TITLE: Oxytocin Rest to Reduce Cesarean Delivery in Prolonged Labor: An Open-Label Randomized Controlled Trial (the "ORCA" trial)

PRINCIPAL INVESTIGATOR: Teresa C. Logue, MD MPH

SUB-INVESTIGATORS:
Matthew K. Hoffman, MD MPH; Lindsay Gugerty, DO; Sneha Paranandi, MD; Anne Reed-Weston, MD; Lauren Roby, MD; Amanda Jones MD; Cassidy O'Sullivan, MD; Alexandra Mulliken, MD; Bethany Dus, MD; Nakia Wighton, MD; R. Zach Fender, MD; Samantha Barta, DO; Savanah Richter, MD; Anthony Sciscione, DO

BACKGROUND:

Nearly 1 in 3 births in the United States occur by cesarean.[1] This is a rate substantially higher than other high-income countries.[2] Because cesarean is associated with greater risk for maternal morbidity and mortality, there has been increasing attention to reducing medically unnecessary cesarean deliveries in the United States – particularly in nulliparous, term, singleton, vertex pregnancies.[3] Labor dystocia is one of the most common indications for cesarean delivery among those at low risk for cesarean and has been a focus of national efforts to reduce the cesarean rate.[3-5]

The standard of care for prolonged labor is active management with continuous oxytocin infusion and amniotomy, with the goal of improving uterine contraction efficacy.[6] However, a small subset of women will develop protracted labor that persists even after these interventions. About half of these patients will ultimately deliver by cesarean.[3,7,8] Few interventions have been proposed to improve labor progress and prevent cesarean in this group. Recent studies have shown no evidence of benefit to propranolol as an adjunctive agent for prolonged labor.[7,9]

Oxytocin "rest" or washout has been described in the literature as an alternative strategy to resolve protracted labor in patients who have received prolonged oxytocin stimulation. This strategy involves discontinuing oxytocin then restarting infusion after a period of time – typically 30 to 60 minutes, though no ideal time has been established – under the theory that this will re-sensitize the oxytocin receptor and improve myometrial contractility.[10,11] There is limited *in vitro* evidence that prolonged exposure to synthetic oxytocin can result in down-regulation or desensitization of the oxytocin receptor[12] but the clinical utility of oxytocin washout has not been demonstrated. One single-institution retrospective cohort study did find an association between oxytocin rest of >8 hours and decreased risk for cesarean,[10] though this interval may not be practical following amniotomy due to increased infection risk associated with prolonged rupture of membranes.[13]

There is no randomized or prospective data to support oxytocin rest. A PubMed search using several terms ("oxytocin rest," "oxytocin break," "oxytocin washout," "oxytocin" AND "discontinue," "oxytocin" AND "stop") indicates that no randomized controlled trial has previously been published on this topic.

The purpose of this study is to assess whether oxytocin rest of 60 minutes in patients with prolonged labor reduces risk for cesarean delivery.

STUDY OBJECTIVES:

Primary Outcome:

The primary outcome is cesarean delivery.

Secondary Outcomes:

- Measures of length of labor:
  - Time to delivery (hours), defined as time from enrollment to delivery time, regardless of mode of delivery
  - Time to vaginal delivery (hours), defined as time from enrollment to delivery time, for patients with vaginal delivery (cesarean delivery censored)
  - Time to active labor (hours), defined as time from enrollment to first exam with cervical dilation ≥6cm (cesarean delivery at <6cm dilation censored)
  - Duration of active labor (hours), defined as time from first exam with cervical dilation ≥6cm to delivery time (cesarean delivery censored)
- Composite maternal adverse outcomes (CAMO):
  - Operative vaginal delivery (OVD)
  - Obstetric anal sphincter injury (OASIS)
  - Postpartum wound complications

        - Wound cellulitis requiring antibiotics
        - Wound reopened for fluid collection or infection
        - Wound dehiscence during delivery hospitalization
    - Incidence of intraamniotic infection (IAI), determined via chart abstraction as:
        - (1) maternal temperature ≥ 38.0°C in the intrapartum period AND
        - (2) initiation of antibiotics in the intrapartum period
    - Incidence of postpartum endometritis, determined via chart abstraction as:
        - (1) maternal temperature ≥ 38.0°C in the postpartum period AND
        - (2) initiation of antibiotics in the postpartum period
    - Incidence of postpartum hemorrhage, determined via chart abstraction as:
        - Quantitative blood loss ≥ 1000 mL (preferred) OR
        - Estimated blood loss ≥ 1000 mL
    - Deep vein thrombosis (DVT)/pulmonary embolism (PE)
    - ICU admission
    - Maternal death
- Composite neonatal adverse outcomes (CANO):
    - Neonatal intensive care unit (NICU) admission ≥48 hours
    - APGAR score at 5 minutes <7
    - Cord pH <7.00
    - Severe respiratory distress (defined as intubation and mechanical ventilation for a minimum of 12 hours)
    - Culture proven-presumed neonatal sepsis
    - Hypoxic ischemic encephalopathy
    - Stillbirth or neonatal death
- Measures of patient autonomy and sense of control:
    - Labor Agentry Scale (LAS) score. The LAS is a validated tool that captures patient perception of control over the labor process.[14,15] It will be administered to all enrolled patients between 6 and 96 hours after delivery.

Maternal Demographic and Clinical Characteristics:

- Age
- Race/ethnicity
- Gestational age
- Parity
- Maternal medical comorbidities
- BMI at delivery
- Cigarette use during pregnancy
- Substance use during pregnancy
- Insurance status

Additional Clinical Measures (including Process Measures):

- Induction of labor versus spontaneous labor
- Agents used for induction of labor
- Duration of continuous oxytocin infusion
- Maximum oxytocin dose achieved during induction or augmentation
- Use of intrapartum interventions after randomization
    - Interventions associated with management of nonreassuring fetal heart tracing:
        - Amnioinfusion
        - Fetal scalp electrode/intrauterine pressure catheter
        - Terbutaline
        - Fetal bradycardia alert
    - Interventions associated with management of abnormal labor progress in the active stage:
        - Intrauterine pressure catheter
- Indication for cesarean delivery (if performed), determined via chart abstraction and grouped into the following standard categories:

    - Labor dystocia (failed induction, arrest of dilation, arrest of descent)
    - Non-reassuring fetal status
    - Cephalopelvic disproportion
    - Fetal malpresentation
    - Other
- Intrapartum analgesia (epidural) use before randomization
- Estimated blood loss (EBL) at delivery
- Quantitative blood loss (QBL) at delivery
- Use of interventions associated with management of postpartum hemorrhage:
    - Uterotonics
        - Methergine
        - Hemabate
        - Cytotec
    - Tranexamic acid
    - JADA device
    - Other (Bakri balloon, uterine embolization, B-Lynch sutures, etc.)
- Receipt of blood transfusion during delivery hospitalization
- Receipt of antibiotic medications commonly used for IAI or postpartum endometritis, either intrapartum or postpartum:
    - Tobramycin/gentamycin, piperacillin-tazobactam, ampicillin/gentamicin, cefazolin/gentamicin, clindamycin, clindamycin/gentamicin, vancomycin/gentamicin, ampicillin-sulbactam, cefotetan, cefoxitin, ertapenem, etc.
- Maternal length of stay (days), defined as length of time from admission to discharge postpartum

Additional Demographic Characteristics:

- CDC ATSDR Social Vulnerability Index score (if available)

CHARACTERISTICS OF STUDY POPULATION:

Target Population:

18 to 55-year-old women with singleton pregnancies at ≥36 weeks gestation.

Inclusion Criteria:

- ≥18 years of age
- Singleton gestation in vertex presentation
- ≥36 weeks gestation as determined by routine obstetrical guidelines
- Prolonged latent labor, defined as cervical dilation <6cm after ≥8 hours since rupture of membranes and on continuous oxytocin[7]
    - We will include both patients undergoing induction of labor and patients undergoing augmentation of spontaneous labor
- No contraindication to continuous oxytocin infusion at time of randomization
- Cesarean section not anticipated at the time of randomization
- ≤18 hours between rupture of membranes and randomization

Exclusion Criteria:

- <36 weeks gestation
- Multifetal gestation
- Fetal demise
- Any contraindication to vaginal delivery
- Maternal eclampsia
- Any contraindication to continuous oxytocin infusion at time of randomization
    - We will exclude patients with nonreassuring fetal heart rate tracing for whom discontinuation of oxytocin infusion is indicated for fetal resuscitation at time of randomization
- Cesarean section anticipated by the clinical team

    - We will exclude patients for whom cesarean section is anticipated for nonreassuring fetal heart rate tracing or any other indication (excepting labor dystocia) at time of randomization
- Prolonged rupture of membranes, defined as >18 hours between rupture of membranes and randomization
- Intraamniotic infection (IAI), defined as:
    - (1) maternal temperature ≥ 38.0°C in the intrapartum period AND
    - (2) initiation of antibiotics in the intrapartum period

RESEARCH STUDY DESIGN:

Design:

This study is a prospective, open-label, randomized-controlled trial. We are tentatively planning for the trial to take place at three institutions. Our primary site will be ChristianaCare Health System.

Project Duration:

Two years

Intervention:

Our intervention will be discontinuing continuous oxytocin for 60-minute period and then restarting infusion at 2 mU/min. The best estimate for the half-life of intravenous oxytocin is 3-6 minutes.[12] If oxytocin infusion is started at 2 mU/min and increased by 2 mU/min every 30 minutes (contraction pattern allowing), we anticipate that many subjects will reach a relatively high dose (≥20 mU/min) by the time that they become eligible to participate in the study. We have selected 60 minutes for the duration of the rest period as a conservative estimate for the interval at which this concentration of the drug will be expected to have been cleared.

Power Calculations:

The target sample size is 350. We assume a baseline cesarean rate of 50% in patients who met criteria for prolonged labor, based on evidence reported in the literature.[7,10] We consider a 30% reduction in risk for cesarean delivery to be clinically meaningful. Assuming 80% power, equal group sizes, a two-sided p-value with alpha 0.05, and a 3% crossover rate, we estimate that we will require a total sample size of 350 (175 patients per group).

Randomization:

We will assign subjects to interventions with using blocked randomization via a computer-generated randomization scheme using a 1:1 allocation ratio. Because our trial will be unblinded, large block sizes will be used, and block sizes will be randomly varied to reduce the risk that the assignment schedule may be deciphered by recruiting clinicians.

Statistical Considerations:

Primary statistical analyses will be performed using an intention-to-treat principle. Baseline demographic and clinical characteristics will be reported for the study groups. For bivariate analyses, categorical variables will be compared using chi-squared or Fisher exact tests and continuous variables will be compared using a Wilcoxon signed-rank test. For estimates of the effect of the intervention on length of labor and time to delivery, Kaplan-Meier estimates will be performed, with censoring of cesarean deliveries. A p value of < 0.05 will be considered statistically significant.

Interim Analysis:

An independent statistician will perform an interim analysis of the first 175 patients enrolled in the study. The DSMB will use a group sequential method with the O'Brien-Fleming boundary as a stopping rule for benefit, and conditional power analysis as a stopping rule for futility. A full description of the interim analysis plan, including detailed description of these stopping rules, is included in Appendix A.

RESEARCH STUDY PROCEDURE:

All patients will be admitted to the labor and delivery unit and receive usual care by the clinical team, including confirmation of pregnancy dating and sonography to verify fetal presentation. If indicated by the clinical team, oxytocin infusion will be started at 2 mU/min for labor induction or augmentation. Infusion will be increased by 2 mU/min every 30 minutes to a maximum dose of 30 mU/min or until adequate contractions are noted, per labor and delivery protocol. In all patients receiving continuous oxytocin infusion, continuous fetal heart rate and uterine activity will be monitored per existing protocols.

Potential subjects will be identified through the electronic patient board on the CCHS Labor & Delivery Unit and screened for study eligibility by a member of the study team. At or before the time that they meet eligibility criteria, potential subjects will be approached on the labor and delivery unit by trained study personnel. They will be consented to participation. Written informed consent will be obtained. There will be no monetary incentives for study participation.

Subjects then will be randomized to either 60-minute oxytocin rest or routine care. Subjects in the intervention group will undergo 60-minute oxytocin rest. After 60 minutes, oxytocin will be restarted at 2 mU/min and subsequently increased by 2 mU/min every 30 minutes to a maximum dose of 30 mU/min or until adequate contractions are seen, per labor and delivery protocol. Subjects in the control group will receive continuous oxytocin infusion, increased by 2 mU/min every 30 minutes to a maximum dose of 30 mU/min or until adequate contractions are noted, per existing labor and delivery protocol.

Otherwise, subjects will be managed by the clinical team under existing labor and delivery protocols. If subjects in either group develop persistent abnormal fetal heart rate, standard maneuvers including change in maternal position, bolus fluids, amnioinfusion, subcutaneous terbutaline, and discontinuing or decreasing oxytocin infusion will be performed as directed by the clinical team. If these measures are unsuccessful, urgent or emergent cesarean delivery will be performed at the discretion of the clinical team. If patients in either group develop episodes of uterine tachysystole, defined as ≥5 contractions in 10 minutes averaged over 30 minutes, the oxytocin rate will be halved per labor and delivery protocol. If patients in either group develop an intrauterine infection, they will be treated with standard antibiotics.

All patients who are assessed for eligibility and all patients who are approached about study participation will be counted on a separate log. For patients who do not ultimately meet eligibility criteria and for patients who are approached but decline participation, minimal information on eligibility for the study will be included in this log. No outcome data will be collected on these patients.

ANTICIPATED RISKS AND BENEFITS:

Despite lack of evidence of clinical benefit, oxytocin rest is widely used as a strategy to resolve prolonged labor; and the intervention is broadly considered to be safe. The primary risk of oxytocin rest is further prolonging time to delivery following rupture of membranes. Theoretically, in patients requiring high doses of oxytocin to reach contractions with the strength and frequency to cause cervical change, the intervention may lengthen the time required for induction or augmentation. Prolonged labor following membrane rupture has been associated with increased risk for intraamniotic infection,[13] though current guidelines allow for up to 24 hours before infection risk is considered clinically significant.[3] We will exclude patients with >18 hours since membrane rupture prior to study participation.

The primary potential benefit of oxytocin rest is to reduce risk for cesarean delivery by improving uterine contraction efficacy. Prolonged oxytocin exposure has also been hypothesized to increase risk for postpartum hemorrhage due to atony from diminished myometrial contractility;[11] thus a secondary potential benefit of the intervention is to decrease hemorrhage risk. Finally, *with the permission of the clinical team*, the intervention will provide laboring patients with an opportunity to briefly break from continuous fetal monitoring to rest, shower, walk, or eat a light snack – all of which may also have therapeutic benefit and improve patient sense of control during childbirth.[10]

Safety:

A Data Safety Monitoring Board (DSMB) will be created to ensure patient safety. Members of the DSMB will include:

- Melanie Chichester, BSN, RNC-OB, CPLC, RNC-IAP, FAWHONN
- Casey Bedder, DO
- Ursula Guillen, MD

An independent statistician will perform an interim analysis using the methodology described above, which will then be submitted to the DSMB. The DSMB will review this interim analysis with the potential to halt study enrollment for early benefit or futility if the above prespecified stopping criteria are met. The DSMB will also have the ability to make recommendations to the investigators to modify the conduct of the study if any potential harms to

participants are identified based on their review of maternal and neonatal outcomes. A full description of the role and responsibilities of the DSMB is included in Appendix A.

Training:

Prior to the start of enrollment, all CCHS OB/GYN residents included as sub-investigators will receive training in the ethical conduct of human subjects' research through the Collaborative Institutional Training Initiative (CITI) program. These residents will then be trained the study protocol, recruitment and consent process, and randomization procedures and in use of HIPAA and CITI-compliant methods for entering patient enrollment and consent information. Nursing education will be provided regarding study procedures.

Confidentiality and Privacy:

Patient enrollment and consent information will be collected using paper forms, which will remain in a locked cabinet on the labor and delivery floor. Patient demographic, clinical and outcome information will then be entered and stored into REDCAP – a secure, HIPAA-compliant application for data capture in research.

References

1. Osterman MJK HB, Martin JA, et al Births: Final Data for 2021. *Natl Vital Stat Rep.* 2023;72(1):1-53.
2. Boerma T, Ronsmans C, Melesse DY, et al. Global epidemiology of use of and disparities in caesarean sections. *Lancet.* 2018;392(10155):1341-1348.
3. American College of O, Gynecologists, Society for Maternal-Fetal M, et al. Safe prevention of the primary cesarean delivery. *Am J Obstet Gynecol.* 2014;210(3):179-193.
4. Barber EL, Lundsberg LS, Belanger K, Pettker CM, Funai EF, Illuzzi JL. Indications contributing to the increasing cesarean delivery rate. *Obstet Gynecol.* 2011;118(1):29-38.
5. Frappaolo AM, Logue TC, Goffman D, et al. Cesarean Delivery Trends Among Patients at Low Risk for Cesarean Delivery in the US, 2000-2019. *JAMA Netw Open.* 2023;6(3):e235428.
6. Grobman WA, Bailit J, Lai Y, et al. Defining failed induction of labor. *Am J Obstet Gynecol.* 2018;218(1):122 e121-122 e128.
7. McCoy JA, Walheim L, McCabe MG, Levine LD. Efficacy of Propranolol to Reduce Cesarean Delivery in Prolonged Labor: A Randomized Controlled Trial. *Obstet Gynecol.* 2023;142(1):71-79.
8. Rouse DJ, Weiner SJ, Bloom SL, et al. Failed labor induction: toward an objective diagnosis. *Obstet Gynecol.* 2011;117(2 Pt 1):267-272.
9. Gomez Slagle HB, Fonge YN, Myers EL, Hoffman M, Sciscione AC. A Randomized Controlled Trial of Propranolol in Nulliparous Patients with Prolonged Labor: The PRO-LABOR Trial. *American Journal of Obstetrics and Gynecology.* 2023;228(1):S138-S139.
10. McAdow M, Xu X, Lipkind H, Reddy UM, Illuzzi JL. Association of Oxytocin Rest During Labor Induction of Nulliparous Women With Mode of Delivery. *Obstet Gynecol.* 2020;135(3):569-575.
11. Cochrane E, Huber A, Jou C, Chappelle J. The effect of an oxytocin washout period on blood loss at cesarean delivery. *J Perinat Med.* 2020;48(8):799-802.
12. Uvnäs-Moberg K. The physiology and pharmacology of oxytocin in labor and in the peripartum period. *American Journal of Obstetrics and Gynecology.* 2023.

13. Soper DE, Mayhall CG, Dalton HP. Risk factors for intraamniotic infection: a prospective epidemiologic study. *Am J Obstet Gynecol.* 1989;161(3):562-566; discussion 566-568.
14. Hodnett ED, Simmons-Tropea DA. The Labour Agentry Scale: psychometric properties of an instrument measuring control during childbirth. *Res Nurs Health.* 1987;10(5):301-310.
15. Dude A, Fette LM, Reddy UM, et al. Maternal Sense of Control During Childbirth and Infant Feeding Method. *Obstet Gynecol.* 2020;135(3):583-590.