Mildrede Bonglack, MD	No
Rebecca Chung, BS	No
Colette Gnade, MD	No
Shelby Green, MD	No
Leigh Hess, MD	No
Danielle Ikoma, MD	No
Emily Jacobs, MD, MS	No
Jordan Mattson, MD	No
Laura Rasmussen, MD	No
Hope Richards, MD	No
Keely Ulmer, MD	No
Vincent Wagner, MD	No
Noelle Waldschmidt, BS	No
Heather Winn, MD	No
Cynthia Wong, MD	No

IV. Project Type

IV.1 ***Do you want the IRB to give this project***
Regular (expedited or full board) review

IV2 ***Enter the date you will be ready to begin screening subjects/collecting data for this project. (If you do not have a specified date, add "upon IRB approval")***
upon IRB approval

IV3 ***Are you requesting a waiver of informed consent/authorization (subjects will not be given any oral or written information about the study)?***
No

V. Other Committee Review

V.1 ***Does this project involve any substance ingested, injected, or applied to the body?***

- ***Do not answer yes, if the involvement includes a device, wire, or instrument***

Yes

V.1a ***What is/are the substance(s):***
Intramuscular Methylergonovine 0.2 mg (study drug)
Intramuscular Normal Saline 1 ml (placebo)

V.1b ***Are any of these substances defined as a Schedule I - V Controlled Substance?***
No

V.2 ***Are any contrast agents used for any purpose in this study?***
No

V.4 ***Are all drugs or substances in this study being used within the FDA approved population (i.e., children, adults)?***
Yes

V.5 ***Are all drugs or substances in this study being used within the FDA approved indication (i.e., disease, condition)?***
Yes

V.6 ***Are all drugs or substances in this study being used within the FDA approved dose?***
Yes

V.7 ***Are all drugs or substances in this study being used within the FDA approved route of administration?***
Yes

V.9 ***Will any subject be asked to undergo a diagnostic radiation procedure (including radiographic, nuclear medicine, DEXA)?***
No

V.14 ***Will any subject be asked to undergo a radiation therapy procedure (including external beam therapy, brachytherapy, or nuclear medicine therapy)?***
No

V.20 ***Does this project involve the deliberate transfer of recombinant or synthetic nucleic acid molecules, or DNA or RNA derived from recombinant or synthetic nucleic acid molecules, into one or more human research participant?***
No

V.21 ***Will any portion of this project be conducted in the CRU, or does it use any CRU resources?***
No

V.22 ***Will this project use:***

- ***any resource/patients of the Holden Comprehensive Cancer Center***
- ***involve treatment, detection, supportive care, or prevention of cancer***

No

V.25a ***Will the study involve any of the following activity at UI Health Care, even if subjects or their insurance will not be billed for the item or service, and regardless of the study funding source (including studies with departmental or no funding)?***

- ***Procedures, tests, examinations, hospitalizations, use of Pathology services, use of clinic facilities or clinical equipment, or any patient care services, including services conducted in the Clinical Research Unit; or***
- ***Physician services or services provided by non-physicians who are credentialed to bill (ARNPs, Physician Assistants, etc.)***

Yes

V25b ***Will there be any procedures or services that may happen as part of a subject's regular medical care and as part of the study?***
Yes

V25c ***Will any study equipment or devices be supplied by a study sponsor?***
Yes

V25d ***Please describe the equipment or device(s) being provided and what it will be used for***
As prophylactic methylergonovine prior to a cesarean section is not the standard of care - the department of maternal fetal medicine will be covering the costs of both methyergonovine and normal saline (placebo drug).

This will come out of an MLF account set up by Nicole Masse

V25e ***Is there or will there be an internal budget for this study?***
Yes

V25f ***Is there or will there be an external budget for this study?***
No

V.26 ***The study involves Department of Nursing Services and Patient Care nursing, nursing resources or evaluates nursing practices at UI Health Care.***
No

VI. Subjects

VI.1 ***How many adult subjects do you expect to consent or enroll for this project?***
3000

VI.2 ***What is the age of the youngest adult subject?***
18.0

VI.3 ***What is the age of the oldest adult subject?***
50.0

VI.4 ***What is the percentage of adult male subjects?***
0

VI.5 ***What is the percentage of adult female subjects?***
100

VI.6 ***How many minor subjects do you expect to consent or enroll for this project?***
0

VI.13 ***Describe EACH of your subject populations***

- ***Include description of any control group(s)***
- ***Specify the Inclusion/Exclusion criteria for EACH group***

Control Group: at the time of cesarean section, patients in the control group will receive the standard oxytocin infusion plus 1 ml of normal saline following delivery of the infant
Study Group: at the time of cesarean section, patients in the study group will receive the standard oxytocin infusion plus 0.2 mg of intramuscular methylergonovine following delivery of the infant

Inclusion: Pregnant patients who are least 18 years of age, laboring patients requiring a cesarean section.
Exclusion: Known placenta or uterine anomalies. Patients with a history of chronic hypertension, gestational hypertension or preeclampsia will be excluded as these conditions are contraindications to the administration of methylergonovine given the risk of hypertension associated with administration. HIV/AIDS patients on protease inhibitors (PIs) will be excluded as the concomitant use of administration with PIs have been associated with exaggerated vasoconstrictive responses.

VI.14 ***Provide an estimate of the total number of subjects that would be eligible for inclusion in each of your study populations (include your control population if applicable)***

With the exception of patients scheduled for a cesarean delivery and patients who have a contraindication to the study drug, all patients will be consented during their prenatal visit or at the time of arrival to labor and delivery. We chose to consent patients on arrival or at their prenatal visit to avoid consenting patients in labor at the time the cesarean section is called as this can be a stress provoking time for patients.

Of the patients consented (~3000), 160 patients will undergo a cesarean section. 80 patients will be enrolled in the control group, 80 in the experimental group.

VI.15 ***Describe how you will have access to each of your study populations in sufficient number to meet your recruitment goals.***

These patients will be identified by chart review to see if they meet inclusion for our study.

VI.16 ***Do you plan to recruit/enroll non-English speaking people?***

No

VI.18 ***Do you propose to enroll any of the following in this study as subjects?***

- ***Employee of the PI or employee of a research team member***
- ***Individual supervised by PI or supervised by member of research team***
- ***Individual subordinate to the PI or subordinate to any member of the research team***
- ***Student or trainee under the direction of the PI or under the direction of a member of the research team***

No

VI.20 ***Will subjects provide any information about their relatives?***

No

VI.23 ***Will anyone (other than the subject) provide you with information about the subject (e.g. proxy interviews)?***

No

VI.26 ***Is this project about pregnant women?***

Yes

VI.27 ***Will this project involve fetuses?***

No

VI.28 ***Does this project involve adult subjects who may be incompetent or have limited decision-making capacity on initial enrollment into the study?***

No

VI.32 ***Does this project involve subjects whose capacity to consent may change over the course of the study?***

No

VI.37 ***Does this project involve prisoners as subjects?***

No

VII.A. Project Description (A)

VII.A.1 ***Where will project procedures take place (check all that apply)?***

- UIHC - Labor and Delivery, UIHC Clinics

VII.A.2 ***Is this project also being conducted by other researchers at their own sites (e.g. a multi-site collaborative project)?***

No

VII.B. Project Description (B)

VII.B.1 ***Does this project involve any of the following (Check all that apply):***

- ☐ **Registry** – The collection and maintenance of data (not including biologic samples) in which: (1) the individuals in the registry have a common or related condition(s), and/or (2) the individuals in the registry are interested in being contacted for future studies by investigators other than those listed in Section II of this project.(UI Guide)
- ☐ **Repository** – The collection, storage, and distribution of human biologic samples and/or data materials for research purposes. Repository activities involve three components: (i) the collection of data and/or specimens such as blood, tissue, saliva, etc.; (ii) the storage of data or specimens, and data management function; and (iii) the sharing of data/specimens with recipient investigators other than the original investigators. (paraphrased from OHRP)
- ☐ **Expanded Access** – A process regulated by the Food and Drug Administration (FDA) that allows manufacturers to provide investigational new drugs to patients with serious diseases or conditions who cannot participate in a clinical trial. Examples of expanded access include non-protocol access to experimental treatments, including protocol exception, single-patient IND, treatment IND, compassionate use, emergency use, continued access to investigational drug, and parallel track (ClinicalTrials.gov & FDA).
- ☑ **Clinical (or Treatment) trial** – A prospective biomedical or behavioral research study of new treatments, new drug or combinations of drugs, new devices, or new approaches to surgery or radiation therapy. (NIH and ClinicalTrials.gov & FDA)
- ☐ **Physiology intervention/study** – A pharmacologic or measurement study aimed at understanding basic mechanisms of disease and/or of normal human physiology, often without any therapeutic intent (though a clinical trial could include such components, often labeled as "translational" or "basic science" aims.) Measurements in such studies could include, but are not limited to, a blood draw, EKG, EEG, MRI, auditory or sensory testing, checking vital signs, DEXA scans, eye tracking, specimen collection, exercise, fasting, special diets, etc.
- ☐ **Behavioral intervention/study** – May be used to refer to studies of individual or group behavior. This option does not include drugs, biologics, or devices but could include psychotherapy, lifestyle counseling, behavior modification, etc.
- ☐ **Diagnostic trial** – Protocol designed to evaluate one or more interventions aimed at identifying a disease or health condition (ClinicalTrials.gov & FDA)
- ☐ **Non-clinical** – any college/department that would regularly submit to IRB-02
- ☐ **Other**

VII.B.1.a ***Does this project involve any of the following (Check all that apply):***

- ☐ **Phase I trials** – include initial studies to determine the metabolism and pharmacologic actions of drugs in humans, the side effects associated with increasing doses, and to gain early evidence of effectiveness; may include healthy participants and/or patients (ClinicalTrials.gov & FDA)
- ☐ **Phase II trials** – include controlled clinical studies conducted to evaluate the effectiveness of the drug for a particular indication or indications in patients with the disease or condition under study and to determine the common short-term side effects and risks(ClinicalTrials.gov & FDA)
- ☐ **Phase III trials** – include expanded controlled and uncontrolled trials after preliminary evidence suggesting effectiveness of the drug has been obtained, and are intended to gather additional information to evaluate the overall benefit-risk relationship of the drug and provide an adequate basis for physician labeling(ClinicalTrials.gov & FDA)
- ☑ **Phase IV trials** – studies of FDA-approved drugs to delineate additional information including the drug's risks, benefits, and optimal use(ClinicalTrials.gov & FDA)

VII.B.1.b ***Provide the NCT (National ClinicalTrials.gov Identifier) number***
NCT03904446

VII.B.2 ***Does this project involve a drug washout (asking subject to stop taking any drugs s/he is currently taking)?***
No

VII.B.6 ***Will any subjects receive a placebo in this study when, if they were not participating, they could be receiving an FDA-approved treatment for their condition?***
No

VII.B.11 ***Is there a separate, written protocol that will be submitted in addition to this IRB New Project form? (Note: a grant application is not considered to be a protocol)***

No

VII.B.18 ***Does this project involve testing the safety and/or efficacy of a medical device?***
No

VII.C. Project Description (C)

VII.C.1 ***Does this project involve any research on genes or genetic testing/research?***
No

VII.D. Project Description (D)

VII.D.1 ***Check all materials/methods that will be used in recruiting subjects (you will need to attach copies of all materials at the end of the application):***

- Use of any information available to the researchers or their colleagues because this person is a patient OR use of any information considered to be Protected Health Information (PHI) OR review of patient/clinic records - EPIC would be used to review medical and surgical history to see whether patients meet inclusion/exclusion criteria for the study.

VII.D.2 ***List the individual data elements you will need to access/use from the patient or clinic records to identify potential subjects for recruitment***
The obstetrical history (vaginal versus cesarean section) will need to be reviewed. Patients scheduled for a planned cesarean delivery would be excluded from the study.
The medical history would also need to be reviewed as patients with hypertension (chronic hypertension, gestational hypertension, preeclampsia) would be excluded from the study as methylergonovine (study drug) can lead to vasoconstriction and worsen hypertension.

VII.D.3 ***Describe why you could not practicably recruit subjects without access to and use of the information described above***
As the study drug methylergonovine should be avoided in patients with hypertensive disorders, the chart will need to be reviewed to exclude these patients from the study.

Patients scheduled for a cesarean section (either elective or medically indicated) will be excluded, thus the chart will need to be reviewed beforehand to exclude these patients.

VII.D.4 ***Describe why you could not practicably obtain authorization from potential subjects to review their patient or clinic records for recruitment purposes.***
Patient identifiers are needed to determine eligibility for the study. As ~ 1/4 of the patients will likely not meet study criteria, reviewing charts a head of time is more practicable. In addition, reviewing patients charts to assess eligibility involves no more than minimal risk to the privacy of individuals.

VII.D.5 ***Describe plans to protect the identifiers from improper use or disclosure***
After cesarean delivery, the envelope which contains the patients information and which study drug was given will be placed in a secure location in the anesthesia work room. The envelope will be picked up by Nicole Masse (NM). Information will then be stored in RedCap. The envelope with patients information will then be destroyed by NM.

Subjects will be de-identified with the use of a separate document correlating subjects medical record number with the study ID number. At the conclusion of the research project, the key will be destroyed.

Files will not be shared with non-study personnel.

VII.D.6 ***Describe plans to destroy identifiers at the earliest opportunity consistent with conduct of the research***
When the pregnancy is over, the sticky note (in EPIC) which will be used to document whether the patient was enrolled in the study disappears after the patient delivers therefore will not remain part of the medical record.

Additionally, at the conclusion of the research study, all data collected will be destroyed by Nicole Masse.

VII.D.7 ***Does the research team agree that the requested information will not be reused or disclosed to any other person or entity, except as required by law, for authorized oversight of the study, or for other research for which the use or disclosure of the requested information would be permitted by the HIPAA Privacy Rule***

Yes

VII.D.8 ***Will a member of the research team discuss the study with the subject in person prior to the subject agreeing to participate?***
Yes

VII.D.9 ***Describe the physical location where the consent process will take place:***
Nicole Masse (or designated members of her research team) will be responsible for discussing the study and reviewing consent with all patients. The consent process will take place at both clinic visits (UIHC clinics) and on labor and delivery.

VII.D.10 ***Will a member of the research team discuss the study with the subject by phone prior to the subject agreeing to participate?***
No

VII.D.12 ***Who will be involved in the consent process (including review of consent document, answering subjects' questions)?***

Name	Consent Process Involvement
Nicole Masse, MD	Yes
Mildrede Bonglack, MD	Yes
Rebecca Chung, BS	Yes
Colette Gnade, MD	Yes
Shelby Green, MD	Yes
Leigh Hess, MD	Yes
Danielle Ikoma, MD	Yes
Emily Jacobs, MD, MS	Yes
Jordan Mattson, MD	Yes
Laura Rasmussen, MD	Yes
Hope Richards, MD	Yes
Keely Ulmer, MD	Yes
Vincent Wagner, MD	Yes
Noelle Waldschmidt, BS	Yes
Heather Winn, MD	Yes
Cynthia Wong, MD	No

VII.D.15 ***Check all materials that will be used to obtain/document informed consent:***
- Consent Document

VII.D.16 ***Are you requesting a waiver of documentation of consent (either no subject signature or no written document)?***
No

VII.D.19 ***Before the subject gives consent to participate are there any screening questions that you need to directly ask the potential subject to determine eligibility for the study?***
Yes

VII.D.20 ***List any screening questions you will directly ask the potential subject to determine eligibility.***
Prior to consenting patients to the study I will confirm they do not have any contraindications to the study drug (i.e. hypertension, preeclampsia, gestational hypertension, HIV, cardiac disease).

VII.D.21 ***Will you keep a screening log or other record that would include information on people who do not enroll in the study?***
Yes

VII.D.22 ***Describe the information being collected and the purpose for keeping this information.***
This information will only be used to look at enrollment and how many patients assessed for eligibility were excluded from the study after declining to participate.

This information will be kept in a secure platform - RedCap. I plan on recording patients medical record number. This information will be destroyed at the completion of the study.

VII.D.23 ***Will this information be shared with anyone outside the UI research team members?***
No

VII.D.25 ***After the subject agrees to participate (signs consent), are there any screening procedures, tests, or studies that need to be done to determine if the subject is eligible to continue participating?***
No

VII.D.27 ***Discuss how much time a potential subject will have to agree to consider participation and whether or not they will be able to discuss the study with family/friends before deciding on participation.***
The potential subject would have from the time they are approached up until the time a cesarean section is required. As patients will be approached both in clinic and upon arrival to labor and delivery, patients will have weeks to days to discuss study with family and friends prior to deciding on participation.

VII.D.28 ***How long after the subject agrees to participate do study procedures begin?***
If patients are consented in clinic, study procedures may take weeks as the study procedure will not take place until the patient arrives for delivery.
If patients are consented upon arrival to labor and delivery, many patients are in labor for 24-72 hours before deeming a cesarean section necessary.

VII.D.29 ***Provide a description of the enrollment and consent process for adult subjects***

- ***Describe each study population separately including control population***
- ***Include when recruitment and consent materials are used***
- ***Use 3rd person active voice "The Principal Investigator will identify subjects. For example, the principal investigator will identify potential subjects, the study coordinator will discuss the study with subjects over the telephone and schedule the first study visit, etc..."***
- ***Describe the steps that will be taken by the research team to minimize the possibility of coercion or undue influence during the consent process***

Nicole Masse (NM) or designated members of her research team will be responsible for reviewing patients charts through EPIC to determine eligibility. If patients are found to meet study criteria, NM or members of the research team will review both consent form and consent summary and obtain consent if patients wish to participate in the study. Patients will be consented in clinic or upon arrival to labor and delivery. This will avoid consenting patients prior to when a cesarean section is deemed necessary during the labor process as this can be an anxiety provoking time for patients. Patients will be given the opportunity to discuss enrollment with their family and friends.

NM (primary investigator) will meet with all members of the research team prior to the start of the study to review the consent process. NM will make herself available at all times (through cell phone and pager), in the event questions were to arise.

VII.D.37 ***Does the study include any form of deception (e.g., providing participants with false information, misleading information, or withholding information about certain study procedures)?***

Examples:

- ***Procedure includes a cover story that provides a plausible but inaccurate account of the purposes of the research.***
- ***Participants will be provided with false information regarding the particular behaviors of interest in the research.***
- ***Procedures include a confederate pretending to be another participant in the study.***
- ***Participants will be told that the research includes completion of a particular task, when in fact, that task will not be administered.***
- ***Study is designed to introduce a new procedure (or task) that participants are not initially told about.***
- ***If yes, a waiver of informed consent must be requested under question IV.3.***

No

VII.E. Project Description (E)

VII.E.1 ***Will subjects be randomized?***
Yes

VII.E.1.a ***Will any subjects be blinded to which study arm they have been assigned?***
Yes

VII.E.1.b ***Does the protocol permit telling subjects their treatment assignment at the end of the entire study?***
No

VII.E.1.d ***Justify why subjects cannot be told what study arm they have been assigned. You will need to disclose to subjects in the consent document that they cannot receive this information.***
Knowledge of whether patients received study drug/placebo might impact one of our secondary outcomes - the need for blood transfusion.

Determination of the need for a blood transfusion is dependent on hemoglobin levels and maternal symptoms concerning for anemia (fatigue, heart palpitations, shortness of breath). If the patient is aware of whether they received the treatment drug/placebo this could impact the results of this outcome as patients reported symptoms could be impacted by their knowledge of whether study drug/placebo was given.

Additionally, in our current practice, it is not standard of care to disclose if uterotonics were given in the procedure to assist with uterine atony or hemorrhage.

If a patient requests to know which treatment assignment she was randomized to, she will be given the option of receiving a letter (either emailed or mailed to her home address) at the completion of the study.

VII.E.2 ***Describe randomization scheme/assignment including ratio such as 1:1, 2:1 etc.***
A 1:1 allocation ratio with randomized block design using mixed block sizes. A computer generated list of random numbers will be used to generate the allocation sequence using nQuery Advisor.

VII.E.3 ***Will any questionnaires, surveys, or written assessments be used to obtain data directly from subjects in this study?***
No

VII.E.5 ***Does this project involve creating any audiotapes, videotapes, or photographs?***
No

VII.E.6 ***Provide a detailed description in sequential order of the study procedures following the consent process - DO NOT cut and paste from the Consent Document.***

Describe study populations separately if they will be participating in different procedures - include CONTROL population if applicable.

DESCRIBE:

- ***What subjects will be asked to do/what happens in the study (in sequential order)***
- ***The time period over which procedures will occur***
- ***The time commitment for the subject for individual visits/procedures***
- ***Long-term followup and how it occurs***

All patients who meet eligibility for the study will be consented during their clinic visit or upon arrival to labor and delivery. If patients elect to participate in the study, enrollment in the study will be noted in their sticky note in EPIC which will be ready available to all members of the health care team.

If patients during the labor process require a cesarean section, the anesthesiologist will pick up a sealed envelope (which will contain the allocation sequence and group assignment). The sealed envelopes will be readily available to the anesthesiologist and kept in the anesthesia workroom. Following delivery of the infant, the patient will receive the standard oxytocin infusion. Following administration of the oxytocin infusion, the patient will be given either methylergonovine 0.2 mg IM (intramuscular) or placebo (1 ml of normal saline, intramuscular). This will be drawn up and administered by the anesthesiologist. The obstetrician (delivering provider performing the cesarean section) will be blinded to the group assignment. Documentation of the drug will be recorded in epic in the medication administration record.

The delivering provider will be responsible for determining and relaying to the anesthesiologist whether additional uterotonics are needed throughout the procedure. Additional uterotonics will be given in accordance to the current guidelines outlined by the American Congress of Obstetricians and Gynecologists (ACOG). The delivery provider will assess uterine tone at 4 minutes (satisfactory versus unsatisfactory). The registered nurse will be responsible for

setting up a timer to let the OB provider know when 4 minutes have passed. Nursing will call out once the 4 minutes have passed and the OB provider will state whether adequate tone was noted. The anesthesiologist will be responsible for documenting whether a placebo/study drug was given and uterine tone after 4 minutes. This documentation will be placed back into the sealed envelope by the anesthesiologist and placed in the anesthesia workroom. Nicole Masse will pick up folders on a regular basis (every 1-3 days) and store folders in a secured, locked file cabinet within the Maternal Fetal Medicine offices.

As routinely done at the time of cesarean delivery, the registered nurse will be responsible for measuring and documenting the quantitative blood loss. As routinely performed on all are patients who undergo a vaginal or cesarean delivery, preoperative hemoglobin and postoperative day one hemoglobin levels will be collected.

In the event a delayed postpartum hemorrhage was to occur, the obstetrician will be un-blinded at the conclusion of the cesarean delivery as management of a delayed hemorrhage will be driven by the uterotonics received in the operating room. Because all drugs administered during the procedure will be documented in the patients medical record, the obstetrician will have access to the medications given during the cesarean section.

The majority of our outcomes (including a primary outcome - need for additional uterotonics) will be assessed in the operating room. The outcomes we plan on assessing in the operating room include uterine tone, quantitative blood loss). Outcomes we plan on assessing in the immediate postpartum period include: postpartum hemoglobin values, need for a blood transfusion, admission to the intensive care unit, endometritis).

No long-term follow will be needed.

VII.E.7 ***Will you attempt to recontact subjects who are lost to follow-up?***
No - followup is not required in this study

VII.E.9 ***Will subjects be provided any compensation for participating in this study?***
No

VIII. Risks

VIII.1 ***What are the risks to subjects including***
- emotional or psychological
- financial
- legal or social
- physical?
Discomfort at the injection site.
The risk of giving the drug when not necessary.
Rarely observed reactions have included: acute myocardial infarction, transient chest pains, vasoconstriction, vasospasm, hypertension, coronary arterial spasm, bradycardia, tachycardia, dyspnea, hematuria, thrombophlebitis, water intoxication, hallucinations, seizures, leg cramps, dizziness, tinnitus, nasal congestion, diarrhea, diaphoresis, palpitation, rash, and foul taste

There will be no financial risks to the patient as the Department of Maternal Fetal Medicine we will be covering both the costs of the study drug and the placebo.

VIII.2 ***What have you done to minimize the risks?***

- ***If applicable to this study ALSO include:***
  - ***How you (members of your research team at Iowa) will monitor the safety of individual subjects.***
  - ***Include a description of the availability of medical or psychological resources that subjects might require as a consequence of participating in this research and how referral will occur if necessary (e.g. availability of emergency medical care, psychological counseling, etc.)***

We have minimized risks by excluding patients with a documented hypersensitivity to methylergonovine or patients with contraindications to the drug (i.e. hypertension, preeclampsia, coronary artery disease, HIV on a protease inhibitor).

VIII.3 ***Does this study have a plan to have an individual or committee review combined data from all subjects on a periodic basis (such as summary or aggregate safety and/or efficacy data)?***
Yes

VIII.4 ***Describe the plan to review combined data from all subjects, such as summary or aggregate safety and/or***

efficacy data. Include the following:

- ***Describe what data will be summarized and reviewed***
- ***Describe how frequently data will be reviewed.***

Andrea Greiner MD will review aggregate data every for every 25 randomized subjects to check for any unexpected safety findings related to either study arm

VIII.5 ***Will overall safety monitoring be performed by individual(s)/committee at The University of Iowa. (NOTE: If this study involves more than minimal risk, in most cases these should be individuals who are not members of the study research team.)?***
Yes

VIII.6 ***List names:***
Andrea Greiner MD (MFM Fellowship Director)

VIII.7 ***Will overall safety monitoring be performed by individuals or committee not associated with The University of Iowa (such as a study Data Safety Monitoring Board)?***
No

IX. Benefits

IX.1 ***What are the direct benefits to the subject (do not include compensation or hypothesized results)?***
No direct benefit to patients

IX.2 ***What are the potential benefits to society in terms of knowledge to be gained as a result of this project?***
Uterine atony is the leading cause of postpartum hemorrhage. Postpartum hemorrhage is the leading cause of maternal mortality worldwide. It is well known that laboring patients who ultimately require cesarean delivery are a subset of women who are at increased risk for uterine atony. We anticipate the use of multimodal prophylactic uterotonics in these patients at the time of cesarean section will serve to prevent uterine atony, therefore reduce the morbidity and mortality associated with postpartum hemorrhage.

X. Privacy & Confidentiality

X.1 ***What are you doing to protect the privacy interests of the subjects?***
All discussion of the study will take place in a private room - either in clinic or in a labor and delivery room.

We also plan on collecting the minimal amount of data needed to answer the research questions.

X.2 ***Are you collecting the Social Security Number of any subjects for any purpose?***
No

X.4 ***How will information/data be collected and stored for this study (check all that apply):***

- Paper/hard copy records (hard copy surveys, questionnaires, case report forms, pictures, etc.) - All records containing protected health information will be transported in a manner that no identifiable information is visible. All hard copy material will be kept in Nicole Masse's office within a locked file cabinet.
- Electronic records (computer files, electronic databases, etc.) - Electronica data will be collected by reviewing patients medical chart through EPIC. All protected health information obtained will be stored through REDCap (research electric data capture) a secure web based interface for storing study information.
  - Name - Nicole Masse
  - Title - Physician
  - University Job Classification - Maternal Fetal Medicine Fellow

X.5 ***Do the confidentiality protections indicated above allow only members of the research team to access the data/specimens?***
Yes

X.7 ***Does your study meet the NIH criteria for a Certificate of Confidentiality or will you be applying for Certificate of Confidentiality?***
No

XI. Data Analysis

XI.1 ***Describe the analysis methods you will use, including, if applicable, the variables you will analyze***
Continuous variables will be analyzed using a fishers exact t-test (i.e. hemoglobin value). Categorical variables will be compared using a chi square analysis (i.e need for additional uterotonics).

Multiple logistic regression will be used to model the relationship between the group assignment (methylergonovine vs placebo) and the need for additional uterotonic agents while controlling for potential confounders. $P < .05$ will be considered statistically significant.

XI.2 ***Provide the rationale or power analysis to support the number of subjects proposed to complete this study.***
Preliminary data demonstrated 42% of laboring patients requiring a cesarean section at the University of Iowa over the past 12 months required additional uterotonics at delivery in addition to the standard oxytocin infusion.

To detect a 2 fold decrease in the need for additional uterotonics (42% vs 21%) with a type 1 error of 5% and power of 80%, a sample size of 76 patients per group will be necessary. To account for missing information (i.e. failure to document uterine tone, failure to document in quantitative blood loss in the medical record), we plan to recruit 80 patients per group.

XII. Future Research

XII.1 ***Do you wish to keep any information about subjects involved with this research project so that members of the current research team may contact them in the future for your own research projects?***
No

XII.2 ***Do you wish to keep any information about subjects involved with this research project so that other researchers may contact them for future research?***
No

XII.4 ***Does this project involve storing any data, tissues or specimens for future research?***
No

ROC. Record of Consent

ROC.1 ***Select which option applies to address the University of Iowa Health Care policy IM-MR-06.21 titled "Documentation of patient participation as a subject in a research protocol or use of an investigational medication, study medication, investigational device, or biologic."***
The research related activities proposed in this study **does meet** the registration requirements under the University of Iowa Health Care policy IM-MR-06.21 titled "Documentation of patient participation as a subject in a research protocol or use of an investigational medication, study medication, investigational device, or biologic." **The below information must be completed and approved as part of the IRB application. This information contained within this page will be used to create the Epic Research Study Application Form.**

ROC.2 ***Select a publicly viewable title for this study. (This title will be visible in EPIC)***
Release full title

ROC.3 ***Select research team member who has taken Epic Training***
Nicole Masse

ROC.4 ***Who is a 24/7 contact person for projects involving treatment(s) or procedures that result in complications or side effects?***
Nicole Masse
Other contact information that may be relevant to a subject's clinical care (i.e. may be important if the contact person is not available 24/7 or an alternate contact may be required.)
708-466-2034 (cell phone)

ROC.5 ***Describe the key complications from the study drug(s) listed below or study procedure(s):***
A complication of methlyergonovine is hypertension. As such, patients with hypertensive disorders will be

excluded to avoid exacerbation of a hypertensive disorder. Patients with a history of a hypersensitivity reaction to methyergonovine will also be excluded.

By elimination of relative contraindications to the administration of methylergonovine, I anticipate the risks to patients to be minimal. Methlyergonovine is a medication commonly given on labor and delivery for the treatment of uterine atony. Provided contraindications to medication administration is avoided, patients typically tolerate the drug well.

ROC.6 ***Any other information that may be important to emergency personnel:***
None

ROC.7 ***Would you like to advertise this study on the Iowa Clinical Research & Trials website?***
No

New Project Form Attachments

Attachment Name	Category	Ver	Size	Type	Attached
Multimodal Uterotonics Infomred Consent May 3.rtf	Informed Consent	6	191 k	E	06/17/19
Multimodal Uterotonics Trial Consent Summary Final.rtf	Other Consent Document	2	66 k	E	05/03/19
Screening Log Multimodal Uterotonics Study.xlsx	Screening: Screening Log	1	8 k	E	03/26/19
SKMBT_C454e19040111111.pdf	Assurance Document	1	808 k	E	04/01/19