Title: Low-Dose versus High-Dose Oxytocin Dosing for Induction and Augmentation of Labor: A Randomized Control Trial
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Faculty Supervisor: Luis Pacheco, MD
Funding: Departmental
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1. Introduction and Purpose:

There is a nationwide trend of increasing elective induction of labor (IOL). The national rate of induction of labor in 2020 was 31.4%(1) vs. 27.1% in 2013(2). This trend can only be expected to increase further with the implementation of elective 39-week gestation IOL for maternal and neonatal benefits(3) and maternal medical comorbidities. Elective induction of labor is known to take longer than spontaneous labor(3, 4). Additionally, with any labor (induced or spontaneous), the possibility of failure to progress exists. Currently, the leading cause of primary cesarean delivery (CD) is labor dystocia(5, 6), and cesarean deliveries are associated with worse maternal and neonatal outcomes(7). Therefore, it is vital to research safe but effective methods for induction and augmentation of labor. The optimal regimen would result in the highest percentage of vaginal deliveries within the shortest period, with the lowest maternal and neonatal adverse outcomes. Low-dose and high-dose oxytocin protocols for labor have been endorsed by the American College of Obstetricians and Gynecologists (ACOG)(8). Currently, both regimens are considered standard of care at our institution and are being used during induction and augmentation of labor (AOL). Our hypothesis is that high-dose oxytocin results in a shorter time to vaginal delivery compared to low-dose regimen. The goal of this study is to examine the time from initiation of oxytocin titration to delivery in nulliparous individuals undergoing either induction or augmentation of labor.

2. Background:

ACOG has endorsed low-dose and high-dose oxytocin protocols for labor (8). However, no consensus has been reached regarding optimal oxytocin dosing. Previous research has suggested that high-dose oxytocin protocols may decrease total labor duration without an increase in cesarean delivery rates (5, 9-11). The leading concern regarding high-dose protocols revolves around uterine tachysystole, its hypothetical effect on fetal well-being, and a possible increase in cesarean delivery rates for fetal distress.

Different oxytocin dosing protocols have been studied in induction and AOL. One recent study studying the effect of oxytocin dosing in the augmentation of labor at one institution in the United States showed a reduction of primary cesarean delivery with high-dose oxytocin without an increase in obstetric or neonatal morbidity(9). A similar Swedish study showed no significant change in cesarean delivery rates(10). In that study and a systematic review of oxytocin dosing protocols for AOL, while high-dose oxytocin did increase the incidence of uterine tachysystole, this did not translate to an increase in CD for fetal distress (5, 10). Similar outcomes were seen for the induction of labor. An Australian study showed no change in cesarean or operative vaginal delivery (OVD) with different oxytocin dosing(11). A Cochrane review, including 9 studies, showed no significant difference in the mode of delivery, severe maternal morbidity, and

uterine hyperstimulation resulting in fetal distress with different oxytocin dosing(12). A significant limitation of these studies, however, includes patient homogeneity. While there is more research regarding optimal dosing for AOL, such information is sparse for labor induction.

Currently, at our institution, there is a similar lack of data regarding optimal oxytocin dosing. A change to our standard of care for oxytocin administration for augmentation of labor was introduced at the beginning of 2022, based on data from a randomized control trial performed at another institution (9). Under this new protocol, patients who meet criteria are eligible for either low-dose or high-dose oxytocin. The decision on which protocol to use is based mostly on provider preference while both dosing protocols are considered standard of care. While the safety of high-dose oxytocin has been previously established (5, 9-12), familiarity with low-dose oxytocin leads most providers to choose the low-dose protocol even when patients qualify for high-dose oxytocin. Thus, this study is crucial to further demonstrate the efficacy of high-dose oxytocin in our patient population and provide evidence to guide providers' decision-making regarding oxytocin dosing.

3. Concise Summary of Project:

This will be a randomized control clinical trial. The study period will be between January 1st, 2023 and January 1st, 2025. The number of subjects studied will be 170 patients at UTMB. The target population for our study is women who present for IOL or AOL at term. If the obstetric team decides that oxytocin infusion is required for labor in a subject meeting the inclusion criteria for the study, the subject will be consented and randomized to either the High Pit group (high-dose oxytocin) or the Low Pit group (low-dose oxytocin). Every subject who is enrolled in the study will meet the inclusion and exclusion criteria for both low- and high-dose oxytocin protocols (refer to inclusion criteria for this protocol). A subject meeting criterion for high-dose oxytocin will not preclude her from receiving low-dose oxytocin, and vice versa. Both study groups will otherwise receive the standardized labor management as currently performed at UTMB. The subjects will receive the same care and expertise as any other patient treated in our unit. Decisions regarding intrapartum management outside of oxytocin dosages will be left to the discretion of the obstetric provider. The trial will be considered completed whenever the target sample size number is reached. If we need more than the anticipated subjects to be enrolled, the trial will be paused, and a protocol addendum will be submitted to the IRB.

The **Low Pit group** will receive an infusion to start at 2 milli-units/min and will be increased by 2 milli-units/min every 20 minutes. The maximum rate of infusion is 40 milli-units/min.

The **High Pit group** will receive an infusion to start at 6 milli-units/min and will be increased by 6 milli-units/min every 20 minutes. Maximum rate of infusion is 40 milli-units/min.

Subjects in both group assignments will otherwise receive standard intrapartum care. The total participation time in the study will be considered terminated following delivery. Details for the procedure for the control group and study group can be found below. Both groups will be receiving the standard of care for IOL and AOL as both dosing protocols are currently being used at our institution.

4. Study Procedures:

Visit #1

4.1 Recruitment, Screening, and Consenting:

Under the direction of the PI, trained research staff will be available on the labor and delivery unit to screen and consent eligible subjects according to study protocol. We will review records of all nulliparous pregnant patients admitted to L&D for IOL or AOL at term who have had a decision made by their managing obstetric team to start an oxytocin infusion for induction or augmentation of labor who meet the inclusion and exclusion criteria below. Subjects will be enrolled before oxytocin infusion is ordered but after a decision has been made that oxytocin infusion is necessary. Subjects will be recruited, enrolled, and consented in a private room on labor and delivery or triage units to respect the privacy of potential subjects.

Subjects will be given all the time needed to fully read and understand the consent forms. All efforts will be made by the research staff to answer all questions the subject has and to ascertain that the subjects have the right to refuse to participate in the study. Subjects will be reassured that participation in the study is voluntary and will not interfere with the diagnosis or treatment of her condition. Non-English-speaking subjects are anticipated to be part of the study population and informed consent will be provided in their primary language. For non-English-speaking subjects, a certified interpreter will review the consent with them. Additionally, the consent form will be translated and provided in Spanish after initial IRB approval. A screening log will be used to track all subjects approached for the study using the Oncore system.

4.2 Operationalization

Randomization:
A confidential computer-generated simple randomization scheme (using STATA 17, Dallas, TX) will be prepared. A randomization log with group assignment, subject name, and medical record number will be used to track the randomization process. Subjects will be randomized in a ratio of 1:1 for low-dose or high-dose oxytocin infusion using the prepared computer-generated randomization scheme. Due to the nature of this intervention, blinding will not be possible. The subject will be included in the analysis by intent-to-treat once the randomization assignment has been made. The trial will be considered completed whenever the final enrollment number is reached. If we need more than the anticipated 170 patients to be enrolled, the trial will be paused, and a protocol addendum will be submitted to the IRB.

Labor and Delivery Unit and Staff:
Several training sessions will occur to notify all staff of the trial and the protocol. The training sessions will include a copy of the protocol, which will also be included in a follow-up email communication. All operations will be reviewed with all staff. The PI will be available for questions. An Epic order will be placed by the provider specifying oxytocin dosing according to the randomization assignment using a prepopulated “Order Set”.

4.3 Administration of Oxytocin Infusion

The Low Pit group will receive a controlled infusion pump at a proximal port on the peripheral IV line. The infusion will start at 2 milli-units/min and will be increased by 2 milli-units/min every 20 minutes. Maximum rate of infusion is 40 milli-units/min. Oxytocin infusion rate is adjusted to maintain adequate uterine contractions.

The High Pit group will receive a controlled infusion pump at a proximal port on the peripheral IV line. The infusion will start at 6 milli-units/min and will be increased by 6 milli-units/min every 20 minutes. Maximum rate of infusion is 40 milli-units/min. Oxytocin infusion rate is adjusted to maintain adequate uterine contractions.

Additional information regarding management of the oxytocin infusion in both groups:

- Initiation of the oxytocin infusion will be performed by the managing nurse as is standard of care at UTMB.
- The oxytocin infusion may be continued at a lower rate or discontinued at the discretion of the managing obstetric team for the usual obstetric reasons (e.g., changes in fetal heart tracing indicative of fetal distress, uterine tachysystole, suspected oxytocin adverse effects, and patient request)
- Oxytocin dosing may be decreased for uterine tachysystole (defined as >5 contractions/10 min, averaged over 30 minutes(13)) according to our current standard of care guidelines below
    - Uterine tachysystole with category I FHTs
        - Reposition patient
        - Decrease oxytocin to ½ the current dose
        - If tachysystole persists 15 minutes after the interventions, discontinue oxytocin until contractions return to <5 contractions/10 minutes
    - Uterine tachysystole with category II or III FHTs
        - Decrease (category II) or discontinue (category III) oxytocin infusion
        - Reposition the patient
        - Give IV fluid bolus as ordered by the obstetric provider
        - Notify obstetric provider
        - Immediate evaluation for category III by obstetric provider
        - Consider amnioinfusion or tocolytics as ordered by the obstetric provider
- Oxytocin infusion may be restarted according to our current standard of care guidelines below
    - If oxytocin was off for <30 minutes – restart oxytocin at ½ the rate that cause the uterine tachysystole, then increase as ordered
    - If off for >30 minutes – restart at the initial protocol dose and increase as ordered
    - If obstetric provider can change the rate of increase as deemed clinically appropriate
- The study oxytocin infusion will be discontinued at time of delivery (regardless of mode of delivery) with transition to standard postpartum oxytocin dosing protocols as is standard of care.

Commented [SA1]: Make sure these are the protocols we use for each, confirm with Lisa Spencer on both

Commented [WAM2R1]: I pulled these directly off of the nursing Pitocin protocol

Visit #2

4.4 Additional Baseline Procedures

- Routine intrapartum care will be provided by the patient's managing obstetric team.
- A trained and experienced study team will be responsible for all research data abstraction.
- Maternal outcomes will be assessed following delivery.
- The PI and faculty sponsor will review and validate the diagnosis for all subjects identified to have the primary outcomes. If there is uncertainty, a faculty sponsor will review the chart, discuss with the study team, and make a final determination regarding the outcome.
- Data collection forms will be used during these processes and charts will be reviewed up to 30 days postpartum. We will collect demographic data, as well as data related to the patient's intrapartum course, delivery, immediate postpartum period while inpatient, and neonatal outcomes while inpatient.
- Subject's participation will end following delivery.

4.5 Study Visits/Follow-Up

No extra postpartum follow-up visits will be performed.

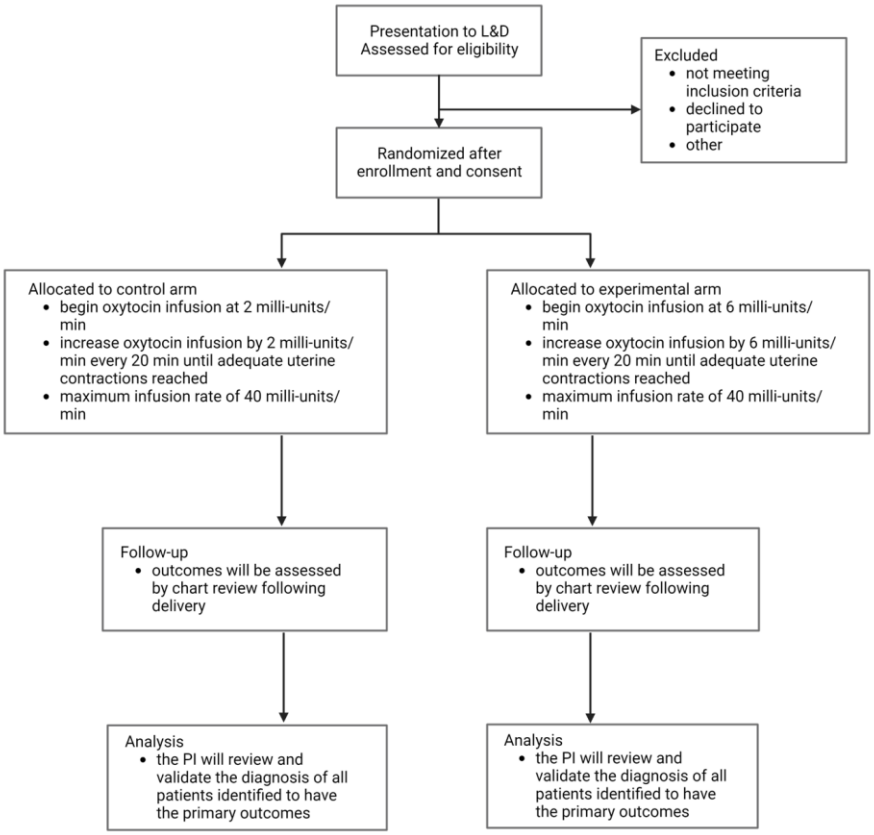
4.6 Withdrawals

Subjects who withdraw from the study will be excluded from further follow-up. Outcomes ascertained up until the time of withdrawal will be reported in intention-to-treat fashion. The patient will be withdrawn from the study if she wishes to discontinue participation. If any of the exclusion criteria listed above are met, or condition changes that leads to inclusion criteria not being met anymore, data collection will be terminated, and the patient will be withdrawn from the study.

4.7 Data Collection

The data collected will not be used for clinical diagnosis or treatment purposes. The data collected will be kept on a password secured UTMB computer. An encrypted USB flash drive will be used to transfer data. The data will be linked to the patient only by the patient's MRN number. This identifier will be needed to access and analyze demographic data. During analysis of the data, all identifiers will be deleted. Data will be collected from the patient's chart and the chart of the neonate. The data collected will include demographics and data needed to assess the primary and secondary outcomes listed below. The data collection sheet is uploaded for review by the IRB. It is imperative that studies involving induction and augmentation of labor and intrapartum care assess the outcomes of the neonate.

Study Summary Flow Diagram



4.8 Primary Outcome

- Length of induction to delivery interval

4.9 Secondary Outcomes

- Rate of primary cesarean delivery
- Mode of delivery (including operative vaginal delivery)
- Maximum dose of oxytocin infusion
- Uterine tachysystole without fetal heart rate (FHR) changes

- Uterine tachysystole with FHR changes
- Uterine tachysystole requiring cessation of oxytocin
- Incidence of postpartum hemorrhage
- Incidence of placental abruption
- Maternal side effects (including nausea/vomiting requiring antiemetics, diarrhea)
- Chorioamnionitis ("IAI" or "triple I")
    - A presumptive diagnosis can be made in women with:
        - Fever ≥39.0°C (102.2°F) one time or 38.0°C (100.4°F) to 38.9 (102.02°F) on two occasions 30 minutes apart, without another clear source, PLUS one of the following:
        - Baseline fetal heart rate >160 beats/min for ≥10 minutes, excluding accelerations, decelerations, and periods of marked variability
        - Maternal white cell count >15,000 mm^3 in the absence of corticosteroids and ideally showing a left shift (bandemia)
        - Purulent-appearing fluid coming from the cervical os visualized by speculum examination
    - A confirmed diagnosis of chorioamnionitis can be made in women with:
        - All the above plus one or more of the following objective laboratory findings:
            - Positive Gram stain of amniotic fluid
            - Low glucose level in amniotic fluid
            - Positive amniotic fluid culture
            - High white cell count in amniotic fluid in the absence of a blood tap
            - Histopathologic evidence of infection or inflammation or both in the placenta, fetal membranes, or umbilical cord vessels (funisitis)
- Endometritis: must meet the following criteria:
    - Infection occurs within 30 days after the operative procedure AND
    - Infection presumed to involve the uterus AND
    - Patient has at least one of the following:
        - Purulent drainage from a drain that is placed through a stab wound into the abdomen or pelvis
        - Organisms isolated from an aseptically obtained culture of fluid or tissue in the organ/space
        - An abscess or other evidence of infection involving the abdomen or pelvis that is found on direct examination, during re-operative, or by histopathologic examination
- Serious maternal morbidity or death (e.g., uterine rupture, admission to intensive care unit, septicemia)
- Neonatal infection, defined as culture proven sepsis, fever, or a suspicious clinical course that warranted treatment with antibiotics
- 5-minute APGAR score <7
- Umbilical artery acidemia (pH <7.0 or base excess >12 mmol/L)
- NICU admission rate

- Composite neonatal outcomes (one of more of the following: perinatal death, severe respiratory distress requiring ventilation, neonatal encephalopathy, neonatal seizure, neonatal sepsis, 5-minute APGAR score <7, umbilical artery acidemia, NICU admission)
- Perinatal death

5. Criteria for Inclusion of Subjects:
- Women aged 18-50 years old
- Singleton gestation
- Nulliparous
- Vertex presentation
- Gestational age ≥ 37 weeks
- No prior uterine surgery
- Presents for elective or medically indicated induction of labor
- Need for augmentation of labor with oxytocin

These inclusion criteria are a subset of the current inclusion criteria for low-dose and high-dose oxytocin use at our institution.

6. Criteria for Exclusion of Subjects:
- Previous cervical ripening using non-mechanical methods
- Patient unable or unwilling to provide verbal consent
- Contraindications to vaginal delivery
- Fetal demise or life-limiting anomaly
- Allergy to oxytocin
- Non-reassuring fetal heart tracing prior to inclusion
- Maternal pulmonary edema prior to inclusion
- Fetal growth restriction

7. Sources of Research Material:

Research material will be obtained from electronic medical records/charts.

8. Potential Risks:
No significant adverse effects are expected with the use of high-dose or low-dose oxytocin as both methods are the standard of care at UTMB. All enrolled subjects will meet the criteria for both low- and high-dose oxytocin protocols and will not be withheld standard of care as the result of randomization to either group. The most significant rare risks are described under section 8.3 below: uterine tachysystole, blood pressure changes, arrhythmias, and hyponatremia. The patient will undergo inpatient IOL or AOL, so any adverse reaction would be promptly detected and addressed.

8.1 Randomization risk
There are no foreseen randomization risks as both the study and control group are currently utilized for induction of labor at UTMB.

8.2 Loss of Confidentiality

There is a potential risk of loss of confidentiality any time information is collected. Every effort will be made to keep patient information confidential; however, this cannot be guaranteed.

8.3 Oxytocin infusion

Oxytocin is a naturally present hormone produced by the hypothalamus and released from the posterior lobe of the pituitary gland. It is one the most widely used medications during labor and delivery(14). The half-life of oxytocin ranges from 3-10 minutes(15). Reported maternal side effects include blood pressure changes, arrhythmias, and hyponatremia, however blood pressure changes and arrhythmias have only been noted in case reports(14). Theoretically, higher doses of oxytocin may increase the risk of uterine hyperstimulation(16, 17), with potential increases in fetal distress which may result in cessation of oxytocin administration or higher cesarean delivery rates(18). Increased exposure to oxytocin has also been associated postpartum hemorrhage presumably due to downregulation of uterine oxytocin receptors(17).

Previous studies investigating low- and high-dose oxytocin infusion protocols for induction and augmentation of labor have not shown any increases in maternal or neonatal morbidity with high-dose regimens, including postpartum hemorrhage or drug adverse effects(9-11, 19). Similarly, studies have failed to show an increase in operative vaginal delivery or cesarean delivery with high-dose oxytocin protocols(9, 11). While there is a theoretical increased risk for uterine tachysystole with increased oxytocin exposure, this has not been shown to increase the rate of CD(10, 12). There is inconsistent evidence for the association between high-dose oxytocin and operative vaginal delivery for fetal distress(10, 11). While increments of dosing increases will be different between both arms, the maximum rate of oxytocin infusion will be the same, reducing the risk of overexposure to oxytocin. Continuous fetal monitoring with cardiotocography will be used throughout oxytocin infusion as is standard at UTMB to monitor fetal status and contraction patterns.

9. Subject Safety and Data Monitoring:

The PI and research collaborators will be responsible for monitoring the safety of this study. A yearly report will include participant demographics, expected versus actual recruitment rates, summary of any quality assurance or regulatory issues, and any changes in the protocol because of these issues.

The PIs and collaborators will ensure all aspects of data quality, including monitoring for adherence to consent procedures, inclusion and exclusion criteria, valid abstraction, correct entry, timeliness, and responsiveness to data queries. The team will be meeting every quarter to review procedures and resolve any issues that need to be addressed. A final report will be submitted yearly with every continuation review IRB application.

The data will be collected and stored with the participant deidentified ID code only. The master enrollment log linking patient identifiers with study ID numbers will be kept in a password-protected database on the OB/GYN department's internal server separate from the data, we will be using the Oncore platform as well. Data collection forms will be used. Data on these forms

devoid of personal identifiers will be securely stored at our perinatal research division. The principal investigator or approved research staff will be available to monitor the data and correct any discrepancies based on source documents if needed.

10: Procedures to Maintain Confidentiality:

- The data collected will be indirectly linked to the subject by the patient's medical record number.
- When the subject accepts to participate in the study, a number will be attributed to the patient, and this number will be entered on the data collection sheet.
- The data collected will be transferred to the PI's password-secured UTMB computer, that is stored in a locked room using an USB flash drive
- The study PI will be the only person to have a list with the number designated to each subject and the corresponding patient's MRN number. This list will be kept in a locked cabinet of the PI's locked UTMB office. This identifier is needed to access and analyze demographic data. During the analysis of the data, all identifiers will be deleted.
- Data will not be disclosed to outside persons or entities.

11: Potential Benefits:

It is important to determine the optimal method for IOL and AOL, with the goal of the highest percentage of vaginal deliveries within the shortest period, with the lowest maternal and neonatal adverse outcomes. The optimal regimen would have the lowest exposure to all labor interventions. While low-dose oxytocin protocols may result in less uterine tachysystole and resulting fetal distress, studies have shown an increased length of labor, with associated increased rates of chorioamnionitis, fetal infection, and postpartum hemorrhage(11). Low-dose oxytocin protocols have also been associated with an increase in OVD for labor dystocia(10).

On the other hand, high-dose oxytocin has been associated with a shorter length of labor(5, 9, 10, 19) without an increase in cesarean delivery rates(5, 9, 11). It is also associated with lower incidences of postpartum hemorrhage and chorioamnionitis(9, 11). Though data is currently mixed, high-dose oxytocin protocols may be associated with decreased CD for labor dystocia(5), which would spare women from a major abdominal surgery. A shorter total labor duration would translate to a shorter overall hospital admission, ultimately decreasing overall utilization resources. This could then decrease medical costs for labor and delivery and optimize use of hospital staffing and resources. Thus, it is of benefit both patients and providers to further investigate the optimal methods for induction and augmentation of labor with oxytocin infusions based on evidence rather than physician preference.

13. Statistical analysis/Sample size:

Analysis will be performed by intention-to-treat. Univariable and multivariable analysis will be used to describe the population in the study and to identify potential confounding variables. For this analysis, normality will be tested using Shapiro-Wilk method. Demographics and descriptive statistics will be used to provide a profile of the study sample. Data will be either shown as median +/- IQR or mean +/- SDEV. Bivariate tests such as t test, Pearson's chi square, and

Mann-Whitney tests will be used as indicated to identify any key differences in the profiles of subjects across study conditions. Statistical analyses of primary and secondary outcomes between study groups will be performed by multilevel regression analysis accounting for both confounding variables as well as adjusting for any potential intra class correlation that may arise from the study design.

Sample size calculations
Sample size was calculated based on the determination of superiority. The primary outcome is time in minutes from oxytocin initiation to delivery. For the sample size calculation, based on our prior unpublished data, the primary outcome in the low PIT arm would be 858.6 ± 494.9 mins. Using a difference rate of 25% (High Pit group: 643.9 mins), power of 80% and 2-sided alpha of 0.05,. Final sample size: 170 (85/group). This difference between both methods is clinically significant.
Detailed:
power twomeans 858.6 644, sd(494.9) power(0.8)

Performing iteration ...

Estimated sample sizes for a two-sample means
test
t test assuming sd1 = sd2 = sd
H0: m2 = m1 versus Ha: m2 != m1

Study parameters:

alpha = 0.0500
power = 0.8000
delta = -214.6000
m1 = 858.6000
m2 = 644.0000
sd = 494.9000

Estimated sample sizes:

N = 170
N per group = 85

This trial will be registered with Clinical Trials Register (Clinicaltrials.gov) before recruitment is initiated and after IRB approval.

References

1. Osterman M, Hamilton B, Martin JA, Driscoll AK, Valenzuela CP. Births: Final Data for 2020. Natl Vital Stat Rep. 2021;70(17):1-50. PubMed PMID: 35157571.
2. Hamilton BE, Martin JA, Osterman MJ, Curtin SC, Matthews TJ. Births: Final Data for 2014. Natl Vital Stat Rep. 2015;64(12):1-64. PubMed PMID: 26727629.
3. Harper LM, Caughey AB, Odibo AO, Roehl KA, Zhao Q, Cahill AG. Normal progress of induced labor. Obstet Gynecol. 2012;119(6):1113-8. doi: 10.1097/AOG.0b013e318253d7aa. PubMed PMID: 22569121.
4. Vahratian A, Zhang J, Troendle JF, Sciscione AC, Hoffman MK. Labor progression and risk of cesarean delivery in electively induced nulliparas. Obstet Gynecol. 2005;105(4):698-704. doi: 10.1097/01.AOG.0000157436.68847.3b. PubMed PMID: 15802393.
5. 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;203(4):296-304. Epub 20100508. doi: 10.1016/j.ajog.2010.03.007. PubMed PMID: 20451894.
6. Obstetric care consensus no. 1: safe prevention of the primary cesarean delivery. Obstet Gynecol. 2014;123(3):693-711. doi: 10.1097/01.AOG.0000444441.04111.1d. PubMed PMID: 24553167.
7. Gregory KD, Jackson S, Korst L, Fridman M. Cesarean versus vaginal delivery: whose risks? Whose benefits? Am J Perinatol. 2012;29(1):7-18. Epub 20110810. doi: 10.1055/s-0031-1285829. PubMed PMID: 21833896.
8. ACOG Practice Bulletin No. 107: Induction of labor. Obstet Gynecol. 2009;114(2 Pt 1):386-97. doi: 10.1097/AOG.0b013e3181b48ef5. PubMed PMID: 19623003.
9. Son M, Roy A, Stetson BT, Grady NT, Vanecko MC, Bond N, et al. High-Dose Compared With Standard-Dose Oxytocin Regimens to Augment Labor in Nulliparous Women: A Randomized Controlled Trial. Obstet Gynecol. 2021;137(6):991-8. doi: 10.1097/AOG.0000000000004399. PubMed PMID: 33957657.
10. Selin L, Wennerholm UB, Jonsson M, Dencker A, Wallin G, Wiberg-Itzel E, et al. High-dose versus low-dose of oxytocin for labour augmentation: a randomised controlled trial. Women Birth. 2019;32(4):356-63. Epub 20181016. doi: 10.1016/j.wombi.2018.09.002. PubMed PMID: 30341003.
11. Prichard N, Lindquist A, Hiscock R, Ruff S, Tong S, Brownfoot FC. High-dose compared with low-dose oxytocin for induction of labour of nulliparous women at term. J Matern Fetal Neonatal Med. 2019;32(3):362-8. Epub 20170926. doi: 10.1080/14767058.2017.1378338. PubMed PMID: 28889775.
12. Budden A, Chen LJ, Henry A. High-dose versus low-dose oxytocin infusion regimens for induction of labour at term. Cochrane Database Syst Rev. 2014(10):CD009701. Epub 20141009. doi: 10.1002/14651858.CD009701.pub2. PubMed PMID: 25300173; PubMed Central PMCID: PMC8932234.
13. ACOG Practice Bulletin No. 106: Intrapartum fetal heart rate monitoring: nomenclature, interpretation, and general management principles. Obstet Gynecol. 2009;114(1):192-202. doi: 10.1097/AOG.0b013e3181aef106. PubMed PMID: 19546798.

14. 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(6):622.e1-7. Epub 20080320. doi: 10.1016/j.ajog.2008.01.039. PubMed PMID: 18355786.
15. Bruton L, Lazo J, Parker K. Pituitary hormones and their hypothalamic releasing hormones. In: Brunton L, editor. Goodman and Gilman: The pharmacologic basis of therapeutics. 13 ed. New York: McGraw-Hill; 2006.
16. Orhue AA. A randomized trial of 30-min and 15-min oxytocin infusion regimen for induction of labor at term in women of low parity. Int J Gynaecol Obstet. 1993;40(3):219-25. doi: 10.1016/0020-7292(93)90834-j. PubMed PMID: 8096473.
17. Tribe RM, Crawshaw SE, Seed P, Shennan AH, Baker PN. Pulsatile versus continuous administration of oxytocin for induction and augmentation of labor: two randomized controlled trials. Am J Obstet Gynecol. 2012;206(3):230.e1-8. Epub 20111107. doi: 10.1016/j.ajog.2011.11.001. PubMed PMID: 22206748.
18. Simpson KR, James DC. Effects of oxytocin-induced uterine hyperstimulation during labor on fetal oxygen status and fetal heart rate patterns. Am J Obstet Gynecol. 2008;199(1):34.e1-5. Epub 20080314. doi: 10.1016/j.ajog.2007.12.015. PubMed PMID: 18342288.
19. Jamal A, Kalantari R. High and low dose oxytocin in augmentation of labor. Int J Gynaecol Obstet. 2004;87(1):6-8. doi: 10.1016/j.ijgo.2004.06.004. PubMed PMID: 15464768.