The HILIO Trial: High vs. Low Oxytocin Dosing for Induction of labor in Pregnant Patients with Obesity

PILOT STUDY

Protocol

NCT 05289869

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1. INTRODUCTION

1.1 Study Abstract

Women with obesity are more likely to undergo induction of labor and have a higher risk of failed induction compared to women with normal weight. The association between maternal obesity and labor dysfunction leading to cesarean delivery is poorly understood. Oxytocin is the mostly common medication used in induction of labor, yet optimal dosing of this medication is unknown. Studies have suggested that women with obesity may be less responsive to oxytocin. This trial will compare a high and low dose oxytocin dosing regimen for the induction of labor in women with obesity.

1.2 Hypothesis

A higher oxytocin dosing regimen (increase by 6 mU/min every 30 minutes) will result in a decreased risk of cesarean delivery compared to a lower oxytocin dosing regimen (increase by 2 mU/min every 30 minutes) in nulliparous women with a pre-pregnancy body mass index ≥30 kg/m^2 undergoing induction of labor at >37 weeks gestation.

2. BACKGROUND

2.1 Introduction

It is estimated that nearly 40% of reproductive-aged women in the United States (U.S.) are obese,[1,2] and rates of obesity are projected to further increase over the next decade.[3] Maternal obesity, defined as body mass index (BMI) ≥30 kg/m^2, is a major risk factor for adverse obstetric outcomes. It has been suggested that the dramatic rise in the prevalence of obesity is, at least in part, responsible for the increase in the cesarean delivery rate that has observed over the past 50 years.[4] It is currently reported that nearly one in three women in the U.S. deliver by cesarean,[5] and women with obesity are twice as likely to have a cesarean compared to normal weight women.[6-9] Overall, abnormal labor progress is the most common indication for primary cesarean delivery in the U.S.,[10,11] but rates of cesarean for this indication are disproportionately higher in obese women.[11] Unfortunately, women with obesity are also more likely to experience complications following a cesarean delivery including wound infections[12-14] and venous thromboembolism.[15] Thus, there is a critical need to develop interventions that optimize labor management in women with higher BMIs in order to curb the rise in cesarean delivery rates in an obstetric population that is becoming increasingly obese.

2.2 Obesity and Labor Outcomes

Multiple studies in the U.S. have shown that there is a dose response relationship between increasing maternal BMI and risk of cesarean delivery.[8,9,11] In a large multicenter U.S. study, Kominiarek et al. reported that there was a 5% increase in the risk of cesarean for each 1-kg/m^2 increase in maternal BMI among both laboring nulliparous and multiparous women without a prior cesarean delivery.[8] Among nulliparous women with cephalic term fetuses who underwent labor, rates of cesarean delivery were 11.1%, 17.7%, 25.1%, 33.0%, and 42.8% for women with delivery BMI <25.0 kg/m^2, 25.0-29.0 kg/m^2, 30.0-34.9 kg/m^2, 35.0-39.9 kg/m^2, and ≥40 kg/m^2, respectively. Furthermore, the association between increasing maternal BMI and cesarean delivery was shown to be independent of age, race, diabetes status, cervical dilation at admission, and induction of labor.

In general, labor progresses more slowly among women with obesity. In a cohort study of women who successfully achieved complete cervical dilation, Norman et al. found that the median duration of time for a women to progress from 4 cm dilation to 10 cm was significantly longer in obese compared to non-obese women (4.7 hours vs 4.1 hours, p <0.01).[16] Similarly, Kominiarek et al. reported that the time to progress from centimeter to centimeter in cervical dilation increases with rising maternal BMI in both nulliparous and multiparous women.[17] Given this association between maternal BMI and impaired labor progress, it is not surprising that the most common indication of primary cesarean delivery in women with obesity is arrest of labor. In a large study that included 66,502 nulliparous women, Kawakita et al. found that a significantly higher proportion of primary cesarean deliveries in obese women were performed for the indication of labor arrest compared to non-obese (47% vs 33%).[11] Interestingly, the higher risk of cesarean in women with obesity seems to be confined to the first stage of labor during which the cervix dilates; once women reach complete dilation, rates of cesarean are similar among women with and without obesity.[18]

While there is strong epidemiologic evidence for the association between maternal BMI and labor dysfunction, the biologic mechanisms underlying this association are largely unknown. One leading theory is that maternal obesity is leads impaired myometrial contractility.[19] Differences in the pharmacokinetics of drugs commonly used for labor induction and augmentation in obese and non-obese women may also contribute to the association between maternal BMI and labor outcomes.[20-22] With these potential biological factors in mind, and the significant individual and public health benefits that would be gained by reducing the chance of cesarean among obese individuals, research focused on the clinical relationship between the medications used to stimulate labor and obstetric outcomes among women with obesity is needed.

2.3 Oxytocin Dosing in Labor

2.3.1 High vs. Low Dosing Regimens

Induction of labor, defined as the artificial initiation of labor before spontaneous labor onset, is performed in approximately 30% of all births.[5] Intravenous synthetic oxytocin is the most commonly used agent for the induction and augmentation of labor since being introduced into the market in the 1950's.[23,24] A non-peptide hormone, oxytocin is released in large amounts during the labor process from the posterior pituitary. Despite its frequent use in the U.S., there remains little to no consensus regarding the optimal protocols for the dosing and duration of synthetic oxytocin in labor.[23,25]

There have been a number of studies that have evaluated the dose of oxytocin for labor augmentation. In a systematic review and meta-analysis of 4 studies including 644 women published in 2013, higher dose oxytocin regimens were associated with lower rates of cesarean delivery and shorter duration of labor compared to lower dose regimens.[26] However, the results of a large single center trial comparing high-dose (6 mu/min) compared to low-dose (2 mu/min) regimens for augmentation of labor that included over 1000 participants was recently published.[27] The investigators found that while the higher oxytocin dosing regimen reduced the time from randomization to delivery and risk of chorioamnionitis, there were no differences in rates of cesarean delivery. This study, however, was within a general population of obese and non-obese individuals, and was specifically targeted toward those having augmentation, not induction.

The question of oxytocin dosing for induction of labor – let alone among obese individuals – has been less well studied. In 2014, Budden et al. conducted a systematic review and meta-analysis to address this clinical question.[28] Nine clinical trials involving 2391 women were included in the review. They found no differences in rates of cesarean or time from induction to delivery among women randomized to high-dose compared to low-dose oxytocin infusion regimens, but reported higher-dose regimens were associated with an increase in the incidence of "hyperstimulation". However, the studies included in the review were heterogeneous, specifically with regards to the dosing regimen used and population studied. In fact, the only study in the review that was published in the past 20 years was not designed to compare high to low dose oxytocin regimens but rather pulsatile versus continuous oxytocin infusion strategies.[29] Additionally, all of the studies included in the systematic review were deemed to be at moderate-to-high risk of bias emphasizing that well-designed, high quality studies are still needed.

2.3.2 Maternal Body Mass Index and Oxytocin Dosing

Women with obesity are more likely to undergo induction of labor, but also more likely to experience failed induction of labor compared to non-obese women.[30] Oxytocin is the most common drug used in induction of labor. Women with a higher BMI seem to be less responsive to oxytocin. In one retrospective study of women who reached the

second stage of labor, only 2.6% of women with BMI <30 kg/m^2 required maximum oxytocin doses >20 mu/min compared to 4.3% of women with BMI ≥30.0 kg/m^2.[31] A subsequent study of women who had a vaginal delivery confirmed that increasing maternal BMI was associated with higher maximum doses of oxytocin as well as increasing cumulative amounts of oxytocin.[20] These data would suggest that women with obesity require higher doses of oxytocin, and are a group who would preferentially benefit from higher oxytocin dosing regimens.

2.3.3 Oxytocin Safety

The use of oxytocin in the United States is ubiquitous, with 78% of women receiving it during labor in one large multicenter study.[32] Nevertheless, intravenous oxytocin is labeled as a “high alert” medication by the Institute of Safe Medication Practices.[33] This risk category was assigned to oxytocin due to risks related to infusion including maternal risks of uterine tachysystole, water intoxication with prolonged use, and fetal risks including intrauterine heart rate changes and neonatal acidemia at birth. Yet, these outcomes are rare. In a recently published large randomized trial of high- versus low-oxytocin regimens for labor augmentation, no differences in neonatal outcomes were reported.[27]

2.4 Rationale for Randomized Trial

There is a general consensus that the current cesarean delivery rate of 31% in the United States is higher than it ought to be.[5,34] The increasing prevalence of obesity among pregnant women is thought to be an important contributing factor. As obesity rates are projected to further increase over the next decade, the development of evidenced-based intrapartum interventions to improve obstetric outcomes for women with obesity are needed. Observational data suggest that women with obesity may benefit from receiving higher doses of oxytocin to achieve a vaginal delivery. Thus, a rigorous trial investigating the optimal dosing of oxytocin in obese women is needed.

3. STUDY DESIGN

3.1 Primary Research Question

This double blinded randomized controlled trial will address the primary research question:

Does a high-dose oxytocin regimen reduce the chance of cesarean delivery compared to a low-dose oxytocin regimen among nulliparous women with obesity undergoing induction of labor at 37 weeks’ gestation or later?

3.2 Design Summary

This study is a pragmatic single center randomized, double blinded controlled trial. Nulliparous women with a pre-pregnancy body mass index (BMI) ≥30 kg/m^2 undergoing induction of labor at ≥37^0 weeks' gestation will be eligible for enrollment. Women will be randomly allocated to receive oxytocin using either a high-dose or low-dose regimen. Patients, providers, and research staff will be blinded to the dosing regimen.

High-dose oxytocin regimen: Starting dose 6 mU/min and increased by 6 mU/min every 30 minutes until adequate contractions achieved, at the discretion of the obstetric providers.

Low-dose oxytocin regimen: Starting dose 2 mU/min and increased by 2 mU/min every 30 minutes until adequate contractions achieved, at the discretion of the obstetric providers.

Adequate contractions will be defined as >200 Montevideo units averaged over 30 minutes in women with an intrauterine pressure catheter (IUPC), or contractions every 2-3 minutes in women without an IUPC.

3.3 Blinding

Participants, research staff, and clinical care providers will be blinded to the dosing regimen. This will be achieved by using identical appearing study drug preparations with different concentrations of oxytocin. In the low-dose group, the oxytocin solution will be prepared using 30 units of oxytocin in 500 mL of normal saline (concentration 60 mU/mL). The oxytocin concentration in the high-dose group will be prepared using 90 units of oxytocin in 500 mL of normal saline (180 mU/mL). The study drug in both groups will be administrated at a rate of 2 mL/hour with an increase in rate of 2 mL/hour every 30 minutes.

3.4 Eligibility Criteria

3.4.1 Inclusion Criteria

1. Nulliparity
2. Maternal age >18 years
3. Gestational age ≥37w0d
4. Induction of labor, defined as initiation of labor with medication or intracervical Foley catheter in a patient without observed spontaneous cervical change and <6

contractions per hour (average of one contraction every 10 minutes) at the time of initial presentation. Women with prelabor rupture of membranes (PROM) can be included if the other criteria are also met with regards to cervical dilation and contractions.

5. Singleton gestation

6. Cephalic presentation

7. Indication for oxytocin use in the first stage of labor

8. No contraindication to labor or vaginal delivery

9. Pre-pregnancy BMI ≥30 kg/m^2 based on patient report and confirmed by pre-pregnancy or first trimester weight as recorded in the medical record

10. Cervical dilation ≤4 cm at time of initiation of induction

3.4.2 Exclusion Criteria

1. Fetal demise

2. Major fetal congenital malformation or known chromosomal abnormality

3. Prior uterine surgery (e.g., cesarean, myomectomy)

4. Non-reassuring fetal wellbeing as indication for induction

6. Intraamniotic infection suspected or diagnosed prior to randomization

7. Non-English

8. Multifetal gestation

9. Gestational age <37 weeks

10. Spontaneous labor

11. Cervical dilation > 4 cm at initiation of induction

12. Initiation of oxytocin in the second stage of labor

13. Use of oxytocin prior to randomization or planned use of oxytocin with foley catheter for cervical ripening

14. Fetal malpresentation

15. Estimated fetal weight >4500 g in a patient with diabetes, or estimated fetal weight >5000 g in a non-diabetic patient

16. Abnormal placentation (e.g. previa, suspected placenta accreta spectrum)

17. Physician/provider or patient refusal

3.5 Informed Consent Criteria

Written informed consent will be obtained prior to randomization into the study. The details of the study will also be reviewed with the patient by research personnel. Participants will be provided with a signed copy of the consent form.

3.6 Randomization

Patients will be approached for possible enrollment in the study when they are admitted to the labor and delivery unit for induction of labor. Women who chose to participate in the study will be randomized to the high- or low-dose oxytocin regimen prior to the initiation of oxytocin in the labor course. Women will be randomized in a 1:1 ratio to the high and low-dose oxytocin regimens.

A block randomization method will be used to generate the randomization sequence because it provides a high probability of balance of treatment assignments. A computer-generated randomization scheme using block sizes of four will be designed by the study statistician. The randomization sequence will be provided to the investigational pharmacy staff who will prepare the study drug for each participant.

4. STUDY PROCEDURES

4.1 Screening for Eligibility and Consent

Women who are admitted for delivery to the Ohio State University Wexner Medical Center Labor & Delivery unit will be screened for potential enrollment. The inclusion/ exclusion criteria will be reviewed in the patient's medical record and documented on the screening log.

If the patient meets all eligibility criteria for enrollment, then she will be approached by research personnel to discuss the study in detail. Patients may be approached any time after admission to the Labor & Delivery unit, but prior to the initiation of oxytocin for labor induction. If the patient is interested in enrollment, the informed consent process will be conducted by trained research staff. The study consent and HIPAA authorization will be signed after all questions have been discussed and answered. The participant will be given a copy of the signed consent form.

4.2 Randomization

Randomization will occur when the obstetric provider decides to begin oxytocin for labor induction. At that time, the patient will be assigned the next sequential study identification number and central pharmacy will dispense the study drug (high- or low-dose oxytocin concentration) depending on the randomization allocation sequence. The pharmacist will not be blinded to the allocation.

4.3 Baseline Procedures

In addition to information collected for eligibility, the following information will be obtained at randomization from the patient interview followed by review of the medical record:

- Demographic information: age, race, insurance coverage, marital status
- Medical history: pre-pregnancy weight, current weight, height, chronic disease history
- Current pregnancy labor data: cervical dilation, cervical effacement and fetal station at time of admission and randomization, time and date of admission and randomization, other labor induction methods used (e.g.; misoprostol, cervidil, foley catheter), membrane status (ruptured or intact) at time of randomization
- Obstetrical history including gravidity and parity

4.4 Patient Management and Follow-up

This is a pragmatic clinical trial. The study drug will be started at a rate of 2 mL/hour (6 mU/min in high-dose group and 2 mU/min in low-dose group) with the intent to increase the rate by 2 mL/hour every 30 minutes until adequate contractions are achieved, defined as >200 Montevideo units averaged over 30 minutes in women with an intrauterine pressure catheter (IUPC),[34] or contractions every 2-3 minutes in women without an IUPC. All changes in study drug administration will be at the discretion of the obstetric provider and nursing staff. Decrease in the rate of administration or discontinuation of the study drug in response to clinical findings should be performed in accordance with local standard of care. All other aspects of obstetric management will be at the discretion of the patient's clinical care team. Cord gases will be collected on all participants enrolled in the study.

Postpartum maternal, neonatal, and delivery outcomes will be collected. Postpartum data through hospital discharge will be collected from the medical record. Information about complications following hospital discharge through 6 weeks after delivery will be collected during a research follow-up telephone call performed 6-8 weeks following delivery. Relevant maternal and neonatal records related to hospital readmissions

outside of the Ohio State University will be requested if indicated based on the follow-up research call.

All participants will be asked to complete two surveys postpartum to assess their experience during labor, delivery, and postpartum. The first survey incorporates the Childbirth Perception Scale, which is a 12-item instrument developed to assess a patient's perception of the labor and birthing experience as well as the first few days postpartum.[35] In a recent systematic review of patient satisfaction instruments, the Childbirth Perception Scale was found to have high validity and reliability.[36] Additionally, our survey incorporates an assessment of pain during labor (worse pain and overall pain) using a visual analog scale as described by Ludington et al.[37] The second survey of Labor Agentry is designed to assess expectants and experiences of control in labor.[38] Research staff will meet with study participants after they have been transferred to the postpartum unit and before hospital discharge to complete the surveys.

4.4.1 Emergency unblinding

Rare clinical circumstances may arise in which unblinding is necessary. The only indication for breaking the randomization code is a life-threatening medical emergency, as in the case of a serious adverse event. Unmasking the study drug assignment is limited to patients in which it is medically necessary in order to know how to treat the patient for their serious adverse event in a way not foreseen in this trial. In this circumstance, the study pharmacist will provide the necessary information about the concentration of the study drug to the participant's obstetric care team.

4.5 Study Outcomes Measures and Ascertainment

4.5.1 Primary Outcome

The primary outcome is cesarean delivery.

4.5.2 Secondary outcomes

1. Indication for cesarean including arrest of dilation, arrest of descent, non-reassuring fetal heart rate, other
2. Time from start of induction to delivery
3. Duration of first stage of labor
4. Duration of second stage of labor
5. Occurrence of tachysystole, defined as more than 5 contractions in 10 minutes averaged over 30 minutes[39]
6. Occurrence of tachysystole with category 2 or 3 fetal heart rate tracing
7. Uterine rupture defined as a complete disruption of all uterine layers including serosa
8. Clinical chorioamnionitis

9. Postpartum maternal infectious morbidity: endomyometritis, puerperal sepsis, surgical site infection within 6 weeks following delivery
10. Maternal death within 6 weeks of delivery
11. Postpartum hemorrhage defined as >1000 mL of blood loss within 24 hours of delivery[40]
12. Maternal blood transfusion defined as need for blood transfusion from randomization through hospital discharge
13. Maternal ICU admission from randomization through discharge
14. Composite neonatal morbidity outcomes: Apgar score <5 at 5 min, arterial cord pH <7.0 or base deficit >12 mmol/dL, perinatal death
15. NICU admission
16. Maternal length of stay
17. Neonatal length of stay
18. Perception of the labor, birth, and postpartum experience

5. DATA SAFETY AND MONITORING

5.1 Data Safety

For this pilot study, patient safety will be monitored closely by the primary investigator and research team. The primary investigator will be responsible for monitoring study data for signs of adverse trends in maternal and neonatal outcomes throughout the duration of the pilot study.

5.2 Definition of Adverse Events

An adverse event (AE) will be defined as any untoward or unfavorable medical occurrence in a study participant, whether or not considered related to the subject's participation in the research. All serious SAEs will be reported to the Ohio State University Office of Responsible Research Practices. Likelihood of relatedness of each AE to study intervention will be determined by the primary investigator upon review of the event.

<u>Maternal Severe Adverse Events:</u>

- Hyponatremia, defined as serum sodium level <135 mEq/L
- Pulmonary edema
- Maternal ICU admission during delivery hospitalization or up to 6 weeks postpartum
- Hospitalization >168 hours (7 days) after delivery
- Readmission to the hospital within 6 weeks after delivery

- Hysterectomy or uterine artery embolization
- Death

Infant Severe Adverse Events:

- Infant hospitalization >96 hours (4 days) after birth
- Readmission to the hospital within 6 weeks after birth
- NICU admission
- Administration of whole body hypothermia
- Death

6. STATISTICAL CONSIDERATIONS

6.1 Data Relevant to the Primary Outcome

Using institutional data collected for a retrospective study evaluating the relationship between BMI and labor management, we estimated that the cesarean delivery rate among nulliparous obese women who labored was 31.6%. This is a similar rate to what has been reported in the literature.[8] The cesarean delivery rate is even higher for those who undergo induction of labor, but will use this as a conservative baseline estimate. Current standard oxytocin dosing at the Ohio State University Wexner Medical Center uses the low-dose regimen.

6.2 Sample Size

This is a pilot study that will be used to inform the design of a future large randomized controlled trial. We plan to enroll 20 participants today. Ten participants will be randomized to the high-dose and 10 participants randomized to the low-dose oxytocin dosing regimen.

6.3 Feasibility

Based on internal institutional quality metric data, there were approximately 250 nulliparous women with prepregnancy BMI ≥30 kg/m^2 who underwent induction of labor at the Ohio State University Wexner Medical Center in 2020. If 40% of obese women undergoing induction meet other eligibility criteria and agree to participate in the study,

then we would anticipate complete the pilot study with a total sample size of 20 women in 10 weeks.

Information about the proportion of eligible women who agree to participant in the study will be used to determine the feasibility of a larger clinical trial.

6.4 Analysis Plan

All analyses will be performed based on the intent-to-treat principle. The primary outcome will be assessed by comparing the proportion of women delivered by cesarean in each of the treatment groups. Relative risks with 95% confidence intervals will be calculated. Similarly, secondary outcomes will be assessed using the chi-square and Fisher's exact tests for categorical variables. Continuous variables will be assessed for normality and compared using a Student's t-test or Mann Whitney U test as appropriate.

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