Cover Page

High Dose vs. Low Dose Oxytocin for Labor Induction in Obese Women: a Randomized Controlled Trial - the OPS (Obese Pitocin Study) Trial

Protocol date 04/04/2017

NCT03140488

F200: Application for Human Research

PROJECT TITLE: **High dose vs. Low dose oxytocin for labor induction in obese women: a randomized controlled trial – the OPS (Obese Pitocin Study) trial**

INVESTIGATOR INFORMATION

Principal Investigator Name, Degree(s):	Meghan Hill, MBBS
Affiliation	☒ UA ☒ B–UMG
Principal Investigator **UA NetID**	meghanhill
Status/Rank:	Maternal Fetal Medicine, assistant professor
Center:	College of Medicine
Department:	Department of Obstetrics and Gynecology, Division of Maternal Fetal Medicine
College:	University of Arizona
Contact phone:	5206266174
Official Institutional Email:	meghanhill@obgyn.arizona.edu

ADVISOR CONTACT INFORMATION (REQUIRED FOR ALL STUDENTS AND RESIDENTS)

Name, Degree(s), **UA NetID**:	
Contact phone:	
Official University Email:	

ALTERNATE/COORDINATOR or Co-PI CONTACT INFORMATION

***THIS INDIVIDUAL WILL RECEIVE COPIES OF ALL CORRESPONDENCE ON THE STUDY**

Name, **UA NetID**:	Co-PI: Ruth Wei, MD
Contact phone:	626-824-4517
Official University Email:	ruthwei@obgyn.arizona.edu

SECTION 1: REQUIRED SIGNATURES

1. PRINCIPAL INVESTIGATOR

I will conduct my study according to the University of Arizona HSPP policies and procedures for research with human subjects.

Signature	Date	Print Name

2. ADVISOR (FOR ALL STUDENTS AND RESIDENTS ACTING AS THE PI)

I will oversee the student researcher according to the University of Arizona HSPP policies and procedures for research with human subjects.

Signature	Date	Print Name

3. SCIENTIFIC/SCHOLARLY REVIEW (SEE HSPP GUIDANCE ON REQUIREMENTS FOR SCIENTIFIC/SCHOLARLY ASSESSMENT - INCLUDE DOCUMENTATION FOR OPTIONS A AND B WITH SUBMISSION MATERIALS.)

a. ☐ Nationally based, federal funding organization (NIH, NSF) subject to full peer review

b. ☐ Nationally based, non-federal funding organization (March of Dimes, Amer Academy of Pediatrics) subject to peer review

c. ☐ Locally constituted peer review (signature required)

Signature	Date	Print Name

4. DEPARTMENT/CENTER/SECTION REVIEW

I have reviewed this application and determined that all departmental requirements are met and that the investigator has adequate resources to conduct the Human Research.

Signature	Date	Print Name/Email

5. RESPONSIBLE PHYSICIAN (PROJECTS INVOLVING MEDICAL PROCEDURES WHICH THE PI IS NOT AUTHORIZED TO CONDUCT)

I am a physician licensed by the State of Arizona (or US license for the SAVAHCS). I will be responsible for ensuring that all procedures that are part of this project and that require the attendance of a licensed physician will have a suitable physician present during the procedures. If at any time this is not possible, I will inform the IRB before any procedures are conducted.

Signature	Date	Print Name

SECTION 2: GENERAL INFORMATION

1. How many Human Research studies does the PI have open?
12

2. How many research staff will be involved in the Human Research?
4

3. What is the expected length of this project?
2-3 years

4. Will the University of Arizona be the coordinating center for a multi-site study?
☒ No ☐ Yes- Complete Appendix C- Multi-Site study

5. Retention of study materials before, during, and after completion of the project:

a. Where will original signed consent and PHI Authorization documents be stored (building name and room)? Location: Room 8237G in the Department of Obstetrics and Gynecology

b. How long will consents be maintained after conclusion of the project?
☒ 6 years (UA standard) ☐ 6 years after child reaches 18 ☐ Other (explain):

6. Is or will the project be funded by an external funding source e? ☒ No ☐ Yes- Complete below:

a. Funding PI:
b. Proposal Title:
c. Funder Name:
d. Total funding amount **OR** per subject amount:
e. UAccess Account Information Provide one of the following below:
   i. Institutional Proposal #:
   ii. Award #:

Submit complete copy, cover-to-cover, of grant or award. If you need help locating any of the UAccess numbers please call Sponsored Projects at 626-6000.

7. Is the project funded by a **For-profit** industry sponsor? ☒ No ☐ Yes- Complete required below:

a. IRB Payment eDoc #:

*Please review **HSPP Guidance, Fees for Human Research**, for more information.*

8. Conflict of Interest (COI):
The Principal Investigator hereby affirms that ALL individuals who meet the definition of *investigator* for this project in the current *Policy on Investigator Conflict of Interest in Research* have completed the mandatory Conflict of Interest training and Disclosure of Significant Financial Interests.

☒ Yes ☐ No (explain):

9. Additional requirements:
Certain types of research require additional regulatory documentation. Please identify which of the following apply to your project. Complete the appropriate Appendix and submit as part of the submission materials.

☒ Appendix A – Children (subjects under 18)
☒ Appendix B – Drugs/Devices (A clinical investigation of a drug or device)
☐ Appendix C – Multi-Site study (The UA IRB will review research activities for an investigator or research staff not affiliated with the UA who is 'engaged in the research' (e.g. consenting, collecting data, or analyzing identifiable information)
☒ Appendix D – Pregnant Women/Neonates
☐ Appendix E – Prisoners
☒ Appendix F – Waivers of consent, waiver of a signature, or waiver or alteration of PHI
☐ Appendix G – Exception From Informed Consent (EFIC)
☐ Appendix H – Native American or International Indigenous populations
☐ None apply to the proposed study

10. Research Site: BUMG-Tucson campus

Location (Explain):
8th floor Labor and Deliver and 8OPC outpatient clinic

If research is taking place at B–UMG or AZCC please check the appropriate boxes below:

Banner – University Medicine Group:

☐ Phoenix Campus	☐ Biological specimens	☐ Clinical Data
☒ Tucson Campus	☐ Biological specimens	☒ Clinical Data
☐ South Campus	☐ Biological specimens	☐ Clinical Data

**Submit a copy of the UAHS Research feasibility review approval*

University of Arizona Cancer Center:

☐ North Campus	☐ Biological specimens	☐ Clinical Data
☐ Orange Grove Clinics	☐ Biological specimens	☐ Clinical Data
☐ Phoenix	☐ Biological specimens	☐ Clinical Data

**Submit a copy of the Scientific Review Committee letter*

SECTION 3. PROJECT NARRATIVE

1) Background

The obesity epidemic

Obesity has become an epidemic in the first world countries. Obesity is defined by BMI ≥30. Within obesity, class I, II, III obesity are defined by BMI between 30-34.9, 35-39.9, and ≥40 respectively. According to the Institute of Medicine Guidelines in 2009, over 30% of women of childbearing age in the United States are obese. Obesity is far more common among racial or ethnic minority groups,

with only 23% of African American women in the normal weight category. The prevalence of class I obesity in African American women approaches 25%, and the prevalence of class II and III obesity each exceed 10% [1]. In addition to the usual health complications, there are consistent clinical data to support that obesity in pregnancy is an independent risk factor for multiple complications in pregnancy during antenatal, intrapartum, delivery and postpartum periods [2].

Complications of obesity in pregnancy

Specifically, obesity in pregnancy is associated with a higher chance of induction of labor, failed induction of labor, longer induction, and a higher rate of cesarean delivery [3-12]. Obese patients are more likely to undergo induction secondary to medical comorbidities, including pregnancy related hypertension and diabetes. They are also less likely to go into spontaneous labor resulting in late term pregnancy and induction of labor. When obese women undergo induction, they are more likely to fail their induction or have labor dystocia resulting in a higher cesarean delivery rate, reportedly up to 50-60% (compared to the national overall cesarean delivery rate of 30%). In patients undergoing a cesarean delivery during labor induction, obese pregnant women are more likely to have their procedures during the first stage of labor (83% vs. 61%, aOR 2.87 [1.35-6.1]). Obese patients are also more likely to undergo cesarean delivery secondary to failure to progress or labor dystocia (22% vs. 12%, p = 0.01) [8,13]. Trends in clinical management may also disproportionately affect obese women due to their prolonged labors. Cesarean delivery in obese patients has its unique set of intraoperative challenges and postoperative complications including prolonged operative times, wound breakdown, infection, and venous thromboembolism [2]. Identifying potential etiologies and interventions to this clinical challenge will decrease morbidity and improve pregnancy outcomes in this population.

Physiology of parturition and oxytocin pharmacokinetics

To decipher the problem with prolonged induction and labor dystocia in the obese cohort, we need to first discuss the normal physiology of parturition and oxytocin pharmacokinetics. In normal pregnancy, the placenta, cervix, amnion and myometrium of the uterus all work in a synergistic fashion to prepare for labor [14]. An increase in oxytocin receptors in the myometrium and its sensitivity to the oxytocin hormone are keys to initiation of labor [15]. Oxytocin is an endogenous hormone synthesized from the hypothalamus and secreted by posterior pituitary gland. The synthetic analog, Pitocin, is widely used on every labor and delivery for induction of labor. An infusion of oxytocin reaches a steady state at 30-40 minutes based on the plasma clearance rate [16]. The half-life for oxytocin is about 4.5 minutes [17,18].

Obesity: a unique parturition phenotype

Biological evidences linking obesity and labor dystocia are largely unknown and currently under investigation. Obesity-related changes in the hormonal milieu seem linked to labor dysfunction. Various obesity related hormones, called “adipokines”, are hypothesized to alter the normal parturition physiology in the obese cohorts and have an inhibitory effect on oxytocin stimulated myometrial contractions. Oxytocin receptors are also found to be decreased in numbers and responsiveness in myometrial biopsies in obese cohorts, however existing evidence is currently weak [14]. Specific mechanisms remain unknown.

More oxytocin requirement in obese patients

While the underlying pathophysiology is still currently unknown, there are known correlations with obesity and increased oxytocin requirement. Currently, a standard low dose oxytocin regimen is

typically used regardless of the BMI of the patient in the United States. While most of the United States uses the low dose protocol, ACOG (The American College of Obstetricians and Gynecologists) states that both the high and low dose protocols are appropriate for labor induction and each hospital's department should develop their own guidelines. Per the ACOG practice bulletin on induction of labor, low dose oxytocin protocol consists of starting at 0.5-2miliunit/min, increasing by 1-2miliunit/min, at an interval of every 15-40 minutes [19]. A high dose oxytocin protocol which is also endorsed by the ACOG practice bulletin, consists of starting at 6miliunit/min, increasing by 3-6miliunit/min, at an interval of every 15-40 minutes. Furthermore, emerging evidences suggest that obese patients may require more oxytocin to achieve labor progression [8,20,21]. Three studies have specifically evaluated the total amount of oxytocin used during the first stage of labor in the obese cohort. They found that a statistically higher amount of oxytocin was needed to achieve vaginal delivery compared to the lean cohort. The principal investigator, Dr Hill, performed her work at the University of Arizona, indicating that this finding applies to this patient population.

Safety of high dose oxytocin protocols

Many randomized controlled trials had previously compared various high and low dose oxytocin protocols and demonstrated safety of both protocols. Meta-analyses including a Cochrane review in 2014 confirmed the safety and utility of high and low dose oxytocin protocols [22-24]. While there were no significant differences in rates of vaginal delivery or cesarean delivery, there was also no difference in serious maternal or neonatal morbidity or death. The Cochrane review as well as the meta-analysis found a statistically significant reduction in time to delivery in the high dose oxytocin group. Otherwise, there were no differences in adverse outcomes, including maternal uterine rupture, postpartum hemorrhage, endometritis, estimated blood loss, abnormal fetal heart tracing, fetal Apgar, newborn resuscitation and neonatal intensive care unit admission.

There were case reports originating from the 1970s about concerns over high dose oxytocin and its association with maternal hyponatremia or water intoxication [25,26]. The hypothesis behind its association is due to the similarity between oxytocin and anti-diuretic hormone. These were largely single case reports in the setting of accidental large overdose of oxytocin in addition to administration of large volumes of electrolyte-free solutions. Since then, the practice of administering oxytocin is only given alongside isotonic lactated ringer or normal saline in a slow intravenous infusion fashion [27,28]. In addition, there were also some case series showing that a large amount of oxytocin given intravenously as a bolus can cause maternal hypotension, tachycardia and EKG changes [29,30]. In a similar fashion, these changes were observed due to a very large amount of IV boluses given over a short amount of time, which is a very different practice than how oxytocin is now administered on labor and delivery via a slow intravenous infusion.

1. IOM (Institute of Medicine) and NRC (National Research Council). 2009. Weight Gain During Pregnancy: Reexamining the Guidelines. Washington, DC: The National Academies Press.
2. Obesity in pregnancy. Practice Bulletin No. 156. American college of obstetricians and gynecologists. Obstet Gynecol 2015; 126:e112-26.
3. Carlson et al. Parturition dysfunction in obesity: time to target the pathobiology. Reproductive and endocrinology (2015) 13:135.
4. Dietz PM, Callaghan WM, Morrow B, Cogswell ME. Population-based assessment of the risk of primary cesarean delivery due to excess pre-pregnancy weight among nulliparous women delivering term infants. Matern child health J. 2005; 9:237-44.
5. Arrowsmith S, Wray S, Quenby S. Maternal obesity and labour complications following inuction of labour in prolonged pregnancy. BJOG. 2011; 118:578-88.

6. Kominiarek M, Zhang J, VanVeldhuisen P, Troendle J, Beaver J, Hibbard JU. Contemporary labor patterns: the impact of maternal body mass index. Am J Obstet Gynecol. 2011; 205:244.e241-8.

7. Norman SM, Tuuli MG, Odibo Ao, Caughey AB, Roehl KA, Cahill AG. The effects of obesity on the first stage of labor. Obstet Gynecol. 2012; 120:130-5

8. Pevzner L, Powers BL, Rayburn WF, Rumney P, Wing DA. Effects of maternal obesity on duration and outcomes of prostaglandin cervical ripening and labor induction. Obstet Gynecol. 2009; 114: 1315-21.

9. Weiss JL, Malone FD, Emig D, Ball RH, Nyberg DA, Comstock CH, Saade G, Eddleman K, Carter SM, Craigo SD, Carr SR, D'alton ME; FASTER research consortium. Obesity, obstetric complications and cesarean delivery rate – a population-based screening study. Am J Obstet Gynecol. 2004 Apr; 190(4): 1091-7.

10. Robinson B, et al. Increasing maternal body mass index and characteristics of the second stage of labor. For the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) of the Maternal-Fetal Medicine Units Network (MFMU). Obstet Gynecol. 2011 Dec; 118(6); 1309-1313.

11. Fye EM et al. Screening for Pregnancy Endpoints Consortium (SCOPE). Risk of first-stage and second-stage cesarean delivery by maternal body mass index among nulliparous women in labor at term. Obstet Gynecol. 2011 Jun; 117(6): 1315-22.

12. Vahratian et al. Maternal prepregnancy overweight and obesity and the pattern of labor progression in term nulliparous women. Obstet Gynecol. 2004 Nov; 104(5): 943-951.

13. Verdiales M, Pacheco C, Cohen W. The effect of maternal obesity on the course of labor. J. Perinat. Med. 37 (2009) 651-655.

14. Carlson NS, Hernandez TL, Hurt KJ. Parturition dysfunction in obesity: time to target the pathobiology. Reproductive biology and endocrinology (2015) 13:135.

15. Fuchs AR, Fuchs F, Husslein P, Soloff M, and Fernstrom MJ. Oxytocin receptors and human parturition: a dual role for oxytocin in the initiation of labor. Science, New series vol 215, No 4538. Mar 12, 1982. 1396-1398.

16. Seitchik, J, Amico J, Robinson AG, Castillo M. Oxytocin augmentation of dysfunctional labor. AM J Obstet Gynecol 1984; 150: 225-8.

17. Thornton S, Davison J, Baylis P. Plasma oxytocin during the first and second stages of spontaneous human labour. Acta Endocrinologica 1992, 126: 425-9.

18. Hayes EJ, Weinstein L. Improving patient safety and uniformity of care by a standardized regimen for the use of oxytocin. Am J Obstet Gynecol 2008; 198:622.e1-622.e7.

19. Induction of labor. ACOG Practice Bulletin No.107. American College of Obstetricians and Gynecologists. Obstet Gynecol 2009; 114: 386-397.

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23. Zhang J, Branch DW, Ramirez MM, Laughon SK, Reddy U, Hoffman M, Bailit J, Kominiarek M, Chen Z, Hibbard JU. Oxytocin regimen for labor augmentation, labor progression, perinatal outcomes. Obstet Gynecol 2011 Aug; 118 (2 Pt 1):249-56.

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25. Jensen I, Bruns BJ. Water intoxication after oxytocin-induced midtrimester abortion. NZ Med J. 1979 April 25; 89(634):300-2.

26. Lauersen NH, Birnbaum SJ. Water intoxication associated with oxytocin administration during saline-induced abortion. Am J Obstet Gynecol. 1975 Jan 1; 121(1): 2-6.

27. Higgins J, Gleeson R, Holohan M, Coone C, Darling M. Maternal and neonatal hyponatremia: a comparison of Hartmanns solution with 5% dextrose for the delivery of oxytocin in labor. European Journal of Obstetrics and Gynecology and Reproductive Biology 68 (1996) 47-48.

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29. Svanstrom MC, Biber B, Hanes M, Johansson G, Naslund U, Balfors EM. Signs of myocardial ischemia after injection of oxytocin: a randomized double-blinded comparsion of oxytocin and methylergometrine during cesarean section. British Journal of Anaesthesia 100 (5): 683-9 (2008).

30. Bhattacharya S, Ghosh S, Ray D, Mallik S, Laha A. Oxytocin administration during cesarean delivery: randomized controlled trial to compare intravenous bolus with intravenous infusion regimen. J Anaesthesiol Clin Pharmacol. 2013 Jan-Mar; 29(1): 32-35.

2) Purpose

The objective of this study is to compare high and low dose oxytocin in obese and lean gravida and their effect in length of time to delivery. The hypothesis is that high dose oxytocin will decrease time to delivery in full term obese cohort undergoing an induction of labor and that their labor cures will more closely approximate those of lean patients. This study is a double blinded randomized controlled trial with an intention to treat analysis.

4 Comparison groups:

1) Control group: Lean cohort: BMI ≤25, at <20 weeks gestation or BMI ≤28 at a term gestation, low dose oxytocin protocol

2) Intervention group: Lean cohort: BMI ≤25, at <20 weeks gestation or BMI ≤28 at a term gestation, high dose oxytocin protocol

3) Control group: Obese cohort: BMI ≥30, at <20 weeks gestation or BMI ≥35 at a term gestation, low dose oxytocin protocol

4) Intervention group: Obese cohort: BMI ≥30, at <20 weeks gestation or BMI ≥35 at a term gestation, high dose oxytocin protocol

Primary outcome: Length of time to delivery (number of minutes from induction of labor to delivery). In case of cesarean delivery, length of time to delivery will be calculated from start time of induction to time when decision was made to proceed with cesarean delivery.

Secondary outcomes:

Length of time in 1st stage and 2nd stage of labor

Total amount of oxytocin, median, mean, and maximum oxytocin rate

Terbutaline use

Rate of cesarean delivery, and rate of cesarean delivery for labor arrest

Maternal and neonatal complications including, postpartum hemorrhage, uterine rupture, tachysystole, chorioamnionitis, abnormal fetal heart tracing, fetal Apgar, neonatal intensive care unit admission rate, cord gas

3) Lay Summary (approximately 400 words)

Obesity is considered one of the biggest public health concern of the 21st century and increases the risk of many comorbid medical conditions. Obesity in pregnancy places women at higher risk of

obstetrical complications during pregnancy, delivery and postpartum. In particular, obese pregnant women have more difficulty going into labor, a longer labor course, and even with pharmacologic treatment, have a higher chance of requiring cesarean delivery.

When pregnant women need help going into labor, they commonly receive a medication called Pitocin on the labor and delivery floor. Pitocin is the brand name and is a synthetic analog to the naturally produced oxytocin, a hormone secreted by mother when they naturally go into labor. This medication has been used widely around the world. There is emerging evidence that obese women need more oxytocin to go into labor compared to their lean cohorts. There are many studies to support the use of different oxytocin dosages and are currently supported by the American College of Obstetricians and Gynecologists. Despite these evidences, a low dose oxytocin regimen is universally used in the United States, regardless of patient characteristics.

This study is a double blinded randomized controlled trial. Both lean and obese cohorts will be recruited for the study. We will randomly place both cohorts into the low or the high dose oxytocin regimen treatment group. The investigators, patients and providers will be blinded and will not know the specific assignments. The purpose of this study is to evaluate the effect of high dose oxytocin in the obese cohort. The hypothesis is that obese patient will have shorter time to delivery with the high dose oxytocin regimen without incurring any additional risks or adverse outcomes.

4) Setting of the Human Research

Recruitment and conduct of research for eligible patients will take place at the 8OPC/outpatient OB GYN clinic and the inpatient Labor and Delivery unit at the Banner University Medical Center.

5) Resources available to conduct the Human Research

The facility and resources at the outpatient 8OPC/OB GYN clinic and the inpatient labor and delivery unit at the Banner University Medical Center will be utilized to carry out this research study. This include 14 clinical rooms in the outpatient setting; 12 labor beds, 8 triage beds, and more than 20 postpartum beds in the inpatient setting. Both sites are staffed by 16 resident physicians, 3 maternal fetal medicine fellows, as well as attending physicians affiliated with the University of Arizona at their regular business hours. Additionally, both sites are fully supported by nursing and other clinical staffs. There are always 24 hours nursing and in house physician care in the inpatient setting.

The department of statistics will be asked to provide a randomization sequence for the lean patients and a separate sequence for the obese patient to be enrolled in the trial. The lists will be provided to the research pharmacy. The research pharmacy will be responsible for creating the different concentrations of oxytocin infusion drugs which will be labeled as “OPS drug” (Obese Pitocin Study). They will also be responsible for the allocation concealment and blinding aspect of the randomized controlled trial. Bags of oxytocin infusion will appear identical but will contain either low dose or high dose concentrations. The bags will be labelled with study number only (the pharmacist preparing the bags will be the only person able to access the information on study allocation via their list).

The principal investigator, Dr. Meghan Hill, Co-PI, Dr. Ruth Wei, the research coordinator, Destiny Dicken, and any other research staffs included in the VOTF will complete the recruitment and consent portion of this study. Recruitment and consent can take place both in the outpatient and inpatient facilities. All physicians included on the VOTF form will carry out the study on the inpatient unit. The nurses and physicians assigned to the patient will carry out their routine clinical duties.

The nursing staff, resident physicians and the attending physicians will have a meeting with Dr. Ruth Wei to go over the protocol of the study to minimize errors, confounding biases, drop outs, and improve protocol adherence. Nursing and physician roles will not change, but the investigator will facilitate the understanding of this study with the staff.

Otherwise, no additional training is required, as administering oxytocin is a daily activity on the labor and delivery unit.

6) Study Population

Term pregnant women over 37 weeks admitted to labor and delivery undergoing induction of labor at Banner University Medical Center will be recruited for this study.

Using the data from a previous retrospective study performed in this institution[1], the average time of the first stage of labor in the obese cohort was 895 minutes. The average time of first stage of labor in the lean cohort was 660 minutes, with a standard deviation of 330 mins. At alpha of 0.05, and power of 80%, to decrease time to delivery in a similar fashion above (30% reduction), from 895 minutes to 660 minutes, we would need 31 patients in each group.

The investigator plans to enroll a total of 35 patients in each of the 4 groups. The projected total sample size will be 140. We anticipate a low risk of loss to follow up as patients are admitted for delivery and data will only be collected during their hospital stay. Withdrawals and protocol deviations will be included into the data analysis in all groups as this study is an intention to treat analysis. We anticipate a low withdrawal rate after enrollment and randomization. We will delay randomization until when patient is ready to receive study drug to minimize withdrawal rate.

Inclusion criteria:

Singleton pregnancy ≥ 37 weeks gestation

Patient presented for induction of labor who is determined to be a candidate for oxytocin

Cephalic presentation

Reassuring fetal health assessment (no abnormal findings in fetal assessment, see below)

The requirement for fetal health assessment for determining candidacy for oxytocin would be no different in a study patient than in a non-study patient.

Meeting one of the following BMI category:

Obese group: BMI ≥30 at <20 weeks of pregnancy, or BMI ≥35 at a term gestation of pregnancy

Lean group: BMI ≤25 at <20 weeks of pregnancy, or BMI ≤28 at a term gestation of pregnancy

Exclusion criteria:

Non-reassuring fetal assessment at the time of recruitment

Positive Contraction Stress Test - late decelerations after 50% or more of contractions

Category III fetal heart tracing

Prolong bradycardia or fetal deceleration

Biophysical profile <4/10

Reverse end diastolic flow of the umbilical artery Doppler

Previous cervical ripening agents (cytotec, cervidil, cervical Foley Balloon)

<18 years of age

Prisoners

Any patients contraindicated for vaginal delivery

Multiple gestations

History of previous cesarean delivery

Patients with history of significant cardiac disease

Fetal demise

Estimated fetal weight greater than 4500 grams in diabetic and 5000 grams in non-diabetic mother

Ruptured membranes

Spontaneous labor (latent or active phase)

Augmentation of labor (latent or active phase)

1. Hill M, Reed KL, Cohen WR. Oxytocin utilization for labor induction in obese and lean women. J. Perinat. Med. 2015 Nov;43(6): 703-6.

7) Recruitment Methods and Consenting Process

a. Recruitment Process: Potential subjects will be identified through the daily census on labor and delivery as well as through the daily clinic schedule at 8OPC/OB GYN clinic (see Appendix F for partial PHI waiver). Recruitment and consent will take place on both labor and delivery unit as well as the outpatient OB/GYN clinic. The recruitment and consent will occur during regular business hours of both locations. There will be no recruitment material in addition to the required informed consent. The study staff will complete the recruitment and consent portion of this study. Though there is not a script that the study staff will read out to the patient, the sections of the consent form will be used as a guide for discussion with the patients before study procedures are undertaken. All questions will be answered to study subject's satisfaction. The study will only be performed after the study consent is signed.

It is possible that previously eligible and consented patients will become ineligible when they present to labor and delivery, because they could have gone into labor on their own or rupture their membrane prior to presentation to labor and delivery. In this case, the patient will be considered a screen failure.

b. Informed Consent: The consent process was described above. All consent will be documented in written format. It will be communicated to the patients that there will be no change in their clinical care, regardless if patient agreed to consent with this study. For example, participation in this study does not affect the options for pain management during labor routinely available to the patient. This will minimize the potential for coercion. Patients who decline enrollment in the trial will have the method of induction chosen by their physician. Additionally, as this study is an induction of labor study, patients will be recruited and consented prior to going into labor so that the consent process is not completed under stress.

8) Research procedures involved in the Human Research

Sequence generation for randomization, Allocation method and Blinding

This portion of the study will be carried out by the research pharmacy. Single (low dose) and triple (high dose) concentration of oxytocin will be premixed in the intravenous fluid bag in the pharmacy. Sequence generation for randomization will be created with 1:1 ratio in both the obese and lean group by the Department of Statistics. After the sequence is generated, this list will be given to the research pharmacy. The premixed oxytocin medication will be sequentially labelled as "OPS drug, patient #1, 2, 3" etc. per the allocation. Allocation concealment will also be carried out by pharmacy as these bags will completely appear identical after they are labelled numerically. Once a patient is randomized, the pharmacy will send up the appropriate concentration of oxytocin already premixed in the intravenous fluid bag, labelled as "OPS drug, patient #". Lean group will be assigned at # 1-70 and obese group will be assigned at #71-140.

Through the above process, the concentration of the drug will be blinded to the investigators, providers, patient and analysts. The patient will continue to have the same concentration of oxytocin until delivery.

Study Drug (please see appendix B)

Low dose oxytocin regimen (the standard at Banner University Labor and Delivery, as well as across the United States): 30 units in 500cc 0.9% normal saline bag (60 miliunit/cc). Starting rate would be 2 miliunit/minute, or 2cc/hour. The medication will be increased by 2 miliunit/minute = 2cc/hr every 30 minutes until adequacy of contraction or cervical change. At 20 miliunit/minute = 20cc/hr, provider will assess patient for eligibility to continue to increase oxytocin dosage.

High dose oxytocin regimen (endorsed by American College of Obstetricians and Gynecologists): 90 units in 500cc 0.9% normal saline bag (180 miliunit/cc). Starting rate would be 6 miliunit/minute, or 2cc/hour. The medication will be increased by 6 miliunit/minute = 2cc/hr every 30 minutes until adequacy of contraction or cervical change. At 60 miliunit/minute = 20cc/hr, provider will assess patient for eligibility to continue to increase oxytocin dosage.

Patient recruitment, enrollment and entering randomization

Pregnant women at ≥ 37 weeks presented to labor and delivery for induction of labor meeting the inclusion criteria with no exclusion criteria as stated above will be approached for recruitment and enrollment into this study. As stated previously, patients can be recruited and consented from the outpatient clinic as well. The study staff will provide informed consent to all patients. Risk and benefits of the study will be explained to each eligible patient.

After the consent is obtained, patient will enter the randomization process when they are ready to receive oxytocin for their induction of labor. The investigator will inform the research pharmacy if the patient should be in the lean or obese cohort. The research pharmacy will then assign the next allocation (already pre-determined by the sequence allocation as detailed above) and send the appropriate medication to the 8th floor L&D. The research pharmacy will track the study allocations. There are 4 comparison group:

1. Control group: Lean cohort: BMI ≤25, at <20 weeks gestation or BMI ≤28 at a term gestation of pregnancy, low dose oxytocin protocol
2. Intervention group: Lean cohort: BMI ≤25, at <20 weeks gestation or BMI ≤28 at a term gestation of pregnancy, high dose oxytocin protocol
3. Control group: Obese cohort: BMI ≥30, at <20 weeks gestation or BMI ≥35 at a term gestation of pregnancy, low dose oxytocin protocol

4. Intervention group: Obese cohort: BMI ≥30, at <20 weeks gestation or BMI ≥35 at a term gestation of pregnancy, high dose oxytocin protocol

Lean cohorts will be randomized into the low dose or high dose oxytocin arm. The obese cohorts will also be randomized into the low dose or high dose oxytocin arm.

Protocol for each comparison group

Management of oxytocin induction in this study follows normal standard of care on labor and delivery nationally. The only part which will be done specifically for research is the higher concentration of oxytocin given in this study in the high dose oxytocin arm.

Per routine care, oxytocin dosage is titrated up or down to achieve labor while maintaining patient safety. Patient safety is continuously monitored with the tocometer (to monitor for maternal uterine contractions) and fetal heart tracing (to monitor for fetal well being). Stopping rules are listed under each arm separately.

1) Lean, low dose oxytocin arm

   Oxytocin will be administered as described above via a slow intravenous infusion pump. Under the supervision of the study investigator, the patient's nurse will increase the oxytocin infusion as described above, start at 2cc/hr, increase 2cc/hr every 30 minutes up to 20cc/hr. The oxytocin will be increased until one of the parameters below were met:

   >200 Montevideo unit on an intrauterine pressure catheter

   3-5 uterine contractions in a 10-minute period on the external uterine tocometer

   cervical change and progression of labor

   Tachysystole is defined as more than 5 contractions in 10 minutes over an average of a 30 minutes period. In the setting of tachysystole with reassuring fetal status, the oxytocin would be decreased by increments of 2cc until tachysystole no longer occurs. In the setting of nonreassuring fetal status (determined by the provider based on the fetal heart tracing), the oxytocin infusion would be turned off and restarted at ½ of the previous dose after 30 minutes, as long as fetal heart tracing recovers.

   Similarly, regardless of tachysystole, if nonreassuring fetal status occur (at the discretion by the provider), the oxytocin infusion will be turned off and restarted at ½ of the previous dose after 30 minutes, as long as fetal heart tracing recovers. If fetal heart tracing does not recover, the general protocol on labor and delivery would generally warrant an expedited delivery via cesarean delivery. This decision will be made at the discretion of the provider. Therefore, cesarean delivery and operative vaginal delivery is reserved for the usual indications determined by the provider.

   Monitoring of maternal urine output is routinely done on labor and delivery every 4 hours. If oliguria occurs (<0.5cc/kg/hour), a basic metabolic panel will be obtained to assess for hyponatremia. If the sodium level is below 130 meq/L, the oxytocin infusion will be turned off until resumption of urine output or rise in sodium level to above 130meq/L.

   Patient will remain in nothing per oral status per routine guidelines on labor and delivery. Patient can receive other common obstetrical intervention per usual, including epidural placement for pain control, artificial rupture of membrane for labor progression, internal intrauterine pressure

catheter or fetal scalp electrode placement for closer monitoring. Similarly, management of 2nd stage of labor after achieving full cervical dilation will be managed per routine care.

Subsequently after delivery, a new bag of usual concentration of oxytocin will be used in all 4 groups for postpartum oxytocin as per routine.

2) Lean, high dose oxytocin arm

Oxytocin will be administered as described above via a slow intravenous infusion pump. Under the supervision of the study investigator, the patient's nurse will increase the oxytocin infusion as described above, start at 2cc/hr, increase 2cc/hr every 30 minutes up to 20cc/hr. The oxytocin will be increased until one of the parameters below were met:

>200 Montevideo unit on an intrauterine pressure catheter

3-5 uterine contractions in a 10-minute period on the external uterine tocometer

cervical change and progression of labor

Tachysystole is defined as more than 5 contractions in 10 minutes over an average of a 30 minutes period. In the setting of tachysystole with reassuring fetal status, the oxytocin would be decreased by increments of 2cc until tachysystole no longer occurs. In the setting of nonreassuring fetal status (determined by the provider based on the fetal heart tracing), the oxytocin infusion would be turned off and restarted at ½ of the previous dose after 30 minutes, as long as fetal heart tracing recovers.

Similarly, regardless of tachysystole, if nonreassuring fetal status occur (at the discretion by the provider), the oxytocin infusion will be turned off and restarted at ½ of the previous dose after 30 minutes, as long as fetal heart tracing recovers. If fetal heart tracing does not recover, the general protocol on labor and delivery would generally warrant an expedited delivery via cesarean delivery. This decision will be made at the discretion of the provider. Therefore, cesarean delivery and operative vaginal delivery is reserved for the usual indications determined by the provider.

Monitoring of maternal urine output is routinely done on labor and delivery every 4 hours. If oliguria occurs (<0.5cc/kg/hour), a basic metabolic panel will be obtained to assess for hyponatremia. If the sodium level is below 130 meq/L, the oxytocin infusion will be turned off until resumption of urine output or rise in sodium level to above 130meq/L.

Patient will remain in nothing per oral status per routine guidelines on labor and delivery. Patient can receive other common obstetrical intervention per usual, including epidural placement for pain control, artificial rupture of membrane for labor progression, internal intrauterine pressure catheter or fetal scalp electrode placement for closer monitoring. Similarly, management of 2nd stage of labor after achieving full cervical dilation will be managed per routine care.

Subsequently after delivery, a new bag of usual concentration of oxytocin will be used in all 4 groups for postpartum oxytocin as per routine.

3) Obese, low dose oxytocin arm

Oxytocin will be administered as described above via a slow intravenous infusion pump. Under the supervision of the study investigator, the patient's nurse will increase the oxytocin infusion as described above, start at 2cc/hr, increase 2cc/hr every 30 minutes up to 20cc/hr. The oxytocin will be increased until one of the parameters below were met:

>200 Montevideo unit on an intrauterine pressure catheter

3-5 uterine contractions in a 10-minute period on the external uterine tocometer

cervical change and progression of labor

Tachysystole is defined as more than 5 contractions in 10 minutes over an average of a 30 minutes period. In the setting of tachysystole with reassuring fetal status, the oxytocin would be decreased by increments of 2cc until tachysystole no longer occurs. In the setting of nonreassuring fetal status (determined by the provider based on the fetal heart tracing), the oxytocin infusion would be turned off and restarted at ½ of the previous dose after 30 minutes, as long as fetal heart tracing recovers.

Similarly, regardless of tachysystole, if nonreassuring fetal status occur (at the discretion by the provider), the oxytocin infusion will be turned off and restarted at ½ of the previous dose after 30 minutes, as long as fetal heart tracing recovers. If fetal heart tracing does not recover, the general protocol on labor and delivery would generally warrant an expedited delivery via cesarean delivery. This decision will be made at the discretion of the provider. Therefore, cesarean delivery and operative vaginal delivery is reserved for the usual indications determined by the provider.

Monitoring of maternal urine output is routinely done on labor and delivery every 4 hours. If oliguria occurs (<0.5cc/kg/hour), a basic metabolic panel will be obtained to assess for hyponatremia. If the sodium level is below 130 meq/L, the oxytocin infusion will be turned off until resumption of urine output or rise in sodium level to above 130meq/L.

Patient will remain in nothing per oral status per routine guidelines on labor and delivery. Patient can receive other common obstetrical intervention per usual, including epidural placement for pain control, artificial rupture of membrane for labor progression, internal intrauterine pressure catheter or fetal scalp electrode placement for closer monitoring. Similarly, management of 2nd stage of labor after achieving full cervical dilation will be managed per routine care.

Subsequently after delivery, a new bag of usual concentration of oxytocin will be used in all 4 groups for postpartum oxytocin as per routine.

4) Obese, high dose oxytocin arm

Oxytocin will be administered as described above via a slow intravenous infusion pump. Under the supervision of the study investigator, the patient's nurse will increase the oxytocin infusion as described above, start at 2cc/hr, increase 2cc/hr every 30 minutes up to 20cc/hr. The oxytocin will be increased until one of the parameters below were met:

>200 Montevideo unit on an intrauterine pressure catheter

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cervical change and progression of labor

Tachysystole is defined as more than 5 contractions in 10 minutes over an average of a 30 minutes period. In the setting of tachysystole with reassuring fetal status, the oxytocin would be decreased by increments of 2cc until tachysystole no longer occurs. In the setting of nonreassuring fetal status (determined by the provider based on the fetal heart tracing), the oxytocin infusion would be turned off and restarted at ½ of the previous dose after 30 minutes, as long as fetal heart tracing recovers.

Similarly, regardless of tachysystole, if nonreassuring fetal status occur (at the discretion by the provider), the oxytocin infusion will be turned off and restarted at ½ of the previous dose after 30 minutes, as long as fetal heart tracing recovers. If fetal heart tracing does not recover, the general protocol on labor and delivery would generally warrant an expedited delivery via cesarean delivery. This decision will be made at the discretion of the provider. Therefore, cesarean delivery and operative vaginal delivery is reserved for the usual indications determined by the provider.

Monitoring of maternal urine output is routinely done on labor and delivery every 4 hours. If oliguria occurs (<0.5cc/kg/hour), a basic metabolic panel will be obtained to assess for hyponatremia. If the sodium level is below 130 meq/L, the oxytocin infusion will be turned off until resumption of urine output or rise in sodium level to above 130meq/L.

Patient will remain in nothing per oral status per routine guidelines on labor and delivery. Patient can receive other common obstetrical intervention per usual, including epidural placement for pain control, artificial rupture of membrane for labor progression, internal intrauterine pressure catheter or fetal scalp electrode placement for closer monitoring. Similarly, management of 2nd stage of labor after achieving full cervical dilation will be managed per routine care.

Subsequently after delivery, a new bag of usual concentration of oxytocin will be used in all 4 groups for postpartum oxytocin as per routine.

When the maximum rate is reached at 20cc/hour, patient will be assessed by the provider for eligibility to continue to increase oxytocin dosage. This will also be done in the routine manner at the discretion of the provider.

All woman/fetus pairs will be continuously monitored via Doppler/TOCO as per standard of care.

Subject participation is expected to last until time of hospital discharge.

Data collection

Standard data points will be collected during the labor of each patient enrolled in the study:

Demographic:

Date of admission and discharge

Age, race, parity, gravidity

Weight, height and BMI

Indication for induction

Associating medical comorbidities

Induction:

Cervical exam and bishop score

Start time for induction

Tachysystole

Terbutaline use

Internal monitoring (intrauterine pressure catheter, fetal scalp electrode)

Time of membrane rupture (spontaneous or artificial)

Time of onset of second stage labor

Time of delivery of fetus, placenta

Birth weight of fetus

Apgar score of fetus at 1 and 5 minutes

Type of delivery (vaginal, vacuum or forceps assisted, cesarean delivery) and indication

If cesarean delivery, time when decision of cesarean delivery was made

Total amount of oxytocin, median, mean, and maximum oxytocin rate

Abnormal fetal heart tracing

Maternal complications

Postpartum hemorrhage

Estimated blood loss

Postpartum fever, chorioamnionitis, endomyometritis

Pre-induction and Lowest postpartum hematocrit

Uterine rupture

Blood transfusion

Incidence of oliguria

Baby:

Type of nursery admission (newborn or NICU)

Umbilical cord gas if applicable

No other PHI will be collected as part of this study.

All the data above will be collected from the medical records and transcribed on a standardized data collection sheet and will be placed in a locked cabinet in the investigator's office (please see attachment for data collection sheet).

9) Cost to subjects

There will be no additional costs to patients due to study procedures. Patients will be billed for their care per treatment received during their hospitalization per usual. Oxytocin is very inexpensive. Any increase in charge due to the high dose oxytocin protocol will be billed to the Department of OB/GYN. The department has awarded a small internal funding to cover the administrative and additional medication cost of this study.

10) Risks to subjects

Low dose oxytocin regimen is the current standard of care on labor and delivery in the United States. High dose oxytocin regimen is widely used internationally. Both regimens' safety profile has been compared and validated in multiple meta-analysis including a Cochrane review as detailed above in the background section. Therefore, the American College of Obstetricians and Gynecologists had endorsed both regimens. It is important to emphasize that the following risks pertain to both the low dose (the current standard of care on L&D) and high dose protocol, and that the Cochrane review did

not find the high dose protocol to have additional risks to patients. Adverse events (AE) and serious adverse events (SAE) to oxytocin in mother includes:

Cardiovascular: Cardiac arrhythmia, including premature ventricular contractions (SAE), subarachnoid hemorrhage (SAE), tachycardia (SAE), hypotension (SAE), hypertension (SAE)

As discussed above, cardiovascular changes with high dose oxytocin were observed in studies in which patients received a large intravenous bolus over a short period (15-30 seconds). Secondary to these concerns, currently the standard of care is to administer oxytocin over a slow intravenous infusion [1,2]. This study does not deviate from the standard of care protocol. Therefore, the investigator predicts a low cardiovascular risk to patients, risks that would be comparable with current standard of care. In addition, the investigator excluded mothers with previous serious cardiac disease to further decrease risks to subjects.

Genitourinary: Uterine hypertonia (SAE), tachysystole (AE), uterine rupture (SAE), postpartum hemorrhage (SAE)

These are well known side effects of oxytocin on the obstetrical floor and the absolute rates remain low. Again, as discussed above, these risks were evaluated and compared directly by multiple meta-analysis and a Cochrane review. There was also no difference in serious maternal or neonatal morbidity or death between the high and low dose regimen. There was no difference in adverse outcomes, including maternal uterine rupture, postpartum hemorrhage, endometritis, estimated blood loss, abnormal fetal heart tracing, fetal Apgar, newborn resuscitation and neonatal intensive care unit admission [3-5]. Therefore, the investigator believes that the risk to the patient will be similar to baseline.

Tachysystole will be monitored continuously as a clinical parameter to direct patient care and protocol management as well as a secondary outcome variable.

Endocrine and metabolic: Water intoxication (SAE), hyponatremia (SAE)

Again, as described above, there were also old case reports originating from the 1970s about concerns over high dose oxytocin and its association with maternal hyponatremia or water intoxication [6,7]. The hypothesis behind its association is due to the similarity between oxytocin and anti-diuretic hormone. These were largely single case reports in the setting of accidental large overdose of oxytocin in addition to large volume administration of electrolyte-free solutions. Since then, the practice of administering oxytocin is only given alongside isotonic lactated ringer or normal saline in a slow intravenous infusion fashion [8,9]. This study does not deviate from the standard of care. Therefore, the investigator predicts a low risk to patients, risks that would be comparable with current standard of care.

The following SAE and AE have been associated with oxytocin but frequency is not well defined and not well reported in the literature.

Hematologic: pelvic hematoma (SAE), fatal afibrinogenemia (SAE)

Misc: Anaphylactic reaction (SAE), nausea and vomiting (AE)

Risks to fetus include:
Due to induced uterine motility: bradycardia (SAE), premature ventricular contractions and other arrhythmias (SAE), permanent CNS or brain damage (SAE), fetal death (SAE), neonatal seizures (SAE)

Due to use of oxytocin in mother: low apgar scores (AE), neonatal jaundice (AE), neonatal retinal hemorrhage (SAE)

Frequency of risks:
The frequency of risks occurring for each risk is not well defined and not well reported in the literature. All above risks are considered to be rare, with the exception of:

Tachysystole: This will be monitored continuously as a clinical parameter to direct patient care and protocol management, as written in the protocol. Also it is important to recognize that tachysystole occurs with the low dose protocol as well, which is the current standard of care.

Nausea and vomiting: This is a common side effect of labor itself with or without oxytocin.

It is important to recognize that these risks exist equally in the low dose protocol, which is the current standard of care on Labor and Delivery. When a patient presents for an induction of labor with oxytocin, they are subjected to all of the above risks, regardless of whether they are enrolled as a study participant. The only way to avoid these risks completely, is for a patient to not receive oxytocin (which is required if patient agreed to undergo an induction of labor). These risks above have been well monitored throughout clinical practice since the 1970s, and large Cochrane review as detailed above had provided good safety profile for this drug in both the low and high dose regimen.

All serious adverse events (SAE) will be monitored and documented closely during the study, and will result in discontinuation of the study protocol immediately. The management of AE is detailed in the protocol. If more than 20% of patients enrolled in the study have an AE/SAE, enrollment in the study will be stopped pending an evaluation of the frequency of AE/SAE.

1. Svanstrom MC, Biber B, Hanes M, Johansson G, Naslund U, Balfors EM. Signs of myocardial ischemia after injection of oxytocin: a randomized double-blinded comparsion of oxytocin and methylergometrine during cesarean section. British Journal of Anaesthesia 100 (5): 683-9 (2008).
2. Bhattacharya S, Ghosh S, Ray D, Mallik S, Laha A. Oxytocin administration during cesarean delivery: randomized controlled trial to compare intravenous bolus with intravenous infusion regimen. J Anaesthesiol Clin Pharmacol. 2013 Jan-Mar; 29(1): 32-35.
3. Wei SQ, Luo ZC, Qi HP, Xu H, Fraser WD. High dose vs. low dose oxytocin for labor augmentation: a systematic review. Am J Obstet Gynecol 2010 Oct; 203(4): 296-304.
4. Zhang J, Branch DW, Ramirez MM, Laughon SK, Reddy U, Hoffman M, Bailit J, Kominiarek M, Chen Z, Hibbard JU. Oxytocin regimen for labor augmentation, labor progression, perinatal outcomes. Obstet Gynecol 2011 Aug; 118 (2 Pt 1):249-56.
5. Budden A, Chen LJY, Henry A. High-dose versus low-dose oxytocin infusion regimens for induction of labour at term. Cochrane Database of Systematic Reviews 2014, Issue 10. Art. No.: CD009701.
6. Jensen I, Bruns BJ. Water intoxication after oxytocin-induced midtrimester abortion. NZ Med J. 1979 April 25; 89(634):300-2.
7. Lauersen NH, Birnbaum SJ. Water intoxication associated with oxytocin administration during saline-induced abortion. Am J Obstet Gynecol. 1975 Jan 1; 121(1): 2-6.
8. Higgins J, Gleeson R, Holohan M, Coone C, Darling M. Maternal and neonatal hyponatremia: a comparison of Hartmanns solution with 5% dextrose for the delivery of oxytocin in labor. European Journal of Obstetrics and Gynecology and Reproductive Biology 68 (1996) 47-48.

9. Moen V, Burdin L, Rundgren M, Irestedt L. Hyponatremia complicating labor – rare or unrecognized? A prospective observational study. BJOG 2009; 116: 552-561.

11) Potential benefits to subjects and/or society

Study patients in the high dose oxytocin groups may experience a faster labor course or lower cesarean delivery rate if our hypothesis is correct.

Benefits to society at large include potential systematic changes to management of obese pregnant women in labor. High dose oxytocin regimen may improve pregnancy outcome with faster labor course without an increase in morbidity, and may affect a change in cesarean delivery rate.

12) Provisions to protect the privacy of subjects and the confidentiality of data

a. **Protection of subject privacy:** Privacy of subjects will be respected always during the study. Patients will only be consented in a private area. Patients are asked during all encounters with a physician whether they would like their family or friends present.

b. **Protection of data confidentiality:**

A data collection sheet will be used to record data. This data will then be stored in a coded fashion with key code assigned, in a computer excel spreadsheet on the principal investigator's computer, located in room 8327G in the Department of Obstetrics and Gynecology. Only the PI will have access to the key code. Because every account on the computer is password protected, the only person who has access to this computer is the PI herself. Only personnel on the VOTF will be granted access to this data/spreadsheet. The data collection sheet and the patient consent forms will be kept in the same room in a locked file cabinet. These data collection sheets, the patient consent documents as well as the key code will be stored for a period of 6 years after conclusion of study and destroyed thereafter.

13) Access to Private Information

a. **Access to medical records (HIPAA)**: Patients agreeing to participate in this study will be made aware that record review of their, and their child's, protected health information will occur as a part of the study. The consent form includes HIPAA consent. Only investigators on the VOTF can access their PHI, as described above. A list of data to be collected is detailed above.

14) Subject compensation

There will be no monetary compensation provided to the subjects for participating in this study.

15) Medical care and compensation for injury

There are no expected maternal or fetal injuries attributed to the high dose oxytocin regimen compared to the low dose oxytocin regimen as discussed above. In the unforeseeable event that a complication occurs, the patient will be billed for their medical care as they would with any other induction of labor.

16) Monitoring for subject safety

The study protocol has built in monitoring measures for specific clinical scenarios in the setting of adverse reactions. These include specific detailed protocols for tachysystole, nonreassuring fetal status as well as oliguria.

For every 10 enrollments, data will be monitored by the principal investigator and reviewed by an independent reviewer within the department of ob/gyn. This personnel will have a background in ob/gyn and will be assigned by the principal investigator. Data will be reviewed in a blinded fashion to prevent introducing bias into the study. In addition, all serious adverse events (SAE) will be monitored and documented closely during the study with each enrollment, and will result in discontinuation of the study protocol immediately. The management of AE is detailed in the protocol. If more than 20% of patient enrolled in the study have an AE/SAE, enrollment in the study will be stopped pending an evaluation of the frequency of AE/SAE. This will be reported to the IRB. The principal investigator and the research staffs will monitor protocol adherence closely with each enrolled participant. Any protocol deviation will be reported to the IRB as required.

17) Withdrawal of subjects

A patient may withdraw from this research at any time. The infusion of the study drug can be stopped at any time. A patient may withdraw for any reason, including a desire to stop induction of labor and undergo an elective cesarean delivery. Subjects will not be at increased risk when they are abruptly withdrawn from the study because of the short half-life of oxytocin (4.5 minutes). Data collection on patients who have completed more than 30 minutes of study drug will be kept and included in the data analysis (intention to treat analysis). Any withdrawal secondary to side effects or adverse effects will be recorded and monitored. Only verbal withdrawal is required.

18) Sharing of results with subjects

The results of the study will not be shared with the subjects, families or the institution. Patients will not be contacted in the future in relation to the results of the research. The intention is to publish the results of this research and patients will have access to the information gained through this forum.

There will be no additional charges billed to the insurance for any procedures associated with this study.

19) Future use and long-term storage of data or specimens

Data will not be kept for future research.

20) Clinical Trials.gov Information

☐ ClinicalTrials.gov "NCT" number for this trial (provide):
☒ Registration pending
☐ Clinical trial does not require registration (explain):

SECTION 4: LIST OF ATTACHMENTS FOR THIS SUBMISSION (REQUIRED) (Items listed here are expected to be attached as separate documents. These documents will appear in the UA HSPP IRB approval letter as 'documents submitted concurrently' with the review.)	
Document Name	**Version Date**
1. F107/VOTF	**1.** 02/27/17
2. Appendix A/Children	**2.** 02/27/17
3. Appendix B/Drugs/devices	**3.** 02/27/17
4. Appendix D/pregnant women and neonate	**4.** 01/31/17

5. Drug information	**5.** 01/31/17
6. Appendix F/waiver of consent	**6.** 02/27/17
7. T503a/consents	**7.** 03/31/17
8. Data collection form	**8.** 01/31/17
9. Biosketch of PI (Meghan Hill) and Co PI (Ruth Wei)	**9.** 02/27/17
10. Protocol	**10.** 03/31/17
11. autographs	**11.** 01/31/17

See HSPP website for submission requirements.

Items needed for approval:

- Word Versions of Application, Consents, Recruitment and Data Collection
- **F107: Verification of Training Form**
- **Current PI/Co-PI CVs or biosketch**, if not included with copy of grant application
- **Informed Consent/Permission/Assent Form(s)** – including study specific release of information documents, DHHS approved sample consent forms. If consent will not be documented in writing, a script of information to be provided orally to subjects

Other Items as applicable:

- **Appendix A - Children**
- **Appendix B - Drug/Device**
- **Appendix C- Multi Site Research**
- **Appendix D- Pregnant Women and Neonates**
- **Appendix E- Prisoners**
- **Appendix F- Waiver of Consent/ PHI**
- **Appendix G- Exception from Informed Consent (EFIC)**
- **Appendix H- Native American**
- **Biosafety Review letter** (for UA - Institutional Biosafety Committee)
- **Certificate of Confidentiality**
- **Compressed Gases Review letter** (for UA – Research Instrumentation)
- **Contract** – complete or draft copy of contract including budget
- **Data Collection Tools** – surveys, questionnaires, diaries not included in the protocol, data abstraction form for records review
- **Data Monitoring Charter and Plan**
- **Drug/Device information** – Investigator's Brochure, drug product sheet, device manual, user's manual, instructions for use, package insert, IND/IDE documentation, FDA 1572 form, 510k indication, FDA exemption, sponsor determination of device risk, etc.
- **Export Control Review**
- **Grant Application(s)** – cover-to-cover copy of grant, regardless of home institution or funding agency, and a copy of the Notice of Grant Award.
- **Multi-site information** (for sites engaged in research where the UA is the IRB of record)
  - Copy of any approvals granted from that site (including determinations if this site has an IRB of its own)
  - Site-specific F107
  - Copy of the site's human subjects training policy
  - CV and medical license (if applicable) of site PI
- **Other Approval letters** (e.g., school districts, Tribal, other IRB approvals)
- **Participant Materials** – written materials to be provided to or meant to be seen or heard by subjects (e.g. study newsletter, physician to participant letter, wallet cards, incentive items, holiday/birthday cards, certificates, instructional videos/written guides, calendars, certification of achievement, etc.)
- **Payer coverage analysis**

- **PHI Authorization Form(s)**
- **Protocol** – including all amendments/revisions, sub- or extension-studies
- **Radiation Safety Review** letter- needed regardless if the radiation device is approved and used standard of care
- **Recruitment Materials** – telephone scripts, flyers, brochures, websites, email texts, radio/television spots, newspaper advertisements, press releases, etc.
- **Scientific Review Committee** letter (for cancer related projects – AZCC SRC; other units as applicable if the unit has a scientific review committee)
- **Site Authorizations** for research purposes and/or access to administrative records/samples
  - External sites (such as schools, other hospitals or campuses, etc.)
  - UAHS Research Portal feasibility review approval
- **Travel Authorization documentation** (for UA – Office of Global Initiatives)
- **Use of retrospective research samples and/or data** – IRB approval letter, original consent under which samples/data were collected, letter allowing access to samples