PROTOCOL TITLE: Comparison of Gastric Volumes by Gastric Ultrasound in Term Parturients undergoing Scheduled Elective Cesarean Delivery with and without Metoclopramide

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STUDY SUMMARY:

Investigational Agent(s) (Drugs or Devices)	Metoclopramide vs. Placebo
IND / IDE / HDE #	
Indicate Special Population(s)	☐ Children ☐ Children who are wards of the state ☐ Adults Unable to Consent ☐ Cognitively Impaired Adults ☐ Neonates of Uncertain Viability ☒ Pregnant Women ☐ Prisoners (or other detained/paroled individuals) ☐ Students/Employees
Sample Size	
Funding Source	
Indicate the type of consent to be obtained	☒ Written ☐ Verbal/Waiver of Documentation of Informed Consent ☐ Waiver of HIPAA Authorization ☐ Waiver/Alteration of Consent Process
Site	☐ Lead Site (For A Multiple Site Research Study) ☐ Data Coordinating Center (DCC)
Research Related Radiation Exposure	☐ Yes ☒ No
DSMB / DMC / IDMC	☒ Yes ☐ No

OBJECTIVES:
Our objective is to compare gastric volumes (mL) between women who receive metoclopramide versus placebo prior to scheduled cesarean delivery in appropriately fasted patients. If metoclopramide is found not to reduce gastric volumes this would inform future practice guidelines for obstetric anesthesia, which currently recommends metoclopramide administration prior to cesarean deliveries.

BACKGROUND:

Aspiration is a rare but potentially serious complication of anesthesia. Pregnancy increases the risk of aspiration due to increased intragastric pressure from the gravid uterus and decreased esophageal sphincter tone from increased levels of progesterone. In addition to the standard pre-operative fasting times recommended by the American Society of Anesthesiologists (ASA) Practice Guidelines, the aspiration prophylaxis for cesarean deliveries recommended by the ASA Practice Guidelines for Obstetric Anesthesia include non-particulate antacids, H2-receptor antagonists, and/or metoclopramide.[1-3] With the enforcement of fasting times and routine aspiration prophylaxis, as well as the increased use of neuraxial anesthesia and utilization of rapid sequence induction for general anesthesia, maternal mortality from pulmonary aspiration with cesarean deliveries have declined to almost negligible levels.[4]

While metoclopramide, a promotility agent, has previously been shown to be effective for intra- and post-operative nausea and vomiting prophylaxis, there have not been any recent studies evaluating the utility of metoclopramide for aspiration prophylaxis in a patient with appropriate fasting prior to surgery.[5] Given the unfavorable side effect profile, including akathisia and dystonic reactions, there may not be any additional benefit in the routine use of metoclopramide in healthy parturients undergoing an elective cesarean delivery who are appropriately fasted.[6,7]

Gastric ultrasound has been shown as a noninvasive method to evaluate the risk of aspiration of gastric contents in pregnant women.[8] It has been validated as an assessment of gastric volume compared with gastroscopic examination.[9] Gastric ultrasound can determine if the gastric volume present is consistent with baseline gastric secretions and negligible risk, or if it is a higher volume posing a significant aspiration risk.[10] Pregnant patients presenting for elective cesarean delivery were found by gastric ultrasound to have an empty stomach after following conventional fasting guidelines.[11]

The objective of this proposed study is to use gastric ultrasound to evaluate the effect of metoclopramide in reducing gastric volume prior to elective cesarean delivery. We hypothesize that metoclopramide given to women with appropriate fasting prior to cesarean delivery does not result in any clinically significant reduction in gastric volume (mL) and therefore does not provide any additional benefit for aspiration prophylaxis but may expose patients to unnecessary side effects. A secondary objective will be to evaluate if gastric volume is a significant predictor of intraoperative nausea and vomiting.

References

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STUDY ENDPOINTS:

Primary study endpoints:

- Change in gastric volume (mL) before medication and 30 minutes after

Secondary study endpoints:

- Rates of intraoperative nausea and vomiting during cesarean delivery and post-operative nausea and vomiting after cesarean delivery (correlated to metoclopramide administration and gastric volume)
- Side effects after administration (akathisia, dystonia, abdominal cramping, extrapyramidal symptoms)

STUDY INTERVENTION(S) / INVESTIGATIONAL AGENT(S):

Metoclopramide 10mg (dopamine receptor antagonist, promotility agent) vs. placebo (normal saline). Metoclopramide 10mg/mL will be pre-drawn and diluted with normal saline into a 10mL syringe and stored with pharmacy. Placebo will be normal saline in a 10mL syringe. Medications will be made and stored by pharmacy. Patients will be randomized 1:1 for either drug by our anesthesia research nurses, who will request the drug from pharmacy.

PROCEDURES INVOLVED:

Study Design: This project will be conducted as a double-blind, randomized controlled trial

Study procedures: A baseline gastric ultrasound examination will be performed in the pre-operative holding area an hour prior to the scheduled cesarean delivery by a study investigator trained in the use of gastric ultrasound. All of the investigators will have been trained in the use of gastric ultrasound by Dr. Banayan, an expert in point of care ultrasonography. Gastric ultrasound will utilize the SonoSite X-Porte Ultrasound System with a low frequency curvilinear probe (C60xp).

After the initial examination, the patient will receive either 10 mg IV of metoclopramide or placebo according to a computer generated, randomized assignment in a double-blind fashion. Thirty minutes after the administration of the study medication, a follow-up gastric ultrasound examination will be completed by the same provider. For the gastric ultrasound examinations, we will position the patients in both the supine and right lateral decubitus positioning. Initially a qualitative assessment will be completed to determine the type of gastric content (empty, fluid, or solid content). Then, the cross-sectional area of the antrum will be measured in the right lateral decubitus positioning. This area can then be used to determine the estimated gastric volume using a mathematical model. There have been multiple models published specifically for third trimester pregnant women including ones by Arzola et al. and Chen et al.[12,13]

Following the second ultrasound, metoclopramide-related side effects will be assessed using the Barnes Akathisia Rating scale, a validated scale for assessing akathisia, and a drowsiness scale.[14,15] All patients will receive odanstetron (4mg) intravenous and after neuraxial anesthesia performed but prior to the start of the surgery and decadron (4mg) intravenous after delivery, which is standard of care. Intraoperative incidence of patient reported nausea and vomiting will be recorded along with the administration any rescue antiemetic medications given intraoperatively or post-operatively. The postoperative period will include the time until the patient is discharged from the post-anesthesia care unit (PACU). Anesthesia staff will be able to record nausea and vomiting episodes in Epic. Intraoperative and PACU data will be collected afterwards by a member of the research team.

Of note, administration of metoclopramide is considered standard of care for cesarean deliveries; at Northwestern Medicine Prentice Hospital, it is usually only given to women who have labored prior to cesarean delivery but administration is recommended to be considered according to the ASA practice guidelines. Decision to give metoclopramide to elective cesarean deliveries ultimately depends on patient characteristics and provider preference.

Data to be collected:	
Patient demographics	Age, race/ethnicity, co-morbidities, GERD with pregnancy vs. currently, NPO time solids and liquids, BMI
Obstetric data	Gravida/parity, gestational age, number of prior cesarean deliveries, indication for cesarean delivery
Ultrasound data	Time of administration of study drug, time to obtaining ultrasound image from study drug administration, type of gastric content (empty, fluid, or solid content), cross-sectional area of the antrum and total gastric volume in supine and right lateral decubitus positioning
Anesthesia data	Method of anesthesia (ie. spinal vs. CSE), dose of neuraxial bupivacaine and neuraxial opioids, incision time, delivery time, administration of systemic opioids, anti-emetics given intra-op and in PACU, nausea/vomiting episodes intraoperatively, time from neuraxial administration to nausea/vomiting
Neonatal data	Apgar, need for resuscitation, admission to NICU, umbilical cord gases.

Survey data	Barnes Akathisia Rating scale, drowsiness score, time of survey

DATA AND SPECIMEN BANKING
All data will be kept for a minimum of 7 years after publication, as required by Northwestern University.

SHARING RESULTS WITH PARTICIPANTS
Individual results will not be shared with participants. Final study results will not be shared with participants.

STUDY TIMELINES
Patients who are scheduled for an elective cesarean delivery who meet inclusion criteria will be invited to participate in the study. We plan to enroll 72 patients (36 in each group) in 1 year. Primary study analyses will occur in the following 6 months.

INCLUSION AND EXCLUSION CRITERIA
Pregnant women greater than 37 weeks gestation who have been scheduled for elective cesarean deliveries will be screened upon admission via chart review. If patient meets criteria for study, the research team will invite them to participate in our study.

Inclusion criteria: Any healthy (ASA Physical Status 2), age >18 years old, non-obese (BMI <40 kg/m^2), age >18 years old term (>37 week), non-laboring parturient, single gestation, scheduled for a cesarean delivery and appropriately NPO is eligible for inclusion.

Exclusion criteria: Systemic disease such as diabetes mellitus (type 1, type 2, or gestational diabetes), multiple gestation, abnormality of upper GI tract, history of GI tract related surgical procedures, use of gastric motility medications, active labor, renal impairment (creatinine >2), non-English speaking, cognitively impaired, history of QT prolongation, and general anesthesia.

VULNERABLE POPULATIONS
Pregnant women, see attachment of checklist

PARTICIPANT POPULATION(S)

Accrual Number:	Category/Group: (Adults/Children Special/Vulnerable Populations)	Consented: Maximum Number to be Consented or Reviewed/Collected/Screened	Enrolled: Number to Complete the Study or Needed to Address the Research Question
Local	Pregnant women	80	72
Study-wide			
Total:		80	72

RECRUITMENT METHODS
Subjects will be approached and recruited by a member of the anesthesia research team after admission for elective cesarean section on the 8th floor labor and delivery of Prentice Women's Hospital. The study team members will use Dashboard from the Labor and Delivery Unit at Prentice Women's Hospital and obstetric medical histories to identify potential participants. The research team will discuss participation with the eligible patients and obtain written consent if amenable to participating in study. Subjects who are willing to participate in the study will provide consent on a tablet provided by study staff. Paper consent forms will also be made available if necessary.

There will be no materials used to recruit participants. There is no need for solicitation or advertising for participation in the study.

COMPENSATION FOR PARTICIPATION IN RESEARCH ACTIVITIES
Participants will not receive compensation for participation in this study.

WITHDRAWAL OF PARTICIPANTS
Participation in the completion of the survey is completely voluntary. Participants can ask to stop the ultrasound or surveys at any point. Participants may withdraw from the study at any time without penalty by notifying the research staff that they would no longer like to participate. For individuals who withdraw from the study, the data collected prior to withdrawal will be maintained

We do not foresee any circumstances which will cause research participants to be forcibly withdrawn from the study without their consent.

RISKS TO PARTICIPANTS
Risks are minimal but include the side effects of metoclopramide including abdominal cramps, akathisia, dystonia, and extrapyramidal symptoms. Metoclopramide also can cause QT prolongation, which may cause arrythmias in patients with QT prolongation. The risk of saline administration includes hypernatremia. We feel that these risks are minimal since we are only administering 10 mL of saline; metoclopramide is routinely administered as part of clinical care.

In addition, the potential for loss of confidentiality and the feeling of being emotionally uncomfortable completing the surveys. We feel that this will cause no more than minimal risk to the participants. Confidentiality will be strictly maintained throughout the study.

Gastric ultrasonography is safe to use during pregnancy. There are no risks to the mother or fetus associated with the performance of two-dimensional ultrasound during pregnancy. The participant may experience some discomfort associated with the pressure of the ultrasound probe on the skin during the procedure which should resolve upon completion of the examination.

POTENTIAL BENEFITS TO PARTICIPANTS
There is no direct benefit to the participants that is associated with completion of the study. Future patients may benefit from the knowledge gained from this study, as it will inform practice guidelines for obstetric anesthesia.

DATA MANAGEMENT AND CONFIDENTIALITY

Statistical analysis: The **primary outcome** will be the change in calculated gastric volume. The secondary outcomes will be the incidence of intraoperative nausea and vomiting and side effects. Categorical data will be compared using the chi-squared test or Fisher's exact test. Normal distribution for continuous variables will be determined using the Shapiro–Wilk test. Normally distributed continuous data will be compared using a two-tailed t-test and non-parametrically distributed data will be compared using the Mann-Whitney U test. The criterion for rejection of the null hypothesis will be $P < 0.05$.

Power calculation: In an equivalence test of means using two one-sided tests on data from a parallel-group design, sample sizes of 36 in the first group and 36 in the second group achieve 81% power at a 5% one-sided significance level when the reference mean is 50 mL, the treatment mean is 40 mL, the standard deviation is 25 mL, and the range of the difference between these means that still results in the conclusion of equivalence is -25 mL to 25 mL.

Data Security and Confidentiality: Each study participant will be assigned a study ID number that will be used to link study data to patient identification information (name and birth date) in a separate database. This database will be stored on a secured, password-protected network, accessible only by the study investigators. The completed data forms will be kept in folders with only the study ID number as an identifier. These folders will be placed in a secure, locked cabinet in the office of the Section of Obstetrical Anesthesiology located in Prentice Women's Hospital 9th floor.

All surveys will be completed and stored in the RedCAP online survey management system that is held in a secured server on the Northwestern University campus. All surveys will be identified with the study ID number and will not include any direct patient identifiers. When the survey is closed, all data will be transferred to a secure Northwestern University computer which is only accessible to study team members.

Only study team members listed in the eIRB will have access to the data files. Data will be password protected using a Department of Anesthesiology dedicated computer which is backed up nightly by the departmental server which is located on the 5th floor Arkes Pavilion. The access is controlled by key card and password protected by the departmental data manager. Only the study ID number will be used to identify participants during data analysis. The data will be stored in the departmental computer until the completion of the study, including the final data analysis. Members of the anesthesia team collecting these data will be educated on the process prior to approaching prospective participants. Under no circumstances will individually identifiable data be released to anyone without the written consent of the subject. Results will be reported as group findings only. Seven years after study completion, all data will be destroyed using departmental standards and current vendors, in compliance with NU policy.

All ultrasound data will be de-identified at the time of enrollment with the participant's six-digit study ID number. The ultrasound images will be exported from the ultrasound machine on Qpath, which is a secure and HIPPA compliant ultrasound workflow manager. These images will only be accessible to study team members. All data will be stored on the same computer and backed up in the PI's office. Seven years after study completion all ultrasound data will be destroyed in compliance with NU policy.

All data access will be password protected and only available to study investigators listed on the IRB application. Data access will be controlled by the Principal Investigator. All members of the study team will have completed Northwestern University requirements for the responsible

conduct of research including the Collaborative Institutional Training Initiative (CITI) Training Modules

PROVISIONS TO MONITOR THE DATA TO ENSURE THE SAFETY OF PARTICIPANTS
A data monitoring committee consisting of the Department of Anesthesiology Director of Research, a statistician, and a faculty member from the obstetrics department along with the study research personnel will periodically evaluate the data collected to determine whether participants remain safe. Safety data and adverse event data will be reviewed using the medical record and data collection form. It will be reviewed once half subjects (40 patients) are enrolled. Any adverse events will be reported to the IRB.

PROVISIONS TO PROTECT THE PRIVACY INTERESTS OF PARTICIPANTS
Research subjects will have a few interactions with study team members. First, they will discuss the study and the research study team member will obtain written informed consent. A second interaction will occur during the first ultrasound and the drug study drug administration. The third interaction will be an assessment survey for side effects. The fourth interaction will be the second ultrasound scan. Participants may be contacted in the PACU after delivery to ask them about any nausea and vomiting they may have experienced. The research study team is only to be allowed to view the data sheets of the mother and REDCap for selected data within the parameters of the study.

COMPENSATION FOR RESEARCH-RELATED INJURY N/A

ECONOMIC BURDEN TO PARTICIPANTS
N/A

CONSENT PROCESS
Written consent will be obtained from all study participants by a member of the study team. The consent process will occur prior to delivery. Consent will occur in the patient's room in the Labor and Delivery Unit, 8th floor, at Prentice Women's Hospital. There is no waiting period. SOP HRP 090 will be followed. The research study team will spend greater than 10 minutes discussing the study. With each subject ample time will be allowed for patient to answer questions regarding the study and the consent document. The subject will also be informed that there is no conflict of interest between the PI and the protocol. The PI will not receive financial remuneration nor will the study participation affect the subject's financial charges for their care.

NON-ENGLISH SPEAKING PARTICIPANTS
We will only be enrolling English speaking patients.

PROTECTED HEALTH INFORMATION (PHI AND HIPAA)
For the purposes of this study we will collect the following Protected Personal Health Information: participant name, birth date, and zip code. We also intend to access the medical chart of all study participants to obtain relevant information about medical history. We have included a section on HIPAA authorization in our consent form.

WAIVER OR ALTERATION OF CONSENT PROCESS

Written informed consent will be required for all patients. There will be no waiver, or alteration of the consent process. Only English-speaking, adult patients, who are not cognitively impaired, and capable of consenting will be recruited.

QUALIFICATIONS TO CONDUCT RESEARCH AND RESOURCES AVAILABLE

There is allotted time for 44 scheduled cesarean deliveries each week at Northwestern Medicine Prentice Women's Hospital. We hope to recruit 72 patients in 1 year, which should be easily achieved, given there could potentially be over 2,000 scheduled cesarean deliveries in one year (3.4% recruitment rate). Recruitment can be performed by our research team members and research nurses. It can occur any day anesthesia fellows or investigators who have been trained in gastric ultrasound are present. Any anesthesia staff will be able to care of the patient in the operating room.