Title:	**Effect of Oral Calcium Carbonate on Uterine Contractility and Labor Outcomes: A Randomized Controlled Trial**
Short Title	RCT: Oral Calcium Supplementation in Labor
NCT Number:	pending
Protocol Date:	4-26-24

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II: Introduction/Literature review:

In the United States, cesarean delivery rates affect one in three women, with labor dystocia frequently cited as a leading cause.[1] Labor dystocia can arise from various factors such as fetal size, positioning, pelvic structure, contractions, or maternal conditions.[1] Clinically we can only correct the amount of uterine activity by oxytocin administration ± amniotomy. The inability to decrease the cesarean section rate has prompted exploration for additional strategies.

One proposed method to improve uterine activity that has sparked interest in numerous social group forums is oral calcium carbonate supplementation, yet it remains largely unstudied in a clinical setting. Both calcium and carbonate components are recognized for enhancing myometrial contractility.[2] Physiologically, calcium plays a vital role in regulating uterine contractility throughout pregnancy.[2] Oxytocin triggers the release of calcium ions from intracellular stores via L-type Calcium channels within myometrial cells, inducing action potentials and thereby uterine contractility.[3] During labor, there's an upsurge in calcium channel expression, facilitating uterine contractility.[3] Additionally, serum calcium levels have been correlated with uterine contractility, as patients with higher calcium levels are more likely to deliver vaginally compared to those undergoing cesarean delivery.[2 4-6]

Given its potential to enhance uterine contractility and potentially reduce the need for surgical intervention, we aim to investigate the effects of calcium carbonate on uterine contractility. We hypothesized that giving calcium carbonate intrapartum can improve uterine contractility and decrease the number of cesarean deliveries.

III: Objectives: research question, purpose of the study, hypothesis

- Research questions:
    - Does calcium carbonate supplementation intrapartum improve uterine contractility, assessed by measuring Montevideo units, contraction frequency, and peak contraction strength.
- Purpose of the Study: The purpose of the study is to investigate whether calcium carbonate supplementation during labor can improve uterine contractility and decrease labor dystocia. By conducting this trial, the aim is to provide evidence-based guidance to healthcare providers regarding the potential use of calcium carbonate as a preventive measure for labor dystocia.
- Hypothesis: We hypothesized that pregnant women, those who receive calcium carbonate supplementation will have improve uterine contractility and a shorter labor course.
- Alternative Hypothesis: Calcium supplementation will have no effect on contractility

IV: Study type: Randomized control trial

V: Methods:

- Location: Labor and Delivery at Arrowhead Regional Medical Center

- Start: Plan to start at the receipt of IRB approval. We anticipate the duration of the study to be about 2 years.
- Type of research: other
- Inclusion:
    - Patients undergoing induction of labor with an intrauterine pressure catheter already in place at the discretion of the OB provider
    - Maternal age: >18 years of age
    - Gestational age > 37 weeks 0 day
    - Cephalic presentation
    - Able to understand/read English and/or Spanish
- Exclusion:
    - Maternal age < 18 years of age
    - Incarcerated patients
    - Active labor
    - Active illicit substance use
    - Multiple fetal gestations
    - Bleeding concerning for hemorrhage/placental abruption/placenta previa, or other contraindications to vaginal delivery
    - Aneuploidy or fetal structural anomaly
    - Prior cesarean deliveries
    - Known maternal arrhythmias, hyperparathyroidism, heart failure, kidney failure, liver failure, and history of kidney stones
    - Medications that affect uterine contractility like Magnesium, Terbutaline, Cytotec (need to be 4 hours after administration to enroll)

- Subject recruitment: All women with a term pregnancy, admitted for induction of labor will be asked to participate if age >18 years of age and English/Spanish speaking. We will plan to recruit when a patient is at least 4 cm and greater with an IUPC already in place. Using a baseline Montevideo unit of 200, if we were to aim for a 20% difference with a power of 80%, a sample size of 80 would be the minimum goal to enroll. Therefore, our goal is to enroll at least 40 patients into each group.

- Consent:
    - The informed consent process will be conducted by trained research staff and will include all aspects of the study and a full disclosure of the risks, benefits, procedures, and alternatives. The study consent and HIPAA authorization will be signed after all questions have been discussed and answered. Collection of baseline information, including such items as contact information, BP measurements, demographic and pregnancy history information, concomitant medications, and lifestyle information will follow the informed consent process.
    - All data will be kept confidential to comply with HIPAA regulations. No patient identifiers will be included in the data sets. All data will be kept in a password protected folder within the ARMC network and will only be made

available to study investigators. The database will be controlled, and password-protected.

- All data and records will be kept confidential in accordance with Institutional policies and HIPAA. There will be extremely limited access to subject information. All data will be anonymized before publication. Patient Data Sets will include identifiers that are strictly limited to medical record number, ethnicity, age and sex, along with associated clinical data. Patient Data Sets will be imported into password protected Excel files located in an encrypted folder accessible only to the investigators involved in the study, IRB, and IT on the ARMC server. All published poster presentations, abstracts and papers will be de-identified, with a medical record numbers and any other identifying material removed. Patient's age, parity, sex and race will be used in publication for educational purposes.

VI: Study Design and analysis:

- All patients admitted for term induction of labor will be asked to participate if they meet the inclusion criteria as described above. Once consented, the participants will be randomly allocated into two groups: control versus intervention group. Randomization will be done as block randomization based on maternal BMI at time of admission, all odd patients will be enrolled into the control group and all even study numbers will be in the intervention group.

  -Control group: no medication

  -Intervention group: Calcium carbonate 500 mg 4 tablets PO x1

  -Calcium carbonate (TUMS) is an over-the-counter antacid medication and common side effects include changes in bowel habits like constipation or diarrhea, bloating, gas, and abdominal discomfort. Rare side effects include allergic reactions and hypercalcemia if taken in large amounts. The daily recommended max dose is 8000mg, we will be giving a max of 2000 mg.[7]
- The primary outcome will determine the effect of calcium carbonate on uterine contraction strength, assessed by comparing Montevideo units (MVU), frequency of contractions, and peak of the contractions 30 minutes before medication administration and at 30 minutes interval for a total of 2 hours afterward. To ensure accuracy in MVU measurement, all patients should already have an intrauterine pressure catheter (IUPC) in place at the discretion of the OB provider before they are enrolled. Secondary outcomes include duration of first and second stage of labor, mode of delivery, neonatal outcomes (NICU admission, low APGAR scores), and maternal outcomes (PPH).
- Other maternal information such as height, weight, BMI, age, parity, race, gestational age, cervical dilation/effacement/station at the time of medication administration and after administration, time to delivery, oxytocin use, epidural use, Apgars, perineal laceration, QBL, birthweight, mode of delivery, delivery complications will be obtained to compare among the two groups to make sure there are no confounding factors. Since Pitocin dose is a confounding variable after receiving the medication, patients must be off Pitocin during study period.

- The data collected will be divided into 2 groups: control versus intervention group. Statistical analysis included descriptive statistics to summarize maternal characteristics and clinical outcomes. Normality testing was performed, and appropriate comparative statistical tests were selected, including two-way Student's t-tests, Tukey's tests, or post hoc Student–Newman–Keuls tests as appropriate. A p-value of less than 0.05 was considered statistically significant. Univariate and multivariate linear regression analyses were conducted to identify associations between maternal, fetal, and labor-related variables and study outcomes.
- Uni- and multivariate analysis with linear regression modeling will be used to identify significant associations between maternal, fetal, or labor characteristics.

VII: Risks and Benefits:

- The risks to the study participants are not greater than minimal as the study does not change the patient's plan of care. Calcium carbonate has been shown to be safe in pregnancy and should not harm the fetus or the participant. We are using less than the maximum recommended dose in pregnancy. The patient's data will be stored on a password protected document to decrease the risk of breach of confidentiality.
- These patients are already admitted for induction of labor and have accepted those risks, benefits, and alternatives. There are risks with induction of labor, that the patient will experience regardless of participation in this study. These risks include discomfort, fetal distress, NICU admission, cesarean section, hemorrhage, infection, failed or prolonged induction, and maternal mental exhaustion.
- Otherwise, this study has no other intervention that could cause harm.
- Risks from breaches in confidentiality are limited as described above.

VIII: Funding source: Department of Obstetrics and Gynecology

IX: References:

1. Safe prevention of the primary cesarean delivery. Obstetric Care Consensus No. 1. *American College of Obstetricians and Gynecologists. Obstet Gynecol*. Mar 2014;123;693–711.
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5. Pehlivanoğlu, Bilge et al. “A close look at the contraction and relaxation of the myometrium; the role of calcium.” *Journal of the Turkish German Gynecological Association* vol. 14,4 230-4. 1 Dec. 2013, doi:10.5152/jtgga.2013.67763
6. Papandreou L, Chasiotis G, Seferiadis K, Thanasoulias NC, Dousias V, Tsanadis G, Stefos T. Calcium levels during the initiation of labor. Eur J Obstet Gynecol Reprod Biol. 2004 Jul 15;115(1):17-22. doi: 10.1016/j.ejogrb.2003.11.032.
7. Epocrates. 2024. Drug information: Calcium carbonate. In Epocrates medical references.
8. Ansari JR, Yarmosh A, Michel G, Lyell D, Hedlin H, Cornfield DN, Carvalho B, Bateman BT. Intravenous Calcium to Decrease Blood Loss During Intrapartum Cesarean Delivery: A Randomized Controlled Trial. Obstet Gynecol. 2024 Jan 1;143(1):104-112. doi: 10.1097/AOG.0000000000005441. Epub 2023 Nov 3. PMID: 37917943.

Arrowhead Regional Medical Center
Informed Consent Form for Participation in a Research Project

Study Title: *Randomized Controlled Trial Comparing the Efficacy of Calcium Carbonate for Preventing Labor Dystocia*
Principal Investigator: *Guillermo Valenzuela*

Introduction:
You are being asked to join a research study. You are being asked to take part in this study because *you are being induced with a singleton pregnancy.* You do not have to participate in this research study. The main purpose of research is to create new knowledge for the benefit of future patients and society in general. Research studies may or may not benefit the people who participate.

Research is voluntary, and you may change your mind at any time. There is no penalty if you decide not to participate, or if you start the study and decide to stop early. Either way, you can still get medical care and services at Arrowhead Regional Medical Center.

This consent form explains what you have to do if you are in the study. It also describes the possible risks and benefits. Please read the form carefully and ask as many questions as you need to, before deciding about this research. You can ask questions now or anytime during the study. The researchers will tell you if they receive any new information that might cause you to change your mind about participating.

Purpose:
You are invited to be part of a research study about *the effects of calcium on uterine contractions*

The purpose of the study is to *assess the effectiveness of calcium carbonate in influencing uterine contractility.* You are invited to be in this study because *you are in labor with a singleton pregnancy and we will see how long it takes for you to deliver.*

The persons responsible for the research project are *Tina Bui, RJ Stowe, Kayla Witcik, Michelle Nelson, Kristy Roloff, Guillermo Valenzuela.* Your doctor is interested in your health as well as conducting this research project. If you feel that your doctor can not represent your best interest, you can ask for another doctor to take care of you.

Description of your Involvement:
If you are eligible and decide to participate in this study, your participation will last approximately *up until delivery.* Your participation will involve *taking a medication during in labor that may or may not improve your contractions and help one delivery vaginally. The study will conclude at the point of delivery. We do not anticipate that these medications will add any further discomfort to your labor. Furthermore, the management of your labor will not change based on these medications. We/I would also record your demographics, medical history including pregnancy history, physical exam, vital signs, height and weight for the purpose of this study. Your name and identity will be protected.*

Risks and Discomforts of Participation:
There may be some risk or discomfort from your participation in this research. This study *minimal risk. There are not anticipated health risks for you or your fetus from your participation in this research.* Participating in this study will involve the following risks: *There are mild medication side effects in some people which include constipation and bloating. There may be some discomfort while undergoing an induction of labor but is no different than the normal course of an induction. The patient's data will be stored on a password protected document to decrease the risk of breach of confidentiality.*

All records and research materials that identify you will be held confidential. Any published document resulting from this study will not disclose your identity without your permission. Information identifying you will only be available to the study personnel. *All data will be kept in a password protected folder within the ARMC network and will only be made available to study investigators. The database will be controlled, and password protected.* Your rights regarding permission to use your health information are described on the attached "Authorization for Use of Protected Health Information" form.

There may be other risks of the study that are not yet known.

Benefits:
You may or may not directly benefit from this study. Although you may not directly benefit from being in this study, others may benefit because *of what we learn about the effects of calcium carbonate on labor.*

Subject Rights:
You do not give up any legal rights to privacy, confidentiality, or safety by participating in this study. Participating in this study is completely voluntary. Not participating in the study will not be held against you and will not affect your access to care or treatment unrelated to this research. Even if you decide to participate now, you may change your mind and stop at any time without affecting your medical care. Your study doctor or primary care doctor can discuss alternatives with you which may include, *not taking any additional medications.* If you decide to withdraw before this study is completed, *your data will not be used.* You will be given a copy of the California Experimental Subject's Bill of Rights and a copy of this Informed Consent to keep.

Potential Costs:
You and/or your health insurance must pay for those services, supplies, procedures, and care required for routine medical care. You will be responsible for any co-payments and/or deductibles as required by your insurance. If you participate in this study, there may be additional costs to you, such as travel for study visits.

Potential Compensation:
For your participation in this research project, *you will not benefit from this study. You will not be paid. You will not receive any results of the measurements either. The only people who will receive the results are the investigators doing the study, and they will not release the results to you or your other physician. Any new information developed during the course of this research that may relate to your willingness to be a participant will be given to you. If there is good information that comes from the study, we may decide to share the information with other physicians through publication of the data. No patient will be*

reported individually, but composite of all patients will be used. In this manner, there is no manner that you are identified.

Injured during Study:
If you feel you have been injured by taking part in this study, consult with a physician or call 911 if the situation is a medical emergency. No funds have been set aside nor any plans made to compensate you for time lost for work, disability, pain or other discomforts resulting from your participation in this research.

Storage and Future Use of Data:
Your privacy will be protected and your research records will be confidential. Your data/specimens (*will be de-identified and used for research. All data sets will be stored in a password protected folder within the ARMC network and will only be made available to study investigators. The database is monitored, and password protected. The data sets will be kept confidential and available until the study is published and then data will be erased.* It is possible that other people may need to see the information you give us as part of the study, such as organizations responsible for making sure the research is done safely and properly like the Arrowhead Regional Medical Center, government offices or the study sponsor*, full sponsor name(s), if any*.

Contact Information for the Study Team:

If you have questions about this research, including questions about scheduling or your compensation for participating, you may contact *Guillermo Valenzuela.*

Contact Information for Questions about Your Rights as a Research Participant:
If you have questions about your rights as a research participant, or wish to obtain information, ask questions or discuss any concerns about this study with someone other than the researcher(s), the IRB Coordinator is an impartial third party who is not associated with the research. You may address complaints or questions about this protocol to this person, who may be contacted at (909) 580-6336.

Participant's Statement of Consent:

- I have read the contents of the consent form and have listened to the verbal explanation given by the investigator.
- My questions concerning this study have been answered to my satisfaction.
- Signing this consent document does not waive my rights nor does it release the investigators, institution or sponsors from their responsibilities.
- I hereby give voluntary consent to participate in this study.

I understand I will be given a copy of this consent form after signing it.

_____

Printed Name of Participant

_____ _____

Signature of Participant **Date**

Subject is unable to consent/sign because _____.

_____

Printed Name of Legally Authorized Representative

_____ _____

Signature of Legally Authorized Representative **Date**

Investigator's Statement

I have discussed the research project with the participant; have explained all of the information contained in the Informed Consent to the participant including any adverse reactions; the participant was encouraged to ask questions; and that all questions were answered.

_____

Printed Name of Investigator

_____ _____

Signature of Investigator **Date**