A Pilot Randomized Control Trial of Topical Capsaicin as Adjunctive Therapy for Nausea and Vomiting of Pregnancy

NCT05098067 – 10/17/22

Key Information

We are asking you to take part in a **research study**.

It is completely **voluntary**. You can choose not to participate.

It involves evaluating if **capsaicin cream** improves symptoms of nausea and vomiting in pregnancy.

You will be **randomly selected** to either capsaicin cream or placebo cream in addition to standard treatment for nausea and vomiting

It involves completing up to 6 **symptom severity scales** during your treatment. These will take about **1 minute** to complete

Women & Infants Hospital of Rhode Island

Informed Consent for Research

Project Title:	**Pilot Trial of Capsaicin Cream as an Adjunctive Therapy for Nausea and Vomiting of Pregnancy**	
Version Date:	**[10/26/2021]**	
Principal Investigator:	**Lauren Murphy, MD**	**Telephone: 210-722-2589**
	Maureen Hamel, MD	**Telephone: 508-479-9190**
Emergency Contact:	**Maureen Hamel, MD**	**Telephone: 508-479-9190**

Key Information about the Research

Please read this form carefully, it will provide you with important information about your participation in a research study. It describes the purpose of this research study, and the risks and possible benefits of participating.

If any of the statements or words in this form are unclear, please let us know. We are here to answer any questions. You have the right to discuss this study with another person who is not part of the research team before making your decision to participate in the study.

Taking part in this research study is up to you. Choosing not to participate will not impact your usual clinical care. You can change your mind at any time. You will not lose any services, benefits, or rights you would normally have if you choose not to volunteer. If you decide to take part in this research study, we will ask you to sign this form. We will give you a copy of this consent form. If you take part, you can leave the study at any time.

In the sections that follow, the word "we" means the study doctor and other research staff. The people in charge of this study are Dr. Lauren Murphy and Dr. Maureen Hamel. We will refer to these persons as the "researcher" throughout this form.

What is the study about?

The purpose of this study is to determine if topical capsaicin cream can be used as a treatment for nausea and vomiting of pregnancy.

What will be done and how long will it take?

If you agree to participate there will be no additional time added to your treatment. During your treatment you will either be given standard therapy and placebo cream or standard therapy and capsaicin cream. You will fill out survey's during your treatment about the severity of your symptoms. Your participation in the study ends once you are discharged from the hospital. There will be no additional costs for your treatment.

What are some of the benefits of taking part in this study?

You may or may not benefit from taking part in this study. Your symptoms could be shortened in their length or severity, you may require less medications; however we cannot guarantee that you will benefit from your participation. Others may benefit in the future from the information that is learned in this study

What are some of the risks of taking part in this study?

The main risks from this study are risks related to capsaicin cream. Capsaicin cream is known to be a safe drug with the most common side effect being skin irritation where it is applied. Rarely, a person could have a severe allergic reaction to the cream.

Additionally there are risks related to a possibility of a breach of confidentiality of your data. Every precaution will be taken to secure your personal information to ensure confidentiality.

What to do if you have Questions or Concerns:

You can take some time to think about whether you want to participate or not. You can talk with the study doctor or research staff if you have questions about the study. You can talk with family, friends, or your own doctor before deciding to participate.

If you would like to learn more about this study:

If you are interested in learning more about the study, please continue to read, or have someone read to you, the information below. It is important that you understand this information before making your decision about participation. If there is anything that you do not understand or if you have questions about the research, be sure to ask any member of the research staff or the study doctor.

A. The Nature, Duration and Purpose of This Study:

As previously stated, the purpose of this study is to determine if topical capsaicin cream is a useful treatment for nausea and vomiting during pregnancy. This is an off-label use of capsaicin cream. Currently the FDA rates capsaicin cream as a pregnancy category B drug meaning: Animal reproduction studies have failed to demonstrate a risk to the fetus and there are no adequate and well-controlled studies in pregnant women. Many medications commonly given to pregnant women fall in this class including Tylenol and prenatal vitamins.

Why are you being asked to take part in this research?

You have presented for treatment of nausea and vomiting during your first trimester of pregnancy. About 30 people will take part in the study at Women and Infants Hospital.

B. The Means By Which The Study Is To Be Conducted:

What will you be asked to do?

This is a randomized control trial. If you agree to be in the study we will ask you to do the following things.

- We will assign you by chance, like a coin toss, to one of two groups. Each group will receive standard treatment for their nausea and vomiting with the addition of a cream applied to their stomach. Neither you or the researcher will know what cream you received. You and the researcher cannot choose your study group. You will have a 50% chance of being assigned to either study group.

- You will otherwise receive conventional, standard treatment for your nausea and vomiting including IV fluids and commonly used anti-nausea medication, Reglan and if needed Zofran
- You will be checked on every 30 minutes regarding your symptom. You will record the severity of your symptoms on a scale every 30 minutes for up to three hours. This is not part of routine care but is part of the study. Should you feel your symptoms have improved to where you would like to go home or your symptoms have resolved, you will be discharged from the hospital.
- If your symptoms have not improved after 90 minutes you will receive the second IV medication, Zofran.
- If your symptoms have not improved after three hours further care will be determined by your provider

If you agree to take part in this study, we will ask you to sign the consent form before we do any interventions.

C. The Risks, Hazards, and Discomforts of the Study:

Taking part in a research study involves inconveniences and risks. The primary risks to this study are risks related with the medications you will receive. You will be monitored in a health care facility throughout duration of your treatment. Aside from the cream the other medications you may receive are commonly used to treat nausea and vomiting during pregnancy. If you have any questions about any of the possible risks listed below, you can talk to your study doctor or your regular doctor.

Examples:
Side effects of the **Capsaicin cream** include:

- Most common side effects are non-severe skin reactions occurring in >10% of people including, application site burning (14%), application site redness (2% to 63%), application site pain (10% to 42%)
- Less common side effects include:
    - Cardiovascular: High blood pressure (2%)
    - Dermatologic: Scratching of skin (2%), dryness of skin at application site (2%), bump on skin (application site: 6%), itching of skin (2%)
    - Gastrointestinal: Nausea (5%), vomiting (3%)
    - Local: Swelling at application site (2% to 4%), itching at application site (6%)
    - Nervous system: Headache (3%)
    - Respiratory: Cough (2%), respiratory tract infection (4%)
- In less than <1% of users:
    - Cardiovascular: Fast heat beat or feeling of extra heart beats
    - Dermatologic: Skin blister
    - Local: Application site allergic reaction
    - Nervous system: Dizziness

- Ophthalmic: Eye itching

Side effects of **Reglan** include:

- A serious reaction called “drug-induced extrapyramidal reaction” may occur. This can cause involuntary movements of your arms, legs, face and mouth
- Common but less severe reactions are drowsiness, restlessness, confusion, and headache
- More severe but less common reactions include changes in your blood pressure or heart rate

Side effects of **Zofran** include:

- A potentially life-threatening side effect of Zofran can lead to abnormalities in your heart rate that can cause life threatening changes in your heart beat
- Most common side effects include constipation, headache, dizziness, and fatigue

Other Potential Physical Risks:
Because this intervention is experimental there may be other side effects we do not know about yet. We can give you other medicines to make any side effects less serious or to make you feel better.

There is always a chance that any medical treatment can harm you. The research treatments/procedures in this study are no different. In addition to the risks described in this consent, you may experience a previously unknown risk or side effect. If we learn about other risks, we will let you know what they are so that you can decide whether or not you want to continue to be in the study.

Privacy and re-identification risks
Through all stages of sample and data collection, storage, sharing, and analysis, your privacy and confidentiality will be protected, with these exceptions: the research team is required to report child abuse and neglect, or substantial risk of harm to self or others to state or local authorities.

A number of efforts will be made to keep your information confidential. These are outlined in the Privacy and Confidentiality of this form. Despite these efforts, it may be possible to identify you based on the information in these databases and other public information (including information you tell people or post about yourself). The risk of this happening is currently very low. It is possible also that someone could get unauthorized access or break into the system that stores information about you. Every precaution will be taken to minimize this risk. There also may be other privacy risks that we have not foreseen.

D. The Possible Benefit You or Others:

Prospect of direct benefits: You may or may not benefit from taking part in this study. We cannot guarantee or promise that you will receive any direct benefit by participating in this study. Possible benefits to you include **reduction in your symptoms severity or duration, a decrease in the amount of medications you require.** The knowledge gained from this study may help doctors determine **if capsaicin cream is a useful treatment for nausea and vomiting in pregnancy** .Others may benefit in the future from the information that is learned in this study.

E. Possible Alternative Procedures:

You may choose not to take part in this research study. Participation in this study is voluntary.

You do not have to take part in this research study to be treated for **nausea and vomiting of pregnancy.** Other treatments available for your condition include: **lifestyle changes, ginger supplements, vitamin B6, doxylamine, and anti nausea medications.**

What if you want to stop?

Taking part in this study is your choice. You are free not to take part or to withdraw at any time for any reason. No matter what you decide, there will be no penalty or loss of benefit to which you are entitled. If you decide to withdraw from this study, the information that you have already provided will be kept confidential. You cannot withdraw information collected prior to your decision to stop participating.

If students are enrolled: You may choose not to be in the study or to stop being in the study before it is over at any time. This will not affect your class standing or your grades at **Brown University** You will not be offered or receive any special consideration if you take part in this research study.

If WIH employees are enrolled: You may choose not to be in the study or to stop being in the study before it is over at any time. This will not affect your job status at Women and Infants Hospital. You will not be offered or receive any special consideration if you take part in this research study.

The researcher may take you out of this study without your permission. This may happen because

- Your condition worsens.
- You no longer meet all the requirements of the study.
- New information suggests taking part in the study may not be in your best interests.
- Other administrative reasons

F. Financial Information

Who is funding this research study?:

The **Obstetrics and Gynecology Department** at Women & Infants Hospital is funding this research.

Please ask **Lauren Murphy or Maureen Hamel** if you have any questions about how this study is funded.

Will you be paid for your participation?

You will receive a $50 Amazon gift certificate upon discharge.

Will it cost you anything to participate?

While you are in this research study, the cost of your routine clinical care will be billed to you/your insurance company in the usual way. If your insurance does not pay for all the costs, you will be responsible for the remaining costs, including any co-payments and deductibles as required by your insurance. If you do not have insurance, you will be responsible for the costs of taking part in this study.

WIH has programs to help uninsured and underinsured families see if financial assistance is available. If you need financial assistance, you can talk with a financial coordinator.

There are no study-related costs to you for taking part in this research study.

Study Sponsor or WIH providing financial support:

WIH is providing financial support and material for this study. The following research drug and placebo that are used in this research will be paid by study sponsor or WIH:

- Cost of capsaicin cream
- Cost of placebo cream

What happens if you are injured as a result of your participation?

A research injury is any physical or mental injury or illness caused by being in the study. If you are injured by a medical treatment or procedure you would have received even if you were not in the study that is not a research injury. To help avoid research injury and added medical expenses, it is very important to follow all study directions carefully.

If you become ill or injured as a result of your participation in the study, you should seek medical treatment from your doctor or treatment center of choice. Doctors at the clinic or hospital can arrange for emergency medical care. You should promptly tell the researcher about any illness or injury. If you think you have been injured from taking part in this study, call **Lauren Murphy** at **210-722-2589**. She will go over things with you, let you know of resources that may be available, and give you information regarding what you may need to do.

The Hospital does not offer financial compensation or payment for illness or injuries due to participation in this research. You and your insurance company will be billed for the costs of any care or injuries. In case of illness or injuries resulting from this study, you will not lose any legal rights by signing this form.

G. Privacy and Confidentiality

How will your information be protected/kept confidential?

We will keep the records of this study confidential by storing your name and an assigned study identification on a secure internet server. A second database of your results will be stored separately based on your study identification number on a secure internet server so that your name and your personal information will not be directly linked to your name. We will make every effort to keep your records confidential. However, we cannot guarantee absolute confidentiality. Your personal information may be disclosed if required by law.

The following people or groups may review your study records for purposes such as quality control or safety:

- The Researcher and any member of her research team
- Authorized members of Woman and Infants Hospital who may need to see your information, such as administrative staff members and members of the Institutional Review Board (a committee which is responsible for the ethical oversight of the study)
- The sponsor or funding agency for this study
- Federal and state agencies that oversee or review research (such as the HHS Office of Human Research Protection or the Food and Drug Administration, if applicable)

The study data will be stored in a secure Care New England Server**.**

The results of this study may also be used for teaching, publications, or presentations at professional meetings to inform other doctors and health professionals. We will keep your identity private in any publication or presentation about the study. If your individual results are discussed, your identity will be protected by using a code number or pseudonym rather than your name or other identifying information.

By law, WIH is required to protect your private information. The investigator and staff involved in the study will keep your private information collected for the study strictly confidential. Please refer to the section at the end of this document titled “Authorization to Use or Disclose Health Information for a Research Study” that explains more specifically how your personal information will be protected.

***Reporting child/elder abuse*:** If, during your participation in this study, we have reasonable cause to believe that child or elder abuse is occurring, this will be reported to authorities as required by law. The researcher will make every reasonable effort to

protect the confidentiality of your research information. However, it might be possible that a civil or criminal court will demand the release of identifiable research information.

Reporting risk of harm to self or others: If, during your participation in this study, we have reason to believe that you are at risk for harming yourself or others, we are required to take the necessary actions. This may include notifying your doctor, your therapist, or other individuals. If this were to occur, we would not be able to assure confidentiality.

Use of your information in future research:

Your data might have your identifying information removed and be stored and shared for future research. They may be shared with researchers/institutions outside of WIH without additional informed consent after the identifiable private information, such as your name and medical record number, are removed.

Additional Information

A Data Safety and Monitoring Board, an independent expert, will be reviewing the data from this research throughout the study.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov as required by U.S. Law. This Web site will not include any information that can identify you. At most, the Web site will include a summary of the results of this research. You can search this Web site at any time.

H. Who to contact if you have questions or concerns about the research, or if you have questions about your rights as a research participant?

You can call us with any concerns or questions about the research. Our telephone numbers are listed below: If you have questions about the study, call the study doctor, **Lauren Murphy** at **210-722-2589.** You may also talk to your own doctor if you have questions or concerns.

The Institutional Review Board (IRB) at Women & Infants Hospital has reviewed and approved this study. The IRB reviews at all research studies and makes sure research subjects' rights and welfare are protected. If you want to speak with someone ***not*** directly involved in this research study, you may contact the Director of IRB Administration at Women and Infants Hospital at (401) 453-7677. You can talk to them about:

- Your rights as a research subject
- Your concerns about the research
- A complaint about the research

Women & Infants Hospital of Rhode Island

HIPAA Authorization

Authorization to Use or Disclose (Release) Health Information that Identifies You for a Research Study

Project Title:	**Pilot Trial of Capsaicin Cream as an Adjunctive Therapy for Nausea and Vomiting of Pregnancy**	
Principal Investigator:	**Lauren Murphy, MD**	**Telephone: (210) 722-2589**
	Maureen Hamel, MD	**Telephone: (508) 479-9190**

What is the purpose of this form?

State and federal privacy laws protect the use and release of your health information. **HIPAA** (Health Insurance Portability and Accountability Act of 1996) is United States legislation that provides data privacy and security provisions for safeguarding medical information. Under these laws, the Women and Infants Hospital cannot release your health information for research purposes unless you give your permission. Your information will be released to the research team which includes the researchers, people hired by the institution or the sponsor to do the research and people with authority to oversee the research. If you decide to give your permission and to participate in the study, you must sign this form for consent and authorization. Authorization is separate from and in addition to informed consent, although the two forms may be combined into one document. This form describes the different ways that WIH can share your information with the researcher, research team, sponsor and people with oversight responsibility. The research team will use and protect your information as described in the attached Consent Form. However, once your health information is released by WIH it may not be protected by the privacy laws and might be shared with others. If you have questions, ask a member of the research team.

By signing this document you are permitting Women & Infants Hospital (WIH) and the doctors, nurses and other staff involved in this research to use your personal health information collected about you for research purposes within our institution. Your Personal Health Information includes health information in your medical records, financial records and other information that can identify you. You are also allowing WIH staff to disclose your personal health information to outside organizations or people involved with the processing of this study as described in this document.

Why is my health information needed?

The researchers want to use your protected health information as part of the research protocol listed above and as described to you in the informed consent. If you sign this

document, you give WIH permission to collect, use or disclose (release) your health information that identifies you for the research study described above.

What health information will be used and disclosed as part of this research?

The health information that we may use or disclose (release) for this research includes: Information from your medical records at WIH including

- Estimated due date, gravidity and parity, BMI, Age
- Medications received, total treatment time, admission versus discharge
- Subjective improvement of symptoms, adverse reactions (skin irritation etc.)

Who may use or disclose my health information during the research?

Researchers and others need to review and/or record your research records to conduct this research, assure the quality of the data and to analyze the data. The health information listed above may be used by and/or disclosed (released) to:

The health information listed above may be used by and/or disclosed (released) to:

- Members of the research team and other authorized staff at WIH;
- People from agencies and organizations that perform independent accreditation and oversight of research.
- Groups monitoring the safety of this study (e.g. study monitoring group, DSMB)
- Your health information will be used or disclosed when required by law.
- Your health information may be shared with a public health authority that is authorized by law to collect or receive such information for the purpose of preventing or controlling disease, injury, or disability, and conducting public health surveillance, investigations, or interventions.
- No publication or public presentation about the research described above will reveal your identity without another authorization from you.
- If all information that does or can identify you is removed from your health information, the remaining information will no longer be subject to this authorization and may be used or disclosed for other purposes.

WIH is required by law to protect your health information. The research staff will only allow access to your health information collected for this study to the groups listed above for the purposes stated. By signing this document, you authorize WIH to use and/or disclose (release) your health information for this research. Some of those persons or organizations listed above who receive your health information may not be required to protect it in accordance with Federal privacy laws (such as the Privacy Rule). If permitted by law, they may be allowed to share your information with others without your permission.

Federal and state law requires us to review any inadvertent disclosure (release) or inappropriate access of your health information that we become aware of. If we become aware your information has been inadvertently disclosed (released)

or inappropriately accessed, Compliance Services at Care New England will complete an investigation to determine if there is a breach of your individual health information that requires us to notify you.

Am I required to sign this Authorization?

You do not have to sign this Authorization. Your decision to sign or not sign this form will not affect your standard medical treatment, payment or enrollment in any health plans or affect your eligibility for benefits. However, if you choose not to sign this form, you may not take part in this research study. Women and Infants Hospital will continue to provide you with health care services even if you refuse to sign this authorization form.

Can I withdraw my Authorization?

You may change your mind and revoke (take back) this Authorization at any time.

If you revoke this Authorization, you may no longer participate in the research described in this Authorization.

Even if you revoke this Authorization, WIH and Lauren Murphy may still use or disclose health information they already have obtained about you as necessary to maintain the integrity or reliability of the current research. Your request to revoke this Authorization becomes effective when WIH receives it.

To revoke this Authorization, you must submit a request in writing to the investigator: **Lauren Murphy, 101 Dudley Street, Providence, RI 02905 or lmmurphy@wihri.org**

Does my Authorization Expire?

This Authorization expires with the conclusion of the research study. By signing this form, you are giving us permission to collect your health information only for this research study (not for future unspecified research).

Will you be able to access your records?

You will be able to request access to the information we collect from you for the study when the study is completed. During your participation in this study, you will not be able to access the results of the tests, surveys, and evaluations we do for the research study. This will be done to prevent the knowledge of study results from affecting the reliability of the study. Your information will be available should an emergency arise that would require your treating physician to know this information to best treat you. You will have access to your medical record and any study information that is part of that record when the study is over or earlier, if possible. The investigator is not required to release to you research information that is not part of your medical record.

Signature Page
Consent to Take Part in this Research and Authorization to Use and Disclose Health Information for the Research

SIGNATURE OF PERSON OBTAINING AUTHORIZATION
The research study and Consent/Authorization to Use and Disclose Health Information form have been explained to you by:

_____
Name of Person Obtaining Consent

_____ _____
Signature of Person Obtaining Consent/Authorization Date

SIGNATURE OF SUBJECT
By signing this form, you are indicating that you have read the information in this Consent form and the Authorization to Use and Disclose Health Information for the Research form including risks and possible benefits; You have been given the chance to ask questions and your questions have been answered to your satisfaction; and you agree to participate in the research study and agree to allow your health information to be used and shared as described above. If you don't agree to the collection, use and sharing of health information, you cannot participate in this study.

_____
Name of Subject

_____ _____
Signature of Subject (**18 year or older**) Date

SIGNATURE OF TRANSLATOR (IF APPLICABLE)

_____
Name of Translator

_____ _____
Signature of Translator Date

SIGNATURE OF WITNESS (IF APPLICABLE)

_____
Name of Witness

_____ _____
Signature of Witness Date

Principal Investigator: Lauren Murphy, Maureen Hamel
IRBNet ID: 1763191-1

Overview: At the time of emergency department evaluation for a chief complaint of nausea or vomiting of pregnancy, we will enroll 30 women across Women and Infants Hospital in Rhode Island. Participants will be randomized to either adjunctive capsaicin cream treatment or placebo cream. All participants will receive an IV fluid bolus of 1000cc of lactated ringers, Reglan 10mg IV and will have 5g of the appropriate cream administered topically immediately after administration of the IV Reglan. If an additional agent is needed 8mg of IV Zofran will be administered.

Eligibility criteria will include pregnant women in the first trimester (0-14 weeks gestation) ages 18-50 YO presenting to the emergency room at Women & Infants Hospital in Rhode Island with a chief complaint of nausea and vomiting of pregnancy. Eligible participants will be English or Spanish speaking, and will not have taken an anti-emetic such as Reglan or Zofran within the 6 hours prior to presentation. Exclusion criteria will include allergy to Reglan, capsaicin or Zofran, another identifiable source for nausea and vomiting (i.e. gastritis, COVID, diabetic ketoacidosis), molar pregnancies, or patients with a history of gastroparesis or preexisting diabetes mellitus. Women who present to the emergency room with a chief complaint of nausea and vomiting of pregnancy will be approached for enrollment and if interested and eligible (as determined by a brief questionnaire), will be consented by a key study personnel. The questionnaire will be completed by the KSP obtaining consent and will be thrown away after determination of eligibility. The questionnaire will be completed in the subjects preferred language with interpreter services used as needed. No identifiable PHI will be on the questionnaire. Study personnel will consist of providers working in the Emergency Room at Women & Infants Hospital. These providers will receive education and training regarding the project's rationale and procedures. Once a patient is identified as eligible, the provider will consent interested women and obtain electronic consent. Women who identify Spanish as their primary language will be consented with the use of a certified in-person medical Spanish interpreter or Cyracom phone Spanish medical interpreters.

Study Aims: Nausea and vomiting is a common medical condition of pregnancy affecting 50-80% of pregnant women; this condition not only impacts a women's quality of life, but also is a significant driver of health care costs because of frequent office visits, emergency room visits, and preterm hospitalizations[1, 2]. Studies have estimated the economic burden of nausea and vomiting of pregnancy to be as high as $1,778,473,782 annually[2]. Hyperemesis gravidarum is an extreme form of nausea and vomiting of pregnancy and results in evidence of acute starvation (i.e. large ketonuria), and weight loss of at least 5% from a woman's pre-pregnancy weight[3]. Some studies note hyperemesis to be one of the leading causes of pre-term hospitalization second only to preterm labor[4]. Despite its prevalence, nausea and vomiting of pregnancy is one of the most challenging conditions to treat and medical regimens vary by geography and institution. Additionally, there is a paucity of data demonstrating effective therapies for this common medical complication.

Societal recommendations for treatment of nausea and vomiting of pregnancy describe step-wise approaches with multiple medications because no one medication or treatment regimen has demonstrated superior efficacy[3]. First line medications include daily vitamin B6 and doxylamine and then escalation to antiemetics. There are multiple classes of antiemetics

including, dopamine agonists (i.e. metoclopramide), phenothiazine medications (i.e. promethazine), and the serotonin inhibitor ondansetron. While these medications are generally accepted as safe in pregnancy, they are not without risk. Specifically, many antiemetics can result in extrapyramidal symptoms and QT prolongation. Importantly, the use of multiple classes of antiemetics can potentiate each individual medication's negative side effects.
Capsaicin cream, a potent TRPV1 agonist, is commonly used to relieve muscular and neuropathic pain. Recent studies have also implicated the TRPV1 receptor in the modulation of nausea and vomiting The TRPV1 receptor is located in both the central and peripheral nervous system. Though the mechanism for improving symptoms of nausea and vomiting is not entirely clear, it is hypothesized that activation of TRPV1 receptors and capsaicin sensitive nociceptors is associated with hormonal regulation, and modulation of neurotransmitters implicated in nausea and vomiting. Examples include inhibiting the pro-emetic neurotransmitter histamine, desensitizing vagal nerve cholinergic transmission, and reducing substance P in the chemoreceptor trigger zones[5,6].

Recently, the use of capsaicin cream has gained popularity in Emergency Medicine for the treatment of hyperemesis secondary to cannabis use with studies demonstrating significant reduction in symptoms 60 minutes after application of 0.1% capsaicin cream[7]. Capsaicin cream has an excellent safety profile with side effects predominantly limited to skin irritation and erythema at the application site. Importantly, it does not cause the neurologic or QT prolongation effects seen with the previously mentioned antiemetic medications. Additionally, animal studies have demonstrated that capsaicin cream does not have teratogenic effects and the FDA has classified it as category B, the same category as commonly used and prescribed antiemetics.

Although pregnant women have been excluded from large clinical trials using capsaicin cream to treat nausea and vomiting, there are small studies and case reports demonstrating safety and efficacy of both ingested and topical capsaicin in pregnancy. Yuan et al performed a randomized control trial of women between 22 to 33 weeks gestation with gestational diabetes mellitus (GDM) assessing the effects of oral capsaicin powder on pregnancy outcomes. The study demonstrated a decrease in large for gestational age newborns in the capsaicin group compared with the placebo group but did not demonstrate any adverse maternal or neonatal outcomes[8]. Additionally, a case series by Yosipovitch et al of topical capsaicin for treatment of acute lipodermatosclerosis and lobular panniculitis included a single pregnant individual in her second trimester. The patient was treated with 0.075% capsaicin cream five times a day for three weeks with the only adverse effect reported being minimal burning at the site of application[9]. Finally, Abedian et al used 0.075% capsaicin cream to treat intraoperative nausea during cesarean section without reported adverse effects on maternal or neonatal well-being and additionally found a statistically significant reduction in need for antiemetics in the treatment group[10].

While the data on the safety of capsaicin cream in pregnancy is mounting, its utility as an antiemetic has not been well studied in pregnancy. This proposal will be one of the first, if not the first to randomize pregnant women presenting with nausea and emesis to this safe, potential treatment. This pilot study could be the first step in revolutionizing the treatment of hyperemesis.

Our *long-term* goal is to find an effective treatment regimen for a common yet elusive medical complication of pregnancy while improving women's quality of life and reducing health-care costs. The *overall objective* of this application is to assess the effectiveness of capsaicin cream as an adjunctive medication in improving perceived nausea and vomiting symptoms as well as

decreasing the need for additional treatments and total time in the emergency room. We also want to determine the feasibility of this treatment as an adjunctive agent in the outpatient setting. Our *central hypothesis* is that women assigned to adjunctive treatment with capsaicin cream will have decreased time to symptom control, decreased need for additional treatment and decreased length of stay in the emergency department. We will test our central hypothesis by pursuing the following *specific aims*:

Aim 1: Determine whether adjunctive treatment with capsaicin cream decreases patient's perceived time to symptom control. *H1: Women treated with capsaicin cream will have decreased time to perceived symptom control as measured by a validated scale used to measure patient's perception of the severity of nausea and vomiting symptoms (i.e. VAS).*

Aim 2: Determine whether adjunctive treatment with capsaicin cream decreases the need for treatment with additional anti-emetics. *H2: Women treated with capsaicin cream will have decreased need for additional antiemetics.*

Aim3: Determine whether adjunctive treatment with capsaicin cream decreases length of stay in the emergency department. *H3: Women treated with capsaicin cream will have decreased time to discharge from the emergency department.*

It is anticipated that this investigation will demonstrate that women treated with capsaicin cream experience less distress due to their nausea and vomiting symptoms that women who receive routine care; that treatment with adjunctive capsaicin cream reduces perceived severity of symptoms more quickly than placebo leading to the decreased need for additional therapy; and that capsaicin cream decreases the total length of stay in the hospital compared to routine care.

Research Design: Key study personnel (KSP) at Women and Infants Hospital will identify and enroll women during their emergency department visit. Once a patient is identified as eligible, the KSP will approach and consent interested women. Women who identify Spanish as their primary language will be consented with the use of a certified in-person medical Spanish interpreter or Cyracom phone Spanish medical interpreter. Electronic consent will be obtained in English or Spanish as per patient preference.

Women who agree to participate in the study will be randomized using block randomization to one of two groups: treatment with IVF, Reglan and 0.075% capsaicin cream or treatment with IVF, Reglan, and placebo cream. Pharmacy will dispense medication to the research nurse/emergency room provider.

The capsaicin cream and the placebo cream are both unscented and are also the same color and texture; they will both be dispensed in identical packaging to ensure study personnel; ED providers and the participant are blinded to study assignment. All participants will receive an IV fluid bolus of 1000cc of lactated ringers, Reglan 10mg IV and will have 5g of the appropriate cream administered topically. Specifically, the emergency room provider will apply 5g of the cream to the participant's abdomen using a gloved hand immediately after administration of the IV Reglan. The time of cream application will serve as time 0 and the "Intervention start time."

Participants will indicate the severity of their symptoms immediately prior to administration of Reglan, at time 0 and every 30 minutes for a total of 120 minutes after administration of the first medications (or discharge) using a 10 cm **visual analogue scale (VAS)[11,12].** The scale will be provided in English or Spanish as appropriate. The scales will be provided on paper for subjects to fill out and will be marked with a unique patient identifier number. The completed scales will

be collected by KSP and stored in a designated project binder. If at the 90-minute time mark the patient does not report improvement of their symptoms, Zofran 8mg IV will be administered. If a participant's symptoms do not improve after Zofran administration, escalation of care will be at the discretion of the primary covering provider. A participant's request for discharge will be to indicate satisfactory improvement in a participant's perception of his/her nausea and vomiting symptoms. The time elapsed from the "Intervention start time" to request for discharge will be calculated to determine the primary outcome of "Time to symptom relief.

Given that this is a medication intervention study, we have asked Dr. Stephen Carr, Professor of Obstetrics and Gynecology at the Alpert Medical School of Brown University, member of the Division of Maternal Fetal Medicine and former member of the IRB at Women & Infants Hospital to serve as a Data Safety Monitor. Every three to six months he will review the unblended data, review any and all adverse events and ensure proper reporting to the IRB.

Analytical Plan: Variables as outlined below will be extracted from the participants chart:

- Estimated due date, gravidity and parity, BMI, Age
- Medications received, total treatment time, admission versus discharge
- Subjected improvement of symptoms, adverse reactions (skin irritation etc.)

The data will be analyzed with assistance from the Research Division of Obstetrics and Gynecology. We anticipate comparing treatment and placebo groups on all baseline characteristics to ensure effective randomization as well as mean times to symptomatic improvement, mean times to "satisfactory symptomatic improvement", mean length of stay, rate of additional medication administration, mean number of additional medications needed to treat symptoms and admission rates. We will evaluate patients' perception of severity of symptoms using the **VAS (Figure 2)**[11,12], a validated scale currently used in the post-operative and emergency room settings to assess patient's perception of the severity of his/her nausea and vomiting symptoms. The primary analysis will be intention-to-treat. We will test for group differences by T-test or Wilcoxon rank sum test for continuous variables and by Fisher's exact test for categorical variables. If censoring of time to improvement or length of stay occurs, we will estimate group differences by time-to-event approaches and the log-rank test. Setting alpha at 0.05 and power at 80%, a standardized mean difference in time until discharge of 1.1 (Cohen's *d*) will be detectable with 15 patients per group. While our efficacy estimate may not achieve statistical significance at the standard 5% level, estimates of means, standard deviations, and proportions will be used to inform sample size calculations for a larger trial.

Expected outcomes: Nausea and vomiting of pregnancy continues to be a significant cause of morbidity experienced by pregnant women and a large source of health care costs and usage during pregnancy. The majority of therapies are oral or IV medications with potential side effects when taken either alone or in combination. We are proposing the use of capsaicin cream, an easy to administer medication that does not require IV access or the ability to tolerate oral intake. If proven effective, this medication could be used to treat nausea and vomiting of pregnancy in the outpatient setting. Patients could easily self-administer it at home. It is anticipated that this investigation will demonstrate that women treated with capsaicin cream experience less distress due to their nausea and vomiting symptoms that women who receive routine care; that treatment with adjunctive capsaicin cream reduces perceived severity of symptoms more quickly than placebo leading to the decreased need for additional therapy; and that capsaicin cream decreases the total length of stay in the hospital compared to routine care. Through this study we will have a better understanding on the potential for capsaicin cream to be used as an adjunctive treatment for acute presentations of nausea and vomiting in

pregnancy. This project represents a pilot proof of concept study; thus the small sample size of N=30. We anticipate that 15 patients in each group will allow us demonstrate the efficacy of capsaicin as an adjunctive therapy to treat nausea and vomiting of pregnancy among patients with the most severe symptoms. Treatment for nausea and vomiting is always multi-pronged. If capsaicin as an adjunctive therapy is efficacious among the sickest of patients, then the data will inform the feasibility and acceptability of a future larger randomized control trial assessing the potential of capsaicin cream to be utilized as an adjunctive therapy for managing hyperemesis symptoms.

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Figure 1: Study Schematic

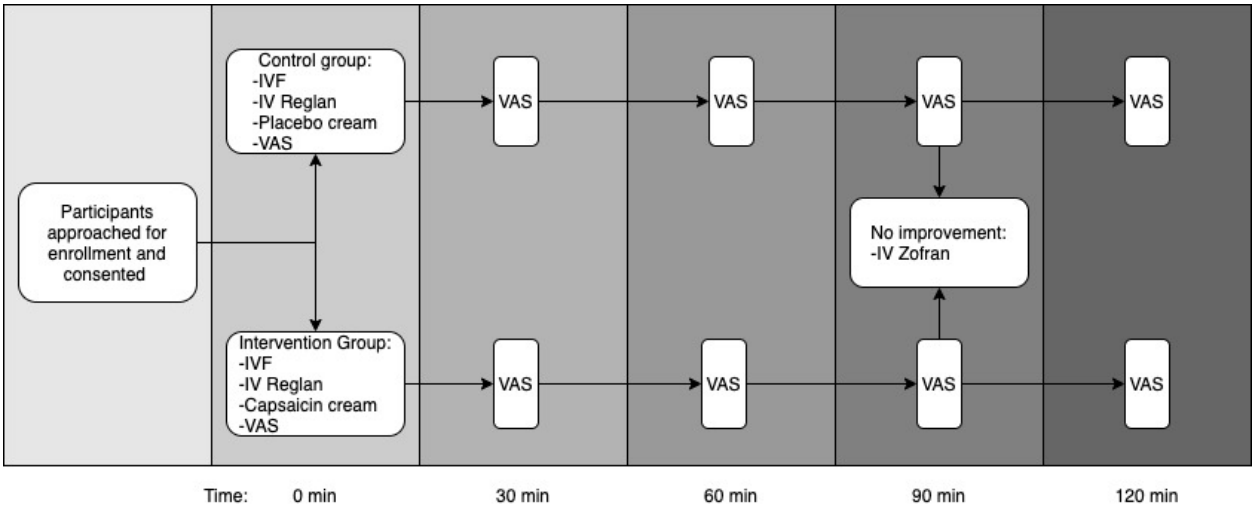

Figure 2: VAS Scale