"Parenteral Lactated Ringers Plus Dextrose 5% vs. Lactate Ringer in Labor: A Randomized Controlled Trial on Maternal and Neonatal Outcomes"

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1. Background

The choice of intravenous fluids during labor is crucial in obstetric care and significantly impacts maternal and neonatal outcomes. Some studies have focused on the relationship between the effects of dextrose solutions and labor duration, cesarean delivery rates, and neonatal hypoglycemia.[1–8] When oxytocin is used as an intravenous medication for labor induction, it is usually constituted in a dextrose solution.[9] While dextrose solutions help maintain energy levels,[3] other types of solutions are important for hydration.[10]

There are conflicting data regarding the use of 5% dextrose (D5) during labor. One meta-analysis indicates that the infusion of D5 compared to Normal Saline (NS) leads to a significant reduction in the duration of the first stage of labor [8]. There are also other studies that do observe a reduction in overall labor duration in nulliparous individuals at low risk (from 560 to 450 minutes) using D5.[11,12] However, other studies found no differences between the two groups.[13]

In previous investigations, the administration of glucose solution to pregnant individuals has been reported to correlate with lower fetal cord pH in some studies,[14] while others have observed a contradictory association15 or found no statistically significant difference.[15–18] A potential explanation for these varying outcomes lies in the proposed mechanism whereby intermittent maternal hyperglycemia leads to fetal hyperglycemia, subsequently causing hypertrophy and hyperfunction of fetal pancreatic beta cells and resulting in fetal and neonatal hyperinsulinemia. Since glucose solution administration can induce maternal hyperglycemia,[14] and maternal hyperglycemia is known to precipitate neonatal hypoglycemia,[19] it is essential to determine whether glucose solution is indeed associated with an increased risk of neonatal hypoglycemia.

Laboring patients often have increased energy and glucose requirements due to uterine activity, triggering metabolic changes. [14,17] Insights from skeletal muscle physiology indicate that glucose supplementation may enhance muscle function during extended physical activity, which parallels the conditions of the uterus during childbirth. Consequently, it is essential to assess the effects of incorporating carbohydrate supplements on the progression of labor. [15]

Two studies have analyzed differences in labor duration between infusion of dextrose and normal saline in individuals undergoing labor induction. One study examined the average duration of labor in induced individuals with a Bishop score greater than 6,[15] while the other one focused on those with a Bishop score less than 6. [13] There was a significant reduction in labor duration for individuals receiving D5/NS compared to those receiving only normal saline in individuals with a favorable cervix (423 ± 35.3 minutes versus 499 ± 25.8 minutes). However, there was no difference in labor duration in individuals with an unfavorable cervix. [5,13,18] Moreover, emerging evidence suggests that the consumption of dextrose solution by nulliparous women reduces the cesarean delivery rate, the need for oxytocin administration, the frequency of prolonged labor, and improves neonatal outcomes, compared to Lactated Ringer's solution (LR) and oral fluids. [20] However, despite these promising findings, there is a significant gap in the literature, with few studies having analyzed the direct comparison between D5/LR and LR alone in the context of labor induction. [16,18,20]

One important risk factor for prolonged labor is labor induction.[13,15] Prolonged labor[21] is a major contributor to complications for both mothers and fetuses, and there are limited interventions known to effectively reduce the duration of labor.

Given that prolonged labor is associated with increased rates of cesarean delivery, chorioamnionitis, maternal-fetal infection, postpartum hemorrhage, perineal injury, and shoulder dystocia, this study aims to evaluate whether the addition of D5 to LR results in a shorter labor duration compared to LR alone, without increasing cesarean delivery rates or neonatal hypoglycemia (**<40 mg/dL** in the first 2 hours of life).[13,15,18]

2. Study Goals and Specific Aims

Aim 1: To investigate the differences between the effects of D5/LR versus LR alone on **labor duration** (in minutes) in nulliparous patients undergoing induction of labor. We hypothesize that D5/LR versus LR alone would reduce the labor duration.

Aim 2: To examine the differences between the effects of D5/LR versus LR alone on **neonatal hypoglycemia** in patients

undergoing induced labor. We hypothesize that D5/LR versus LR alone does not increase the risk of neonatal hypoglycemia.

3. Study design

We plan to conduct a multi-center, single-blind, randomized controlled trial. Hospitals involved in this study will be Sentara Norfolk General Hospital (USA) and Policlinico di Modena (Italy). CONSORT guidelines will be followed [22]. The delivery rate for each Hospital is estimated to be 3,000 deliveries per year.

4. Participants

Nulliparous individuals undergoing labor induction [13,15] at ≥ 37 weeks will be included. Individuals engaged in the research will have no part in determining the viability of a neonate. We will select the following inclusion and exclusion criteria to ensure that the results can be applied to a population with similar characteristics.

Inclusion criteria

1. Nulliparous women
2. Age 18 years or older and able to provide informed consent
3. Singleton pregnancy at term
4. Induction of labor
5. Cephalic presentation
6. Unfavorable cervix (Bishop score $\leq$6)

Exclusion criteria

1. Age under 18 years
2. Involuntarily confined or detained
3. Considered as having a diminished decision-making capacity
4. Spontaneous labor (cervical exam between 5-6 cm) with or without ruptured membranes.
5. Favorable cervix (Bishop score>6)
6. Diabetes mellitus (both gestational and pre-gestational)
7. Structural renal disease
8. Acute or chronic kidney disease resulting in abnormal creatinine or proteinuria
9. Evidence of chorioamnionitis or non-reassuring fetal testing at the time of enrolling
10. Pyrexia (>38.0 $^{\circ}$C) at the time of enrolling
11. Stillbirth
12. Planned cesarean delivery
13. Women presenting with emergent circumstances for labor induction

5. Procedures

5.1 Recruitment

Patients will be enrolled in the study either during outpatient visits or at the time of admission before the induction process begins. The process will follow these steps:

- Outpatient Enrollment:
  In outpatient clinics, eligible participants will be identified during routine prenatal visits. Those who meet the inclusion criteria will be informed about the study, and the research team will provide detailed information regarding the study objectives, procedures, and potential risks and benefits. If patients express interest in participating, informed consent will be obtained at that time, and study procedures will commence upon admission for scheduled induction of labor.

- Hospital Admission Enrollment:
  Participants will also be enrolled at the time of hospital admission for labor induction. Emergent circumstances will not be included in this recruitment process. Prior to the commencement of any intervention or induction procedure, the research team will assess eligibility based on the inclusion and exclusion criteria. Eligible patients will then be provided with full details about the study and asked to provide written informed consent before the

study intervention begins.

Subjects will be given a total of $50 via ClinCard for their participation in the study. The Virginia Health Sciences Department of Obstetrics and Gynecology will provide the funding for subject payment.

5.2 Screening
Subjects' records will be screened, to determine if they meet inclusion and exclusion criteria prior to their scheduled induction of labor or at the time of admission.

5.3 Consenting process
We will have to obtain explicit patient consent, as consent is necessary for participation in the study. A patient may withdraw from the study at any time if either the provider no longer deems participation to be in the patient's best interest or the patient themselves no longer wishes to participate. Providers may also opt out of participation in the study if they do not wish to fulfill the requirements of the randomized controlled clinical trial for the patient.

5.4 Participation Timeframe
While some participants may be enrolled during routine prenatal visits, active participation will only begin during admission for labor induction. Active participation will be up to 24 hours, and follow-up will be 3 days, in order to obtain the outcomes as described in Table 1.

6. Randomization and Blinding

Study participants will be randomly assigned in a 1:1 ratio to one of two treatment groups: the D5-LR group or the LR control group. Randomization will occur before the start of the infusion. The randomization process will be stratified by the clinical site to ensure balanced treatment allocation across the different hospitals involved in the study (Sentara Norfolk General Hospital and Policlinico di Modena). Stratification will account for potential site-specific differences in patient demographics and clinical practices related to labor induction, ensuring a representative sample from each center and minimizing bias in treatment allocation.

Prior to randomization, the two participating medical centers will be stratified based on factors such as historical patient volume and specific clinical characteristics associated with labor induction and maternal outcomes. This stratification ensures a balanced representation of each site in the study, controlling for site-specific variations that could influence treatment outcomes.

Each participant will be assigned to one of the two treatment groups via a computer-generated randomization sequence using randomly permutated block designs.[22] The patients will not know which treatment group they have been assigned to, but the physicians will be aware of the assignment (D5-LR group or LR control group).

A one-liter bag containing the corresponding solutions will be ordered from the pharmacy. The nurse taking care of the participant will seal the bag with an opaque cover. Healthcare providers and the research team will be aware of the treatment allocation to ensure proper medical management. The statisticians will remain unaware of the treatment allocation, and group assignment will only be revealed by the once the statistical analysis is complete. [15]

The study group will receive a 5% dextrose solution with Lactate Ringer, while the control group will be given only Lactate Ringer. In both groups, fluids will be administered using infusion pumps at a rate of 125 ml/h. [12] Regarding labor induction, the induction method will be determined by the Bishop score and at the discretion of the attending physicians.

For those who need intravenous fluid bolus for any reasons such as epidural or spinal anesthesia, non-reassuring fetal heart tracing, or suspected hypovolemia, a 500-1000 mL bolus of Lactate Ringer or Normal saline solution will be administered regardless of the intervention group. The infusion will be discontinued either after delivery or immediately upon the decision to perform a cesarean section.[15]

7. Outcomes

The **primary outcome** of the study will be the induction start to delivery time, measured from the start of induction until delivery. This duration will be compared between the study group, which will receive a 5% dextrose in Lactate Ringer, and the control group, which will receive Lactate Ringer. The induction method will be selected according to the local protocols.

The secondary outcomes of the study include a range of maternal and neonatal parameters that will be evaluated to assess the effects of the treatment on labor and delivery outcomes. (Table 1) This study will include the measurement of neonatal glucose levels from blood draws or fingersticks done as routine care.

Among the maternal outcomes, we will evaluate the type of amniotomy (spontaneous or artificial). The incidence of cesarean delivery will be recorded, compared to vaginal deliveries, in order to assess how the type of fluid administered impacts the mode of delivery. Similarly, the time to active labor will be monitored, which is defined as the time from when the cervix reaches 6 cm of dilation to the onset of active labor. We will also document the delivery within 12, 24, 36, and 48 hours of induction to determine the effectiveness of the fluid treatment within these time frames.

Additionally, perineal lacerations during delivery will be recorded, including any first, second, third, or fourth-degree lacerations. Maternal infection was assessed as a composite, including isolated maternal fever, chorioamnionitis, endometritis, and wound infection. The need for blood transfusion during or after delivery will also be tracked as a key maternal outcome. The study will also monitor the incidence of venous thromboembolism (VTE), hysterectomy, and intensive care unit (ICU) admission for any maternal complications. Maternal death during or following delivery will be documented as well. Other labor-related outcomes include cord prolapse, the use of terbutaline to manage uterine contractions, and the placement of an intrauterine pressure catheter. The use of epidural anesthesia for pain relief will be recorded. [23,24]

Neonatal outcomes will be assessed as composite, including 5-minute Apgar score <7, arterial umbilical cord pH <7.0, neonatal intensive care unit admission, and sepsis. Mild sepsis will be defined by clinical signs of infection with no positive blood culture or negative cultures; severe sepsis will be defined by culture-proven sepsis or sepsis with significant clinical deterioration (e.g. shock, organ dysfunction). Other key neonatal outcomes are the duration of NICU stay (with a focus on admissions lasting longer than 48 hours) and overall neonatal length of stay in the hospital. The incidence of severe respiratory distress syndrome will be tracked, specifically cases that require intubation and mechanical ventilation for at least 12 hours. The need for neonatal blood transfusion will be assessed, as well as the occurrence of hypoxic-ischemic encephalopathy. Additionally, any cases of intraventricular hemorrhage (grade 3 or 4) or necrotizing enterocolitis will be documented. The use of head cooling therapy for neonates to prevent brain injury will be included as part of the neonatal outcomes. Neonatal hypoglycemia, defined as mild (40-45 mg/dL in the first 1-2 hours) or severe (<40 mg/dl in the first 1-2 hours) will also be monitored, following standard protocols for glycemia monitoring. [23,24]

Neonatal glucose will be measured as part of standard clinical care. Neonates born to women in the intervention group may be at increased risk of hypoglycemia due to possible maternal hyperglycemia. All neonates will be checked for hypoglycemia, regardless of the intervention group.

As part of the study, Bishop score will be assessed at randomization for each participant to provide baseline information on the cervical condition. The score, which evaluates cervical dilation, effacement, station, position, and consistency, will help stratify participants based on their likelihood of responding to induction. These measurements will be recorded at various points during labor to monitor cervical progression and assess the relationship between fluid administration and cervical changes.

8. Sample Size Determination

The sample size was estimated a priori based on the primary outcome. We assumed a mean induction to-delivery time of 17.0 ±7.8 hours with vaginal misoprostol based on previously published data.[25,26] A total of 123 patients per group will be necessary to achieve 85% power for detecting a 3-hour difference in mean induction-to-delivery time between the two groups using a two-tailed t-test, an alfa-error of 0.05. [26] This power level is commonly used in clinical trials to ensure a reasonable chance of detecting a true effect. To account for potential patient withdrawals and enrollment errors (5%

per group), the sample size will be subsequently adjusted to 129 patients per group. No interim analyses will be conducted during the trial, and recruitment will conclude once 129 patients are enrolled in each group. [11,15] During enrollment, one patient is equal to one individual presenting for induction of labor (as defined in the recruitment section). As collected data will be on both maternal and neonatal outcomes, the data used in analysis will be of mother-neonate dyads. For patients who undergo operative delivery or cesarean delivery, the duration of labor will be considered censored at the moment the decision to expedite delivery is made [8,15,18]

9. Data Collection Methods

Data at the VHS site will be collected from clinical records (EPIC, AllScripts). The observation will be carried out using standardized protocols to ensure consistency across all cases. Trained personnel will be responsible for documenting maternal vital signs, contraction patterns, cervical dilation, and fetal heart rate monitoring. Data entry will be performed in real-time using an electronic medical record system to minimize errors and ensure the accuracy of information. In addition, labor progress will be documented at regular intervals to track both maternal and neonatal outcomes throughout labor and delivery. All data collected will be anonymized before analysis to protect patient confidentiality. Additionally, electronic health records (EHRs) will be used to capture maternal and neonatal outcomes in real-time, with regular audits conducted by the research team to ensure accuracy. All data will be de-identified and stored in secure, password-protected databases (REDCap), compliant with institutional privacy policies. The ID Key will also be stored in REDCap. The site in Italy will not be entering data to REDCap.

10. Statistical Analysis

Statistical analyses will be conducted to evaluate the outcomes of the study, focusing on the effects of 5% dextrose solution compared to Lactate Ringer on labor duration as well as maternal and neonatal outcomes.

To compare the mean duration of labor between the two groups (those receiving dextrose and those receiving Lactate Ringer), a T-test for independent samples will be employed. If the data does not meet the assumption of normality, a Mann-Whitney U test, which is a non-parametric alternative, will be used to assess the median durations instead.
For categorical outcomes, such as the incidence of cesarean deliveries and other complications, Fisher's exact test will be applied to determine whether there are significant differences between the two groups.

In terms of time-to-event analysis, the primary analysis for the duration of labor will utilize a Cox proportional hazards model, treating the type of fluid administered as a covariate. The Kaplan-Meier product-limit method will be used to estimate the time-to-event distributions for each group, and the groups will be compared using a stratified log-rank test. All statistical tests will be two-sided, and a p-value of less than 0.05 will be considered statistically significant. Additionally, to account for multiple comparisons, a Bonferroni correction may be applied when appropriate.[27]

11. Ethical considerations

The study will receive ethical approval from the relevant institutional review board, ensuring that all procedures adhere to ethical standards.

12. Limitations

While the sample size will be adjusted for potential withdrawals, the generalizability of the findings may be limited due to the specific patient population studied.

13. Conclusion

In conclusion, this study will evaluate the effects of 5% dextrose solution compared to Lactate Ringer on labor duration and associated maternal and neonatal outcomes in low-risk pregnancies. By employing a multi-center, single-blind, randomized controlled trial design, we will aim to minimize bias and ensure robust findings.

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Table 1. Secondary outcomes [23,24]

Outcome Measures	Description
Maternal Outcomes	
Type of amniotomy	Spontaneous vs artificial
Mode of delivery	The incidence of spontaneous vaginal delivery, operative vaginal delivery and cesarean delivery.
Indication for cesarean delivery	Rate of failed induction of labor, arrest of active phase, arrest of descent, non-reassuring fetal condition, maternal request, other.
Time to Active Labor (hours)	Time from 6 cm cervical dilation to onset of active labor.
Delivery within 12 hours of Induction	Incidence of delivery within 12 hours of induction.
Delivery within 24 hours of Induction	Incidence of delivery within 24 hours of induction.
Delivery within 36 hours of Induction	Incidence of delivery within 36 hours of induction.
Delivery within 48 hours of Induction	Incidence of delivery within 48 hours of induction.
Perineal Lacerations (Degree I-IV)	Degree of perineal lacerations occurring during delivery (first to fourth degree).
Postpartum hemorrhage	Blood loss >1000 mL
Blood Transfusion	Incidence of blood transfusions required during or after delivery.
Isolated maternal fever	Incidence of maternal fever (T>38°C)
Endometritis	Diagnosis of endometritis based on clinical signs and diagnostic tests.
Wound Separation/Infection	Incidence of wound separation or infection requiring additional closure or antibiotics.
Intraamniotic Infection	Presence of maternal fever, tachycardia, and/or fundal tenderness suggesting intraamniotic infection.
Venous Thromboembolism (VTE)	Occurrence of venous thromboembolism.
Hysterectomy	Occurrence of hysterectomy related to delivery complications.
Intensive Care Unit (ICU) Admission	Admission to ICU for maternal complications.
Maternal Death	Occurrence of maternal death during or after delivery.
Length of hospital stay	Days between admission and discharge
Labor and Delivery Outcomes	
Cord Prolapse	Occurrence of cord prolapse during labor.

Use of Terbutaline	Use of terbutaline for uterine contractions.
Placement of Intrauterine Pressure Catheter	Placement of intrauterine pressure catheter during labor.
Epidural Use	Use of epidural anesthesia during labor for pain relief.
Neonatal Outcomes	
Severe Respiratory Distress Syndrome (RDS)	Need for intubation and mechanical ventilation for ≥12 hours.
5- minute Apgar score <7	Incidence of 5-minute Apgar score<7
Arterial umbilical cord pH <7	Incidence of arterial umbilical cord pH <7
Neonatal outcome composite	Incidence of neonatal outcome composite
Neonatal Sepsis (Culture-proven or Presumed)	Incidence of neonatal sepsis, culture-proven or presumed.
Neonatal Intensive Care Unit (NICU) Admission	Admission of neonate to NICU.
Hypoxic-Ischemic Encephalopathy	Diagnosis of hypoxic-ischemic encephalopathy in neonates.
Intraventricular Hemorrhage (Grade 3 or 4)	Occurrence of grade 3 or 4 intraventricular hemorrhage in neonates.
Necrotizing Enterocolitis	Diagnosis of necrotizing enterocolitis in the neonate.
Head Cooling Therapy	Use of head cooling therapy for neonates to prevent brain injury.
Neonatal Blood Transfusion	Need for blood transfusion in the neonate.
NICU Stay >48 hours	Incidence of NICU stay lasting longer than 48 hours.
Neonatal Length of Stay (days)	Total length of neonatal stay in the hospital.
Bishop Score	
Cervical Dilation, Effacement, Station, Position, Consistency	Baseline Bishop score and its changes during labor to assess cervical readiness for induction.