IRB Submission AAAR4891
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Title: The effect of vaginal preparation with chlorhexidine gluconate vs. povidine-iodine vs. saline on vaginal bacterial colony counts in pregnant women

Study Purpose and Rationale

Cesarean delivery is the most common major surgical procedure performed in the United States, with one in three babies delivered by cesarean. Women who deliver by cesarean are 5 to 20 times more likely to develop postpartum endometritis than women who deliver vaginally.

Those women who labor prior to cesarean delivery are at greatest risk of infectious complications. Although the use of prophylactic systemic antibiotics prior to cesarean has significantly reduced the risk of endometritis, over 10% of women who undergo cesarean after the onset of labor will develop postpartum endometritis [1, 2]. These infections may lead to extended intravenous antibiotic therapy for new mothers, prolonged hospital length of stay, and increased health care expenditures [3].

At present, preoperative abdominal skin antisepsis and systemic antibiotic prophylaxis are routinely adopted strategies to reduce postoperative infectious complications. Multiple studies have also examined the effect of vaginal preparation (or washing) with povidine-iodine prior to cesarean delivery on postpartum endometritis and infectious complications. A 2014 Cochrane review of seven trials randomizing over 2500 women found that vaginal preparation immediately prior to cesarean significantly reduces the rate of post-cesarean endometritis from 8.3% in the control group to 4.3% in the vaginal preparation group (RR 0.45, 95% CI 0.25-0.81) with even greater effects observed in a smaller subset of women with ruptured membranes [4]. A review of evidence-based practices for cesarean delivery recommended vaginal preparation with iodine-base solution at the time of cesarean with a USPSTF grade of B (moderate certainty that the net benefit was moderate to substantial) [5]. Likewise, a 2015 review of evidence-based practices to reduce surgical site infections after cesarean delivery published in Infection Control & Hospital Epidemiology included preoperative vaginal cleansing among six interventions reviewed in good-quality articles with “strong” strength of evidence for effectiveness [6]. And finally, a recently published meta-analysis of pre-cesarean vaginal cleansing, which included sixteen trials of nearly 5,000 women, also found a significant reduction in endometritis with vaginal cleansing compared to placebo (RR 0.52, 95% CI 0.37-0.72). The authors concluded that preoperative vaginal cleansing with povidone-iodine 10% should be performed prior to all cesarean deliveries in women in labor and with ruptured membranes [7].

Despite this evidence, vaginal preparation immediate prior to cesarean delivery is not widely practiced. Among 167 maternal-fetal medicine fellows who responded

to a survey of preferred techniques at cesarean delivery in 2012, only 5% included pre-operative vaginal preparation among their preferences [8].

In addition to increasing acceptance of this practice, questions remain about the best antiseptic agent for reducing microbes in the vaginal mucosa. Although the majority of studies published on vaginal preparation at the time of cesarean have used povidone-iodine solutions, there is evidence that chlorhexidine preparations may be superior antiseptics. A recent randomized controlled trial published in the New England Journal of Medicine found that chlorhexidine-alcohol was superior to iodine-alcohol abdominal preparations at the time of cesarean for reducing the risk of surgical-site infections [9]. Furthermore, povidine iodine is contraindicated in patients with severe iodine allergy and its antiseptic properties may be affected by both vaginal pH and the presence of blood [10].

There is one published randomized control trial that compared povidone iodine to chlorhexidine for vaginal antiseptis prior to vaginal hysterectomy. Unlike vaginal preparation at the time of cesarean delivery, vaginal antiseptic preparation prior to hysterectomy in gynecological surgical is standard of care. This study showed that chlorhexidine solution was more effective than povidone iodine at reducing bacteria colony counts in the operative field [11].

Current practices
Vaginal preparation or washing in women undergoing cesarean who are not laboring or have rupture of membranes is not standard of care or indicated by current evidence. A vulvar and perineal wash with povidine-iodine solution is routinely perfomed immediately prior to all vaginal deliveries at our institution; however, this is not evidence-based or protocolized. In addition, vaginal preparation with povidine-iodine (or chlohexidine, according to surgeon preference) is standard of care prior to vaginal procedures in pregnant and postpartum women such as cervical cerclage, chorionic villus sampling, or dilation and curretage for postpartum hemorrhage.

Pre-cesarean vaginal preparation is strongly supported by the current evidence discussed above to reduce rates of post-operative endometritis in women in labor or with ruptured membranes prior to cesarean. This is standard of care at certain institutions, and recently has been made standard of care at CHONY by instituting a new Perinatal Practice Guideline; however, because this is a relatively new initiative implementation may not yet be 100%.

Purpose
The purpose of this study is to see whether chlorhexidine is superior to povidine-iodine vaginal antisepsis at reducing bacteria colony counts in women undergoing cesarean by comparing three groups: vaginal washing with chlorhexidine, vaginal washing with povidine-iodine, and vaginal washing with saline alone.

Study design

This is a prospective trial of vaginal preparation (or vaginal cleansing/washing) on pregnancies admitted to CHONY Labor & Delivery unit for cesarean delivery *with three arms.* Randomization allocation would be performed in 1:1:1 fashion for vaginal preparation with chlorhexidine gluconate, povidine-iodine, and saline washes. A saline wash group is included to determine if the act of cleansing the vagina with a sponge alone reduces bacterial colony counts.

Primary outcome

- Aerobic and anaerobic post-preparaton vaginal bacterial colony counts in each group

Secondary outcomes

- Baseline aerobic and anaerobic vaginal bacterial colony counts
- Change in aerobic and anaerobic bacterial colongy counts within each group
- Clinical infectious outcomes (although this study is not powered to detect these differences)

Inclusion criteria (intervention groups)

- Pregnant women admitted for cesarean delivery
- Gestational age ≥ 34 weeks
- Maternal age greater than or equal to 18 years

Exclusion criteria (intervention groups)

- Rupture of membranes or active labor
- Chorioamnionitis (prior to enrollment)
- Recent (within 4 weeks) antibiotic exposure
- Maternal HIV infection or other known immunocompromised state
- Placenta previa or accreta
- Known allergy to shellfish or iodine
- Known allergy to chlorhexidine gluconate

Sampling (for the intervention groups these procedures will be performed in the operating room after anesthesia is placed)

- Three vaginal swabs of posterior fornix (aerobic culture, anaerobic culture, and quantitative PCR) taken immediately prior to vaginal preparation using sterile technique (this will be the only step for the laboring group).
- Vaginal preparation or wash performed over 30 seconds with three sponge sticks soaked in 1) low concentation chlorhexidine gluconate 0.5% solution; 2) povidine-iodine 10%; or 3) saline, according to randomization allocation.
- Additional three vaginal swabs of posterior fornix taken at 5-15 minutes after vaginal preparation is completed using sterile technique

Solution preparation

- A chlorhexidine gluconate 0.5% solution will be prepared by combining chlorhexidine gluconate 4% solution (1 part) with normal saline, i.e. sodium chloride 0.9% (7 parts).
- Povidine-iodine 10% and normal saline will be used directly as the products listed in the drugs/biologics section of the RASCAL IRB submission.

Data collection

- Baseline maternal demographic and pregnancy information will be collected at the time of sample collection (after consent is obtained) by abstraction from the electronic medical record
- Retrospective chart review of maternal and neonatal infectious outcomes at the time of discharge and at the time of the postpartum visit.

Statistical procedures and sample size

To our knowledge, this is the first study to assess vaginal bacterial counts in pregnant women after an antiseptic preparation. Therefore, we have selected a sample size of 10 women in each group for this pilot study.

Due to recent research that has shown race and ethnic-related differences in the vaginal microbiome of reproductive-aged and pregnant women [12, 13], our study will include equal numbers of Hispanic and African American women in each group.

The difference in change in CFUs pre and post intervention will be compared between groups.

Potential risks/benefits/alternatives

Risks:
The greatest risk of participating in the study is experiencing an allergic reaction or localized reaction/irritation to the solution used.

1) Chlorhexidine arm:
Chlorhexidine gluconate solution has an overall low rate of adverse or allergic reactions. All women undergoing non-emergent cesarean delivery at our institution receive abdominal preparation with chlorhexidine-alcohol (unless there is a known allergy) consistent with current evidence of its effectiveness and safety [9]. Chlorhexidine gluconate is not FDA-approved for use on mucosal surfaces. However, chlohexidine with low concentrations of alcohol (4% or less) are safe and effective for vaginal use. The off-label use of chlorhexidine solutions for vaginal preparation is supported by the American College of Obstetricians and Gynecologists in the setting of iodine allergy or surgeon preference [14]. At our institution, chlorhexidine vaginal preparation is routinely used at the time of gynecologic surgery according to surgeon preference. In addition, chlorhexidine-based mouthwashes are approved for use on oral mucosal surfaces in the treatment of gingivitis and periodontitis.

Of note, there is an FDA warning from February 2017 of rare but serious allergic reactions to *skin* antisepsis with chlorhexidine gluconate. However, this has not to our knowledge been reported with vaginal preparation, which generally uses a much lower concentation of chlorhexidine. There have been numerous large prospective published studies on chlohexidine vaginal washing or irrigation in thousands of laboring pregnant patients (these studies had different research aims and therefore are not included under the study purpose and rationale) with no reported adverse effects [15-19].

2) Povidine-iodine arm
Povidine-iodine has an overall low rate of adverse or allergic reactions. In seven trials randomizing over 2800 women to povidine-iodine vaginal preparation prior to cesarean delivery, there were no reported side effects [4]. However, vaginal irritation or reaction is a possible side effect. All pregnant women undergoing vaginal procedures (such as chorionic villus sampling or cervical cerclage) receive vaginal preparation with povidine-iodine. In addition, it is routinely used in gynecologic procedures and surgery according to surgeon preference.

3) Saline arm
There is minimal risk with a vaginal saline wash. Localized irritation or minor discomfort may be possible due to sponge stick washing.

Finally, for all three arms, there is the potential risk of loss of confidentiality of sensitive health information, however this is unlikely. A code number will be used to separate data, biological samples, and health information from the participant's

name and other potential identifiers. The research file that links the code number to the patient's name will be kept in a locked cabinet, encrypted data file, or password-protected computer, and only the investigator and authorized study staff will have access to the file.

Benefits:
There are no personal or direct benefits from taking part in this study. However, the information collected from this research may help others in the future.

Alternatives:
Women may decline to participate in the study and undergo routine care on labor and delivery. Declining to participate will not impact their pregnancy, intrapartum or postpartum care.

Compensation:
The thirty participants undergoing vaginal preparation in the study will receive $50 in cash for their time and effort.

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