A Randomized Trial to Determine if a Pre-operative Wash With a Chlorhexidine Cloth Reduces Infectious Morbidity in Patients Undergoing Cesarean Section

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Mount Sinai	Protocol Name:	A randomized trial to determine if a pre-operative wash with a chlorhexidine cloth reduces infectious morbidity in patients undergoing cesarean section
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	Study Number:	GCO#14-1410

- **Protocol Title**
  A randomized trial to determine if a pre-operative wash with a chlorhexidine cloth reduces infectious morbidity in patients undergoing cesarean section
- **Investigator**
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Brief Summary of Research (250-400 words):

Surgical site infections (SSI) are the second most common cause of nosocomial infections. In obstetric patients, infectious morbidity (i.e. SSI, endometritis) occurs in 5-10% of cesarean sections, which is 5-fold higher than vaginal deliveries.

Chlorhexidine, chemical antiseptic effective on gram positive and gram negative bacteria, reduces skin microflora/colonization but it is not clear if it decreases the risk of SSI. Chlorhexidine has both bactericidal and bacteriostatic mechanisms causing membrane disruption and is useful against fungi and viruses.

There are no randomized studies evaluating interventions to reduce SSI in patients who undergo cesarean sections.

The study will be offered to women who present for a scheduled primary or repeat cesarean section at Mount Sinai Medical Center. The eligible women will be randomized to use of a 2% chlorhexidine gluconate (CHG) cloth or placebo cloth (a fragrance free cleansing cloth) the night before and the morning of their scheduled procedure. Participants will be blinded to the arm in which they have been assigned. This study intends to show that the use of 2 CHG cloths prior to cesarean section will reduce the rate of SSI.

1) Objectives

The objective of this study is to determine if the use of chlorhexidine gluconate cloths prior to cesarean section reduce the rate of infectious morbidity (i.e. SSI, endometritis).

2) Background

Surgical site infections (SSI) are the second most common cause of nosocomial infections accounting for 15% of all nosocomial infections among hospitalized patients and 38% of nosocomial infections in surgical patients. In obstetric patients, infectious morbidity (i.e. SSI, endometritis) occurs in 5-10% of cesarean sections, which is 5-fold higher than vaginal deliveries. SSI is costly, as evidenced by a two-

fold increased risk of death from SSI. Additionally, there is increased risk of SICU admissions and emergency room readmissions.

Chlorhexidine is a chemical antiseptic that is effective against gram positive and gram negative bacteria and has been shown to reduce skin microflora/colonization. However, it is not clear if it decreases the risk of SSI and other postoperative morbidities. Chlorhexidine has both bactericidal and bacteriostatic mechanisms causing membrane disruption and is also useful against fungi and viruses. Further, chlorhexidine is thought to be more effective than other antiseptic agents because of its rapid action, persistent activity (even when exposed to bodily fluids i.e. blood), and residual lasting effect.

Historically, chlorhexidine has been studied and used in orthopedic and cardiac implant surgeries. Research on the use of chlorhexidine for SSI prevention in cesarean sections is limited. The national average for birth by cesarean section is approximately 32.8% of all births, and the number of deliveries by cesarean section at Mount Sinai Medical Center is comparable. This study intends to evaluate the effectiveness of a preoperative chlorhexidine gluconate (CHG) cloth application and its potential effect in reducing SSI in patients undergoing cesarean section. Patients will be randomized to one of two groups: cloth application with a pre-operative CHG cloth at home on the night before and the morning of surgery (approximately 3 hours prior to the scheduled procedure) or application of a placebo cloth (a fragrance free commercial cleansing cloth).

3) Setting of the Human Research

Research will take place at Mount Sinai Medical Center. Patients will be recruited 2 days before their scheduled cesarean section during their pre-admission appointment on labor and delivery, [redacted] of the Klingenstein Pavillion at 1176 Fifth Avenue.

4) Resources Available to Conduct the Human Research

Researchers will have access to all patients scheduled for a cesarean section at Mount Sinai Medical Center. About 1800 deliveries by cesarean section occur each year at Mount Sinai. Of these, approximately 1000 are scheduled cesarean sections. Accordingly, there should be approximately 1000 eligible patients per year. Based on our rate of SSI (6%) and the objective of a 67% decrease in SSI rates and expected rate of eligible patients who do not consent at 10%, 683 patients should be in each group for a total of 1365 participants. We aim to recruit 683patients per group to account for patient drop out or non-compliance.

Eligible study participants will be approached privately on the labor and delivery floor when they come to their pre-admission visit 2 days before their scheduled cesarean section. The nurse who sees patients at this visit will ask if she is interested in participating in the study. If she agrees the

nurse will notify a study team member to consent the patients and is not involved in the cesarean section surgery.

Sage Products Inc, a healthcare product manufacturing company, will be providing the CHG cloths and the placebo cloths, commercial cleansing cloths.

Each research staff member involved in this study has completed all training necessary to conduct human research and the research team has years of experience in clinical research and extensive experience conducting clinical research at Mount Sinai Medical Center.

5) Study Design

a) Recruitment Methods

Eligible study participants will be approached for enrollment during their pre-admission testing visit at the Martha Stewart Center at MSH or the patient's BPP visit at the MFM/OBGYN FPA practice at e E 98th Street.

Once a patient is consented, she will be randomly assigned to one of the 2 arms of the study: the eligible women will be randomized to use of a 2% chlorhexidine gluconate (CHG) cloth or placebo cloth (a fragrance free cleansing cloth). Participants will be blinded to the arm in which they have been assigned.

b) Inclusion and Exclusion Criteria

The study will be offered to women at > 24 weeks gestation who are scheduled for a primary or repeat cesarean section. Exclusion criteria include allergy to chlorhexidine unplanned or emergency cesarean section.

c) Number of Subjects

We aim to enroll 1356 participants, 678 patients in each group. About 1800 deliveries by cesarean section occur each year at Mount Sinai. Of these, approximately 1000 are scheduled cesarean sections. Based on our rate of SSI (6%) and the objective of a 67% decrease in SSI rates and expected rate of eligible patients who do not consent at 10%, we plan to enroll 1356 patients in total to account for drop-outs or non-compliance. This number was modified last year based on our sponsor monitoring report in order to account for patients who delivered early or forgot to complete the pre-op wipe treatment. We currently have 1,338 enrolled and need 18 more for recruitment completion.

d) Study Timelines

After informed consent has been obtained, the duration of the subject participation will occur from the time they present for preoperative admission

testing until 6 weeks post procedure. We expect to complete enrollment by September 1, 2019 and complete data analysis by November 1, 2019.

e) Endpoints

The primary outcome will be SSI and postpartum endometritis. Secondary outcomes include other maternal complications or interventions, neonatal ICU admissions, maternal length of stay or readmissions.

f) Procedures Involved in the Human Research

This study intends to evaluate the effectiveness of a chlorhexidine gluconate (CHG) shower in reducing SSI in patients undergoing cesarean section. Patients will be randomized to one of two groups: administration of a 2% CHG cloth at home on the night before and approximately 3 hours prior to cesarean delivery on the morning of the surgery or cloth with the placebo (commercial cleansing cloth). Patients will receive a phone call, text message, and/or email reminder to apply the wipes (method of PrepCheck reminder will be decided by the patient). Currently, there is no wash or cloth used prior to cesarean section as a standard of care.

Sage Products Inc will be blinding the study groups. The study team will be provided with pre-prepared packages that contain a 4 digit number indicating the product. Only Sage Products Inc will know which number indicates which group. Patients, recruiters, and statisticians will all be blinded. Once data has been analyzed, Sage Products Inc will inform the study teams as to which packages contain the CHG product number and which contain the placebo.

Each patient will be assigned a unique identification code. The code will be linked to the name and date of birth in an encrypted password-protected linking key code file which will be stored on the PI's personal network folder in the Hospital IT server, accessible by the PI only. The data will be stored in a separate password-protected database by the unique identification code. The database will be stored on a secure desktop at Mount Sinai hospital.

There is minimal risk associated with the use of CHG in a surgical setting. Use of CHG in surgery has been well described in the literature as safe with minimal risks. Enrollment in this study does not place a patient at increased risk over other patients undergoing a cesarean section. The only potential unforeseeable and minimal risk is an allergic reaction to the chlorhexidine gluconate.

Data collected will include demographic variables such as age, parity, BMI, race will be collected, as well as gestational age, number of previous cesarean sections, time from incision to delivery, type of anesthetic, and type of wound closure. Maternal outcomes including EBL, length of incision to delivery, length of operation, type of skin closure, type and use of prophylactic antibiotics, type of skin incision, type of skin closure, indication for cesarean, number of prior cesarean sections, and parity. Charts will be reviewed through the 6 week post partum visit in order to determine how well the skin at the incision site is healing. If patients do not visit Mount Sinai Medical Center for their 2 week wound check, they will be called and asked the following questions: Were you treated for wound infection? Did you experience wound separation or any other wound complications?

g) Specimen Banking

N/A

h) Data Management and Confidentiality

No specimens will be sent out or received in this trial.

All data is de-identified; patients are followed by subject number. Identifiable patient information (consent forms & consent documentation) are kept separately from any data collected. All consent documentation is stored in a locked cabinet at 5 East 98th Street, 2nd Floor. Identifiable enrollment statistics are kept in a password-protected computer (Excel) spreadsheet that is only accessible by members of the research team on a departmental J Drive.

Data will be analyzed on an intention to treat basis. Statistical analysis will be performed by SAS using X 2 test or Fisher exact test (categorical variables) and student t test or Mann-Whitney U test (continuous variables). Statistical significance will be set at $p<0.05$.

i) Provisions to Monitor the Data to Ensure the Safety of Subjects

Part I: Elements of a Data and Safety Monitoring Plan

MSSM Principal Monitor:
The principal monitor for this study is the PI:
Last Name: Stone
First Name: Joanne
Academic Title: Professor
Department: OB/GYN – Maternal Fetal Medicine
Mailing Address: [redacted]
Phone: 212-241-5681

Fax: 212-348-7438
E-mail: joanne.stone@mssm.edu

Dr. Joanne Stone has years of experience in research and clinical practice and is qualified to serve as the principal monitor to ensure the safety of participants. All adverse events, subject compliance with the protocol, drop outs, and all study data will be closely monitored and reviewed on an annual basis.

Standard of care and labor floor protocol will be followed in order to ensure standard of care for all cesarean sections.

If there is a temporary or permanent suspension of the study, in addition to the PPHS, the FDA and clinicaltrials.org will be notified.

j) Withdrawal of Subjects

There are no anticipated circumstances under which subjects will be withdrawn from the research without their consent.

6) Risks to Subjects

The risks to subjects are inherent to the cesarean section process itself outside of the study. The only difference in care is use of chlorhexidine gluconate in one arm of the study. This may result in a decreased rate of infection morbidity.
If used as instructed, the only potential unforeseeable risk is an allergic reaction to the chlorhexidine gluconate. Allergic reaction could include itching or hives, swelling in your face or hands, swelling or tingling in your mouth or throat, chest tightness, and/or trouble breathing.

The patients in our study are all scheduled for cesarean section by the patient's physician. The inherent nature of cesarean section requires an abdominal surgery. As standard of care, all women in this study will be provided with analgesia. In addition, enrollment in this study will not alter the current strategies regarding cesarean section.

There is always the risk of loss of confidentiality; however, there are procedures in place to minimize this risk. To ensure confidentiality, the following system will be adhered to: When subjects are enrolled in this study, they will be assigned a unique identification code. Corresponding medical record numbers for each code (key code) will be stored in a password locked document on the MFM server that can be accessed only by members of the research team. At the conclusion of the data extraction, the outcome variable will be assessed and the key codes to the medical record numbers will no longer be necessary and that information will be permanently erased from the key code file. Electronic data with identifiers will be encrypted according to Data Security Standards.

7) Provisions for Research Related Harm/Injury

The patients will receive standard obstetric care and have access to the obstetric staff (physicians, nursing) as well as all of the resources on the labor floor including the use of the ORs, blood bank, continuous fetal monitoring. Any potential adverse events are inherent to the operative delivery itself and regardless of the study. Any complications that occur during cesarean section will be managed by the obstetricians and anesthesiologists. As standard of care, a physician is present during a cesarean section and is experience in managing complications. The patient is billed as per standard scheduled cesarean section regardless of complications due to the surgery.

8) Potential Benefits to Subjects

Direct benefit to subject is unknown. However, the potential benefit is that we may find a reduction in infectious morbidity related to the cesarean section surgery.

9) Provisions to Protect the Privacy Interests of Subjects

The patients will be approached by the nurse during pre-operative appointment to determine if they are willing to be included for randomization. Their participation will not require any additional examinations. All research-related discussions will be held in a private location. Any questions will be answered and fully discussed to maximize patient comfort. If they choose to participate they will be randomized and receive care within the accepted standards. If a patient must be called to find out how the wound is healing, the research team members placing the class will not leave a message or speak to anyone except the patient herself. When called, she will be asked if she can discuss the research study at that time, ensuring patient privacy and comfort.

10) Economic Impact on Subjects

There are no foreseeable costs that subjects may incur through participation in the research.

11) Payments to Subjects

There will be no payment to subjects.

12) Consent Process

The patient will be consented during the pre-operative appointment and informed consent will be obtained in a private location. As eligible participants had been scheduled for cesarean section prior to arrival, the patient's doctor has already decided that this procedure is necessary and planned. A copy of the consent form will be available in referring doctor's offices and the OB clinic, so that subjects will have some information about the study ahead of time, although consent will be

obtained at the time of pre-admission testing. Study participants can be English or Spanish speaking. Resources to translate the consent in Spanish are available. We will be following SOP HRP-090 Informed Consent Process for Research.

13) Process to Document Consent in Writing

Consent will be documented in writing on the form. A copy of the signed informed consent will be placed in the patient's chart along with a brief progress note indicating study enrollment with a brief discussion of the consent process.

14) Vulnerable Populations

Include	Exclude	Vulnerable Population Type
	X	Adults unable to consent
	X	Individuals who are not yet adults (e.g. infants, children, teenagers)
	X	Wards of the State (e.g. foster children)
X		Pregnant women
	X	Prisoners

15) Multi-Site Human Research (Coordinating Center)

N/A

16) Community-Based Participatory Research

N/A

17) Sharing of Results with Subjects

N/A

18) External IRB Review History

N/A

19) Control of Drugs, Biologics, or Devices

N/A