Post-Cesarean Endometritis and Misoprostol: Is Fever a Marker of Infection or Side Effect of Misoprostol?

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Abstract:

Introduction:

Endometritis, a polymicrobial infection resulting from ascending cervicovaginal bacteria into the uterus, complicates 6-27% of cesarean deliveries. A recent meta-analysis showed a reduction in endometritis in women who received 30 seconds of vaginal cleansing (4.5% vs 8.8%). Our study will look at the rates of endometritis from two time periods – prior to and after the implementation of vaginal cleansing at time of cesarean delivery. We will also investigate the influence of misoprostol on the clinical diagnosis of post-cesarean endometritis.

Methods:

Retrospective chart review was performed on 580 women undergoing cesarean delivery prior to, an interim group between the two periods, and after the policy change. The policy change required 30 seconds of vaginal cleansing with povidone-iodine immediately prior to Cesarean-section. Administration of 400 μg buccal Misoprostol was also recorded in each period. Statistical analysis was performed to calculate odds ratios of the primary outcome, endometritis, which is defined as either a diagnosis code or having three or more symptoms.

Results:

There were 207 patients in the pre-policy group and 149 patients in the post-policy group, and 220 in the interim group. The frequency of fever was not found to be statistically significant between all study periods. The frequency of endometritis with misoprostol administration was 8% and 3% excluding misoprostol (P=0.01). During all three time periods, the odds of receiving a diagnosis of endometritis was 3 times higher if a subject received misoprostol (OR 3.2, P=0.004).

Conclusion/Implications:

The frequency of fever was not significantly different, however, rates of endometritis increased with misoprostol administration. Since the odds of being diagnosed with endometritis was 3 times higher if a subject received misoprostol, we can conclude that misoprostol was a cofounder in the original study. There is a possibility that the diagnosis codes were wrong in the charts or that the rates of fevers lead to endometritis being frequently diagnosed. More data

analysis will be needed to determine whether either of these policies produce clinically significant benefits.

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Background/Introduction:

Cesarean delivery of a neonate is one of the most common surgical procedures performed in the United States. Incidence of cesarean deliveries in 2015 was estimated by the CDC to be 32.0% of all deliveries with over 1 million procedures performed per year. This increase in incidence has been associated with the increase of multiple gestation pregnancies as well as women electing to have a cesarean delivery. Over the past 50-years, the safety has improved which could explain why more women have an elective cesarean delivery. During this time, the routine use of antibiotics has been introduced which has reduced rates of endometritis.[3]

One cause of infection after a cesarean delivery is endometritis which is an infection of the uterus. It is a common cause of postpartum febrile morbidity. The microbiology is usually polymicrobial and can be a result from ascending bacteria from the vaginal canal. The risk for endometritis does increase after the onset of labor as a risk factor for this infection is prolonged rupture of membranes (>18 hours). Endometritis is formally defined as an infection of the endometrial layer of the uterus. Clinical features include fever, tachycardia, midline lower abdominal pain, and uterine tenderness. Diagnosis is largely clinical and based on the presence of postpartum fever that cannot be attributed to another etiology after a thorough history and physical examination.

Since this is the most common cause of infection in the postpartum period, there has been research that has been aimed at reducing the rates of endometritis. A decrease in endometritis was > 60% in both elective and non-elective groups with the use of prophylactic antibiotics has been described.[1] These antibiotics could be a single dose of ampicillin or a first-generation cephalosporin.[3] The same review also reviewed the use of preoperational vaginal preparation with an iodine solution and stated that it should be considered. This was based on a Cochrane review that evaluated four trials. This review found that with immediate preoperational vaginal preparation there was a significant reduction in endometritis (4.5% vs 8.8%)[3].

With this recommendation in mind, we did a literature review to see how preoperational vaginal cleansing fared in trials. The first trial showed a decrease in endometritis with vaginal cleansing using an iodine solution, however, their findings were not statistically significant.[5] Another randomized control trial found that rates of endometritis was 7.0% of those who received preoperative vaginal preparation and 14.5% of controls.[5] Adjusted odds ratio for developing endometritis after a vaginal preparation was 0.44 (95% CI 0.193-0.997).[5]

With these conflicting results, we turned again to the literature to see if iodine solutions do indeed kill the type of flora found in the vaginal canal. A study looked at the reduction of bacterial organisms before and after the use of a betadine scrub in 50 premenopausal patients.[7] 281 species of organisms were isolated from samples taken from the vagina before the scrub for an average of 5.62 types per patients. This includes gram negative bacilli, aerobic and anaerobic gram positive cocci, especially Enterococcus species. After the betadine scrub, 4 types of organisms were obtained 4 of the 50 patients while 46 yielded no growth. The reduction was statistically significant with a p value of < 0.0001.[7] This study helps show that we do know that iodine can kill the type of organisms that are normally the cause of endometritis.

Another randomized control trial looked at the use chlorhexidine vaginal irrigation for the prevention of endometritis. They found that the rates of infection did not differ significantly between the two groups.[11] They did find that the benefit of the vaginal rinse was greater if it was performed after rupture of membranes with a relative risk of 0.5 (95% CI 0.3 to 0.8).[11] Another study looked at the use of vaginal metronidazole did report a lower incidence of endometritis but that study was limited to its small sample size.[8]

During the original study, a period prior to after the implementation of vaginal cleansing was studied to see if there was a reduction of endometritis rates. There was paradoxically found an increased incidence of both fevers and endometritis in the post-policy during. Between these periods, the routine use of 400 µg of buccal misoprostol was used after cesarean delivery was implemented. Misoprostol is a Prostaglandin E_1 analog that was under the brand name of Cytotec™. It has many indications for use in obstetrics such as in medical abortions and for the prevention of postpartum hemorrhage due to its effect on the uterus.

There was a policy introduced in April 2016 at Maricopa Integrated Health System that supported the routine use of 400 µg of misoprostol after cesarean deliveries to reduce the incidence of postpartum hemorrhage based on literature supporting its use. It has a longer half-life than oxytocin which is standard practice for prevention of postpartum hemorrhage, so it was felt to be a potentially useful adjunct to prevent this outcome. It causes uterine contraction but can cause some unwanted side effects such as fever, shivering, and diarrhea. Fever usually peaks between 1-2 hours after administration and gradually subsides within 2-6 hours. With this in mind, we wondered if the side effect of fever with misoprostol can be mistaken for an infection. This could be confusing since endometritis is a clinical diagnosis. In a study using fever as a marker for intrauterine infection, the researchers found that fever had a sensitivity of 55% and specific of 58% for intrauterine infection positive predictive value of 4% and negative predictive value of 98%.[6]

Three randomized control trials were found which looked at the use of misoprostol as an adjunct along with oxytocin in reducing the incidence of postpartum hemorrhage. Both looked at groups of women who either receive misoprostol and oxytocin or just oxytocin. The first study looked at women undergoing cesarean delivery and used two tablets 200 µg of sublingual misoprostol. They found that most frequent adverse effects were shivering and pyrexia defined as a temperature greater than 38˚ C.[2] Relative risk was 3.8 (95% CI 2.0-7.2) for shivering and 3.3 (95% CI 1.1-9.8) for pyrexia.[2] The second study also divided their subjects into one group receiving both 400 µg of misoprostol and 20 U of oxytocin or just receiving 20 U of oxytocin. The women in the group receiving misoprostol were 7.4 and 9.0 times more likely to experience shivering and fever respectively.[13] The third study looked at the use of misoprostol in the active management in the third stage of labor during a vaginal delivery. They found that there was a significantly increased incidence of fever in the group that received misoprostol (30.4% vs. 6.3%, $p< 0.001$).[9]

At Maricopa Integrated Health Systems (MIHS), the original study explored the use of preoperational vaginal cleansing in the reduction of the rates of endometritis looking at two time periods. The first time period was before a policy was implemented of performing preoperative vaginal cleansing from July 2015 to November 2015 and the second time period is

after the policy was implemented from February 2017 to June 2017. This retrospective chart review included 353 charts (204 pre-policy and 149 post policy). They found there was an increase in the incidence of fever between the two groups with the incidence being 4.5% in the pre-policy group compared to 22.2% in the post-policy group. Between the two time periods, a policy was implemented for the routine use of misoprostol 400 μg after cesarean delivery in April of 2016. Since misoprostol is a known pyretic, the new question that this study looks at is whether or not misoprostol was a potential cofounder in the original study.

Methods:

The original study is a retrospective chart review which looked maternal outcomes from women who underwent cesarean delivery during two time periods. The first period is prior to the implementation of the vaginal cleansing policy ranging from July 2015 to November 2015 and after the implementation of the vaginal cleaning policy ranging from February 2017 to June 2017. There were 207 charts reviewed in the pre-policy period, 149 charts reviewed in the post-policy period, and 224 in the interim period. The inclusion criteria included all women undergoing non-emergent cesarean delivery (Category II-IV) and had postpartum visit. The exclusion criteria include allergy to iodine containing solutions and planned cesarean hysterectomy. Definition of the outcome measure was endometritis which is clinically defined as postoperative fever ≥ 38˚C plus fundal tenderness, in the absence of clinical or laboratory evidence of alternative source of infection, and wound infection. Endometritis was defined in this study as either having a diagnosis code of endometritis or having 3 or more symptoms. These symptoms are defined as fever, tachycardia, and/or fundal tenderness.

The current study collected additional data regarding misoprostol use from three time periods, pre, interim and post depicted in figure 1 in the results section We added an interim group to the study which was from February 2016 to June 2016 during which misoprostol prophylaxis was phased-in. The total number of charts reviewed was 602 spanning all three time periods and included a larger number of subjects in the post time period. This included whether or not a dose of misoprostol 400 µg was used along with the date and time of administration was recorded. The presence or absence of a fever within the first 24 hours was also recorded along with the time, date, and degree of the temperature. Fever was again defined as being greater than or equal to 38 ˚ C. The fevers were then graded according to the follow scale: 1. Likely: onset within 2 hours and resolution after 6 hours. 2. Possible: fever 2-6 hours after administration. 3. Not likely but possible: fevers 6 to 24 hours after administration. 4. Unlikely fever 24 hours or after and 5: fever in the absence of misoprostol administration.

Statistical analysis was performed to calculate odds ratios of the primary outcome defined as endometritis as well as fever. The odds ratio was also calculated of the primary

outcome of endometritis in relation to those who received misoprostol to try to access its effects.

Results:

Fever and Endometritis

Looking at the rates of fevers across the study period, we found that there was no significant difference between periods despite what the original study had shown. Incidence of fever in the pre-policy period was 6%, interim 1 had an incidence of 7%, Interim 2 was 9% and Post-policy was 8% (p=0.8875. In the pre-policy group, 1.5% of patients had endometritis defined as a diagnosis code or 2+ symptoms while 6.5% of patients in the post policy group had the same (P>0.016). Breaking down the diagnosis and symptoms groups, 1.5% had an endometritis diagnosis code and 1.5% had 2 or more symptoms in the pre-policy group while 6.0% had an endometritis diagnosis code and 7.0% had 2 or more symptoms in the post-policy group. The difference rates of endometritis were statistically significant with a p value=0.0497. When comparing study groups, we found no statistically different between pre-policy and interim 1 (p=0.6468), interim 1 and interim 2 (p=0.213), and interim 2 and post-policy (p=0.6242). Figure 1 shows the breakdown of each policy period along with dates. Graph 1 shows the difference in the percentages found in the original study and the current study. Graph 2 shows the percentage of fever across time periods. There were no significant differences in fever frequency across the periods. Graph 3 shows the percentage of endometritis across study periods, with a significant difference across the time periods, p=0.04. When the time periods prior to misoprostol administration were compared to those after that intervention, pre-policy and interim 1 versus interim 2 and post policy the frequency of endometritis was increased, 2% versus 6%, p=0.01. Also, no significant differences were found when comparing pre-policy vs interim 1 or interim 2 vs post-policy.

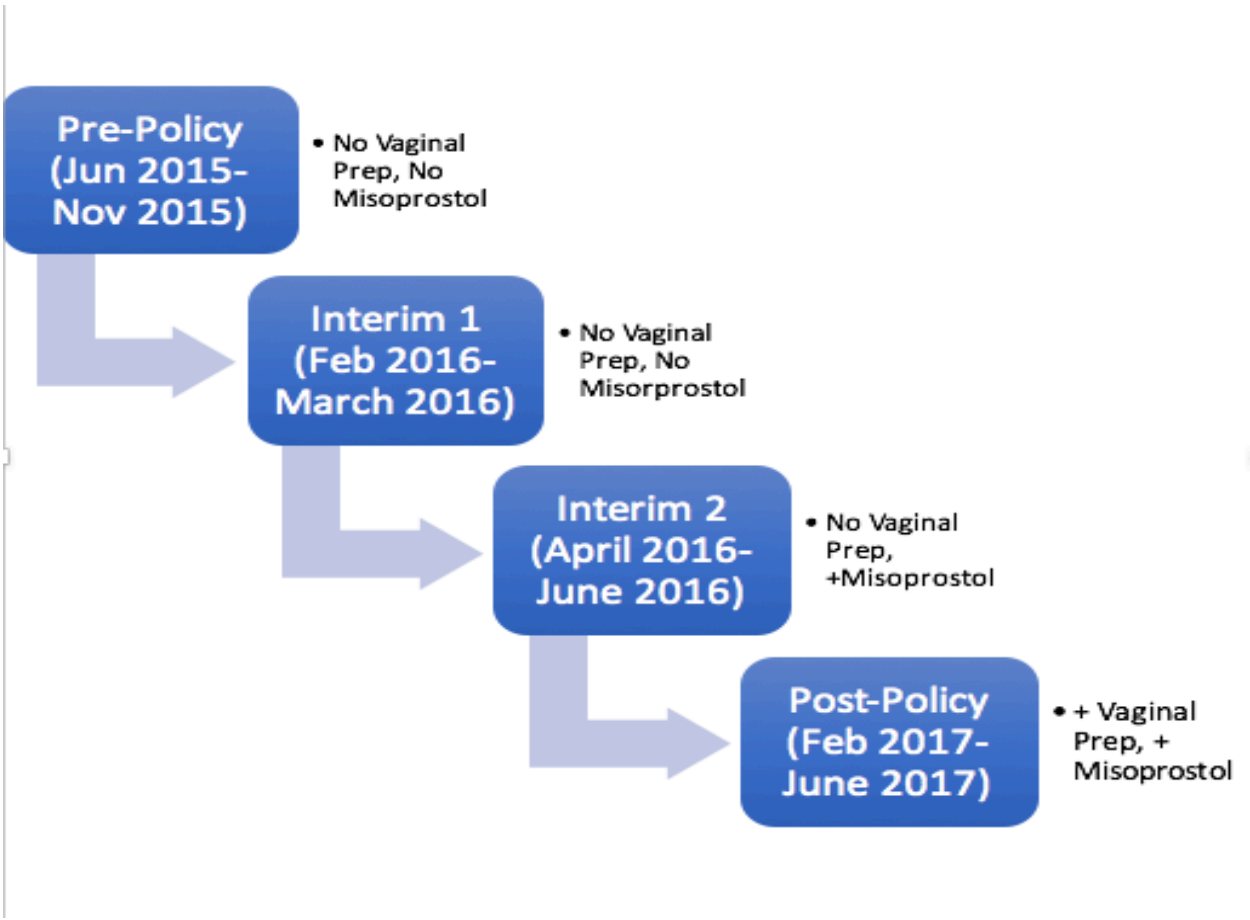
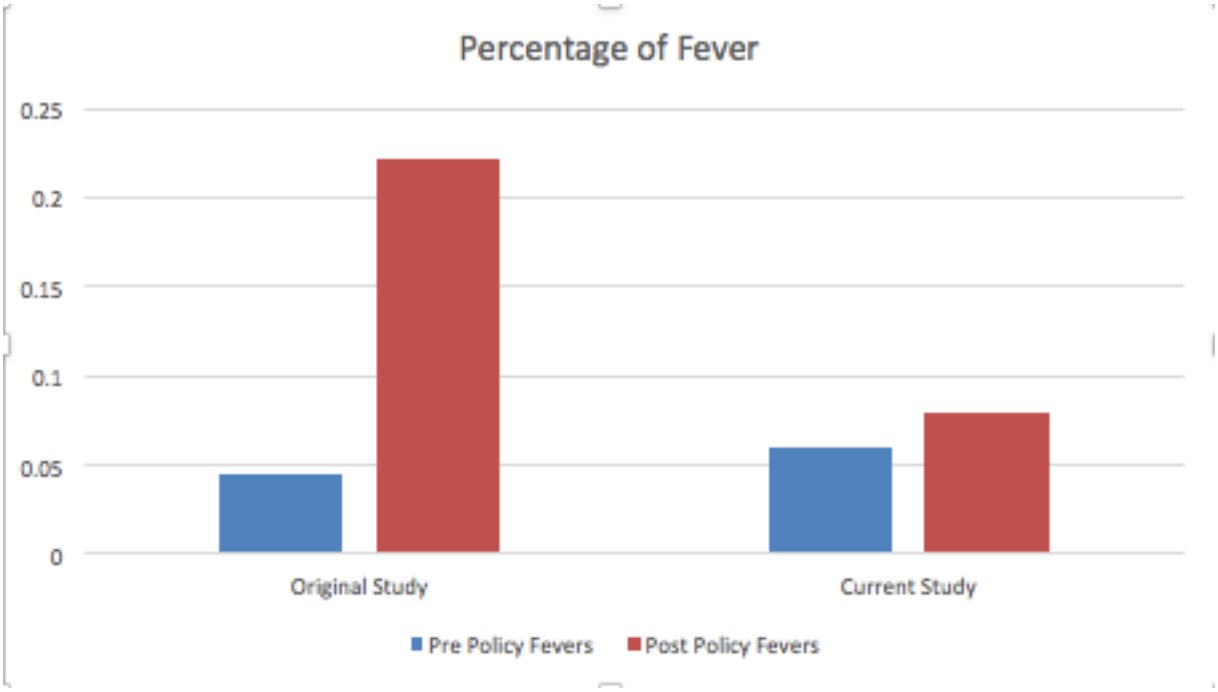
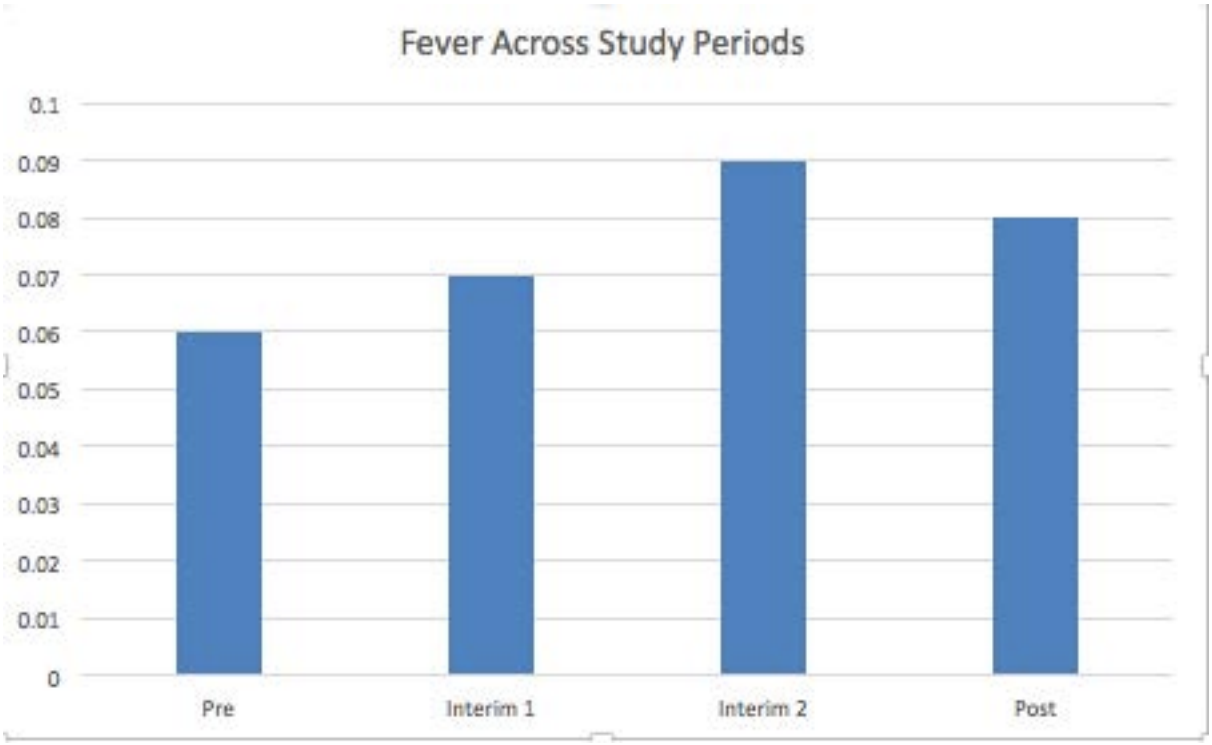


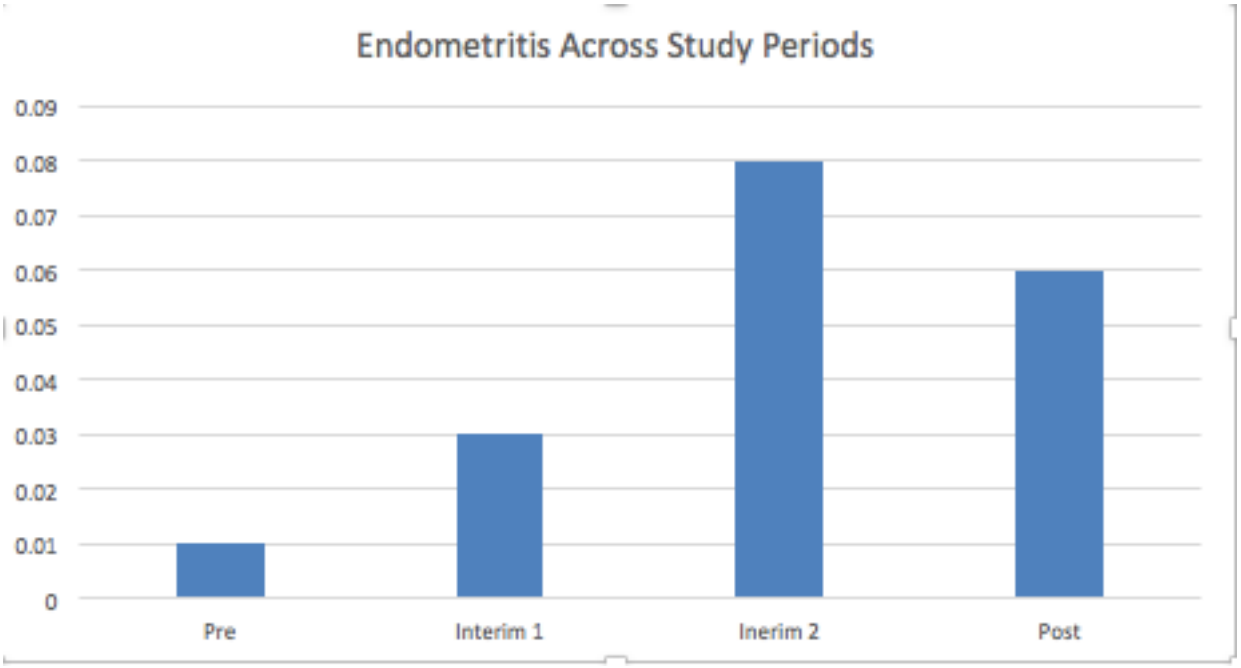
Figure 1: Breakdown of Study Period Variables and Dates



Graph 1: Difference in percentage of fevers found in the original and current study



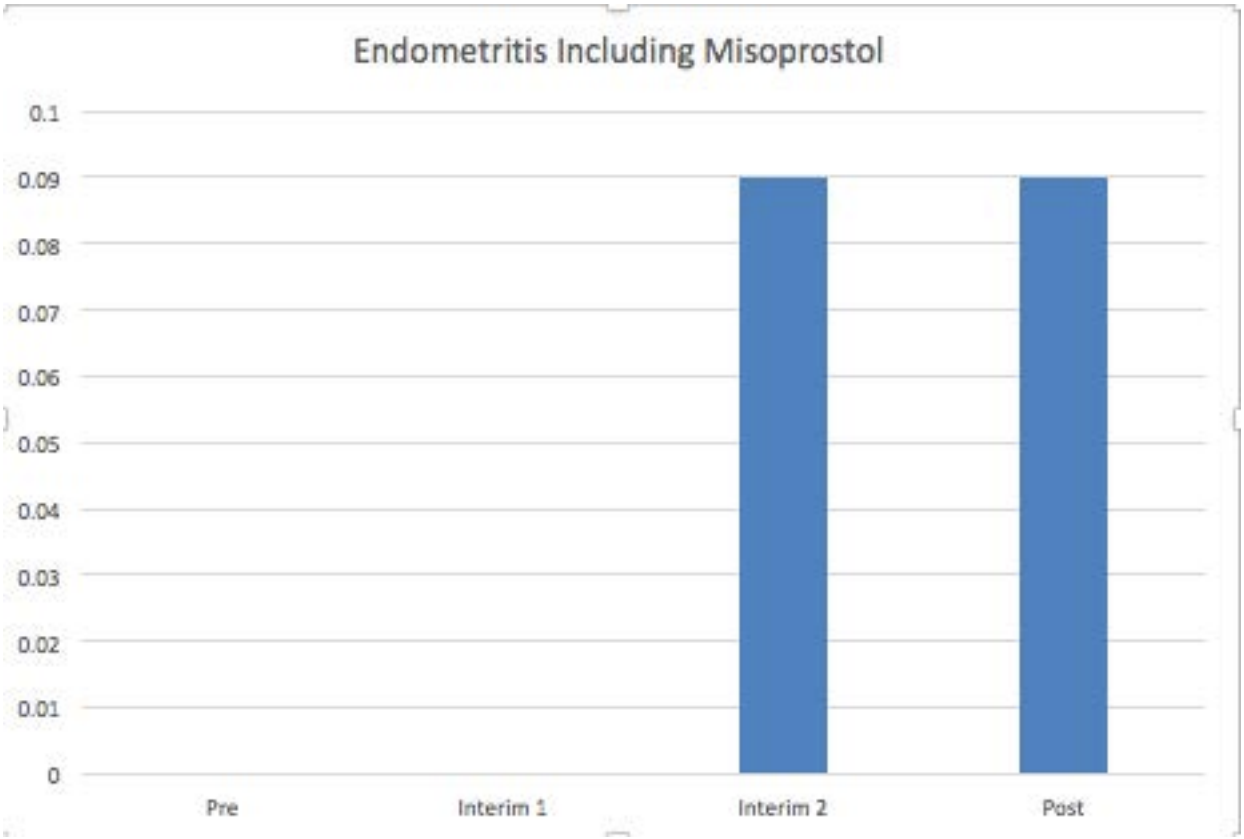
Graph 2: Percentage of Fevers Across Study Periods



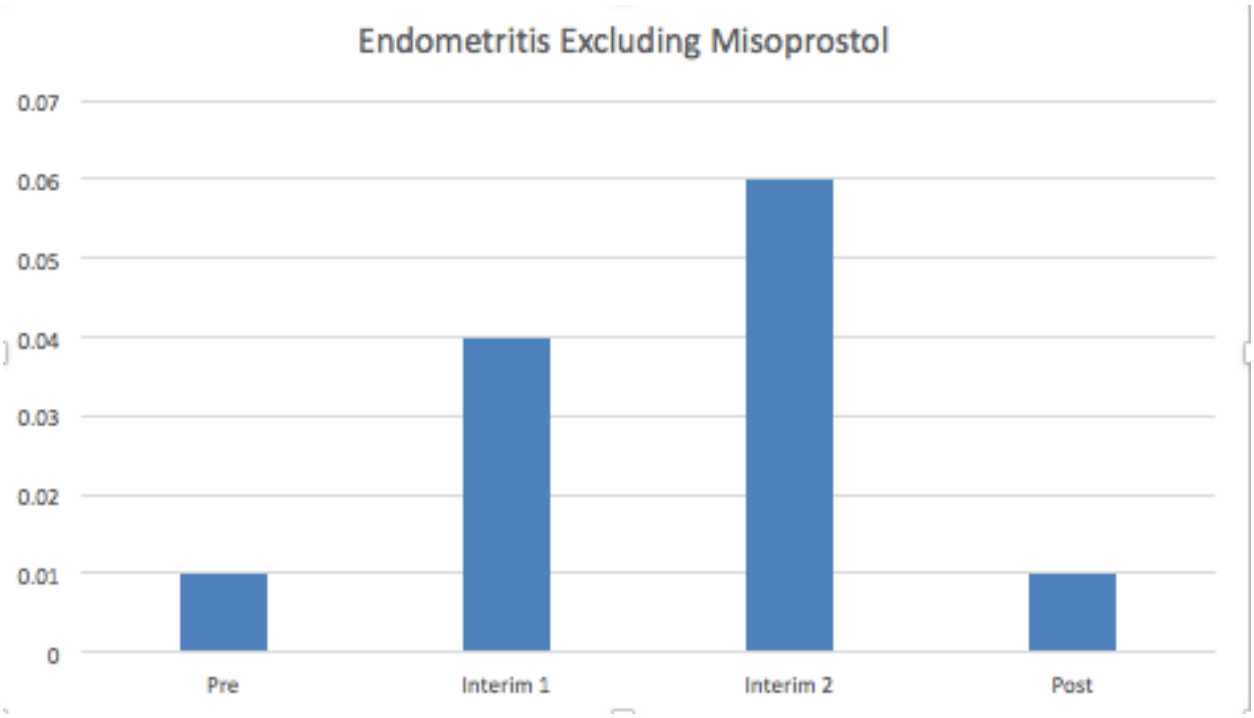
Graph 3: Percentage of Endometritis Across Study Periods

Misoprostol and Endometritis:

Analysis was performed looking at endometritis rates during all four study periods with all subjects and then excluding subjects who had received misoprostol to see if there was a significant difference. With misoprostol subjects included, the frequency of endometritis was 0% in the pre-policy period, 0% in interim 1, 9% in interim 2 and 9% in the post-policy period. When the subjects who received misoprostol were excluded, the frequency of endometritis was 1% in the pre-policy period, 4% in interim 1, 6% in interim 2, and 1% in the post-policy period. The overall frequency of endometritis is 8% but changes to 3% if misoprostol subjects were removed ($p=0.005$). This yielded a relative risk of 3.03 95% confidence interval (1.42, 6.46). Graph 4 shows the percentage of endometritis including subjects who received misoprostol and Graph 5 shows the percentage of endometritis excluding subjects who received misoprostol.



Graph 4: Percentage of Endometritis in patients who received misoprostol



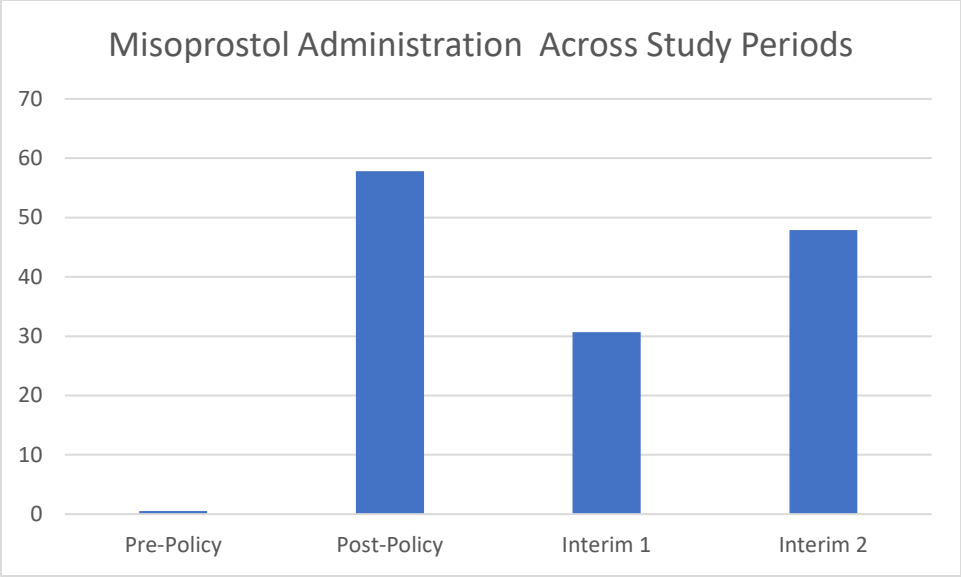
Graph 5:Percentage of Endometritis excluding misoprostol

Endometritis Diagnosis Code vs. Symptoms

Analysis was performed to see if there was any difference in terms of frequency if we separated subjects who had a diagnosis code of endometritis from those who had 2+ symptoms. There was no significant difference if we excluded subjects who had 2+ symptoms from our analysis and included only those who had a diagnosis code. There was also no difference if we placed subjects who had 2+ symptoms in the denominator when calculating the frequency. The difference in the rate of endometritis was still statistically significant.

Misoprostol Use In the Study:

In regards to misoprostol administration, we found that out of 624 total patients, only 1 received misoprostol in the pre-policy group while 115 received it in the post-policy group. In the interim 1 group, we found that 31 of the 101 patients in that group received misoprostol. In the Interim 2 group, 57 of the 119 patients received misoprostol. When we looked at the rates of endometritis with regards to misoprostol administration, we found that 47.7% of patients in the study had a diagnosis code of endometritis and 60.0% of patients had two or more symptoms of endometritis. Graph 6 represents the patients who received misoprostol across the study period. As noted above subjects who received had a relative risk of endometritis of 3.03 which as significant.



Graph 6: Percentage of Patients who received misoprostol across all time periods

Discussion:

The original study had surprising results. It found that there was a higher incidence of endometritis in the post-policy period. This is both counter intuitive and not what has been found in other recent studies regarding preoperational vaginal cleansing. However, once gathered a greater sample size (n=99 in the post policy period in the original study) it was found that there was no significant difference in terms of frequency of fever across the study periods. The original finding of an increase in the frequency of fever was thought that perhaps be due to the fact that misoprostol was being routinely used during the post-policy period as adjunct therapy for postpartum hemorrhage prophylaxis. Fever does not appear to be a component in the increase incidence of endometritis in the post policy period even though misoprostol is a known pyretic. Something else is driving the increased rates of endometritis other than fever in this study. However, it was found that the patient was 3 times more likely to be diagnosed with endometritis if they had received a 400µg dose of misoprostol.

There could be a few reasons as to why we obtained the results from the original study outside of misoprostol use. In terms of fevers, it could be that the sample size was too small. The incidence of fever went from 22.2% with a subject number of 99 to 8% when the subject number was expanded to 200. The frequency of fever in this study was possibly closer to the real frequency and exposes that there wasn't the same difference seen in the original study.

The studies that have been performed before show that there is a baseline rate of endometritis is between 10% to 20% and the sample sizes was around 400 in each group. This was needed in order to detect a 50% reduction in the rate of endometritis. The baseline rate at Maricopa Integrated Health System may not have even reached the baseline level required to achieve that reduction. This may have not been known prior to the original study taking place.

Another reason could be due to the diagnosis codes used in the chart. With the data showing that there was an increase in the rates of endometritis during the post-policy period, this could be due to the way endometritis was documented in the chart. It is hard to say since the diagnosis of endometritis is a clinical one which is usually is only made if there an absence of any other infectious explanation for the physical exam findings. It could also be that the higher incidence of fever in the post-policy group was a cause for increased evaluations by

providers. This increase in evaluations may have led to this increase in endometritis being diagnosed since no other explanation could be found for the fevers.

Thirdly, we cannot rule out that the increased incidence of endometritis was from the vaginal cleansing itself. This could be that the cleansing may not have killed the bacteria, although in theory it should have, but pushed the bacteria further up into the cervical canal allowing it to contact into the endometrial lining. Our study was also a retrospective chart review so cause and effect is hard to pinpoint. Many randomized control trials have been published supporting the use of vaginal cleansing to reduce the rates of endometritis. Suggestions for further research at MIHS is to conduct a randomized control trial to truly test the effects of vaginal cleansing in the reduction of endometritis with a sample size of at least 400 per study group.

Lastly, we can at least draw some conclusion that misoprostol was involved in the increase in the rates of endometritis in the post-policy group. Since only one patient received it in the pre-policy group, it was a nonfactor during that time period. This isn't too surprising since misoprostol is a known pyretic and could have led to the increase in provider equation and frequency of endometritis diagnosis.

Future Directions:

To accurately determine if preoperational vaginal cleansing works in practice on the patient population at MIHS, the next direction would be to do a randomized control trial of patients. We would need to recruit more patients in each group to be able to achieve the appropriate rate reduction to be able to determine the usefulness of vaginal cleansing at this facility. Since our baseline rates of endometritis are low, this would require a bigger sample size in this future study to be able to achieve that rate reduction.

The next step with this study would be to look at the rates of fever and its relation to the time of misoprostol administration. The data has been added to the current database and needs to be analyzed. This would help further sort out the effect of misoprostol on the rates of endometritis.

Conclusion:

The original study found results were the opposite of what we hypothesized, which is both counterintuitive and not consistent with similar prior studies. The study found higher rates of endometritis in the post-policy period as well as increased frequency of fevers. However, there was no significant difference between the frequency of fevers across any of the study periods. This shows that the increased rates of endometritis is being driven by something other than the increased incidence of fevers. Although we cannot dismiss the possibility that vaginal preparation leads to higher rates of post-cesarean endometritis, a more likely explanation for the original results was thought to be confounding effect of misoprostol.

When we compared the pre-policy period to the post-policy period in terms of diagnosis of endometritis including the extra data point of misoprostol, we found that there was not a statistically significant difference between the two groups with an odds ratio of 1.78. When we removed the patients that had received misoprostol, we also found that there was no significant difference between the two periods and our odds ratio failed to be significantly different. When adding the interim period, we looked at misoprostol across the entire study population. It was found that endometritis was 3 times more likely to be diagnosed if misoprostol was given. This result was statistically significant, therefore, we can conclude that misoprostol was a confounder in the original study and possibly lead to the higher incidence of endometritis in the post-policy period.

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