Published in final edited form as:

Am J Obstet Gynecol. 2016 March ; 214(3): 373.e1–373.e12. doi:10.1016/j.ajog.2015.10.012.

Effectiveness and short-term safety of modified sodium hyaluronic acid-carboxymethylcellulose at cesarean delivery: A randomized trial

Daniel G. KIEFER, MD^{1,2,3}, Jolene C. MUSCAT, MD², Jarrett SANTORELLI, MD^{3,4}, Martin R. CHAVEZ, MD², Cande V. ANANTH, PhD, MPH^{4,5}, John C. SMULIAN, MD, MPH¹, and Anthony M. VINTZILEOS, MD²

²Department of Obstetrics and Gynecology, Winthrop University Hospital, Mineola, NY

³Department of Obstetrics, Gynecology, and Reproductive Medicine, Stony Brook University, Stony Brook NY

⁵Department of Epidemiology, Mailman School of Public Health, Columbia University, NY

Abstract

Background—The rising cesarean birth rate has drawn attention to risks associated with repeat cesarean birth. Prevention of adhesions with adhesion barriers has been promoted as a way to decrease operative difficulty. However, robust data demonstrating effectiveness of such interventions are lacking.

Objective—We report data from a multicenter trial designed to evaluate the short-term safety and effectiveness of a modified sodium hyaluronate-carboxymethylcellulose absorbable (HACMC) for reduction of adhesions following cesarean delivery.

Methods—Patients that underwent primary or repeat cesarean delivery were included in this multicenter, single-blinded (patient), randomized controlled trial. Patients were randomized into either HA-CMC (N=380) or no-treatment group (N=373). No other modifications to their treatment were part of the protocol. Short-term safety data was collected following randomization.

CORRESPONDING AUTHOR: Daniel Kiefer, M.D., Division of Maternal-Fetal Medicine, 3900 Hamilton Blvd, Allentown, PA 18103, Phone: 484-664-7521, Fax: 484-664-7530, Daniel_g.kiefer@lvhn.org.

¹Department of Obstetrics and Gynecology, Lehigh Valley Health Network, Allentown, PA;

⁴Department of Surgery, University of Buffalo, Buffalo, NY; ⁴Department of Obstetrics and Gynecology, College of Physicians and Surgeons, Columbia University, New York, NY;

*Both Drs. Smulian and Vintzileos served as senior authors for this manuscript

SOURCES: Lehigh Valley Health Network, Allentown, PA; Winthrop University Hospital, Mineola, NY; Stony Brook University Medical Center, Stony Brook, NY

CONFLICT OF INTEREST: The authors report no conflict of interest.

PRESENTATION: American Congress of Obstetricians and Gynecologists Annual Clinical Meeting, San Diego, CA, May 5–9, 2012 (safety data); American Congress of Obstetricians and Gynecologists Annual Clinical Meeting, Chicago, IL, April 26–30, 2014 (primary outcome)

TRIAL REGISTRATION: *ClinicalTrials.gov* identifier NCT00565643

URL: <https://clinicaltrials.gov/ct2/show/NCT00565643?term=NCT00565643&rank=1>

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

The location and density of adhesions (primary outcome) were assessed at their subsequent delivery using a validated tool, which can also be used to derive an adhesion score, that ranges from 0–12.

Results—No differences in baseline characteristics, post-operative course, or incidence of complications between the groups following randomization were noted. Eighty patients from the HA-CMC group and 92 controls returned for subsequent deliveries. Adhesions in any location were reported in 75.6% of the HA-CMC group and 75.9% of the controls ($P=0.99$). There was no significant difference in the median adhesion score; 2 (range 0–10) for the HACMC group vs. 2 (range 0–8) for the control group ($P=0.65$). One third of the HA-CMC patients met the definition for severe adhesions (adhesion score >4) compared to 15.5% in the control group ($P=0.052$). There were no significant differences in the time from incision to delivery ($P=0.56$). Uterine dehiscence in the next pregnancy was reported in 2 patients in HA-CMC group versus 1 in the control ($P=0.60$).

Conclusions—Although we did not identify any short-term safety concerns, HA-CMC adhesion barrier applied at cesarean delivery did not reduce adhesion formation at the subsequent cesarean delivery.

Introduction

Cesarean delivery occurs in approximately one-third of all births and has become the most common surgical procedure in the United States. While guidelines have encouraged a reduction in the cesarean births, little progress has been made in significantly impacting the rate. According to preliminary data the Centers for Disease Control and Prevention, the cesarean delivery rate declined slightly in 2013, to 32.7% of all births (down from 32.8% in 2012). The cesarean delivery rate had increased approximately 60% from 1996 to 2009, reaching a peak 32.9%, where it remained unchanged for several years(1). Coincidentally, there has been a decline in the vaginal birth after Cesarean delivery rate, with greater than 90% of women who undergo a primary cesarean section delivering a subsequent pregnancy by repeat cesarean delivery(2). These statistics have prompted investigation into the short- and long-term impact of cesarean delivery on fetal and maternal outcomes (3–5). Post-operative complication rates for both primary and repeat cesarean delivery vary widely and are reported anywhere from 5 to 35% (6–14). The most common causes of maternal peri-operative morbidity associated with cesarean delivery include surgical site infection and wound complications, hemorrhage, bowel/bladder injury and obstruction, and thromboembolic complications. The incidence of many of these complications increases in the presence of adhesion formation (10, 15).

Adhesion prevalence following cesarean delivery have been reported to be 46% after a first cesarean delivery, 75% after a second and 83% after a third (10). There are several adhesion prevention barriers approved by the US Food and Drug Administration for the prevention of post-operative adhesions. One such barrier, which is composed of modified sodium hyaluronic acid and carboxymethylcellulose (HA-CMC) (Seprafilm®, Sanofi-Aventis, Bridgewater, NJ), has been studied in the setting of a variety of procedures. This barrier is FDA approved to reduce adhesion formation following laparotomy for abdominal or pelvic surgery (16). Initial studies on the use of this barrier at the time of cesarean delivery suggest

reduction in the amount and severity of adhesion formation(17). However, the previously reported studies designed to specifically address this indication for use are limited, their sample sizes are small, and their methodologies were not well described. Additionally, they were not designed or powered to reasonably evaluate safety (17, 18).

We performed a multi-center, single-blinded, randomized controlled trial to determine the short-term safety and effectiveness of HA-CMC to reduce adhesion formation when used at the time of cesarean delivery.

Materials and Methods

We performed a multi-center, single (patient) blinded, randomized controlled trial conducted in three sites: Winthrop University Hospital, Mineola, NY; Stony Brook University Medical Center, Stony Brook, NY; and Lehigh Valley Health Network, Allentown, PA from November 2007 through June 2010. Following institution-specific IRB approvals, and with the approval of the managing physician, pregnant women presenting to labor and delivery were screened for enrollment. Some patients presented in the peri-operative period specifically for a scheduled cesarean delivery, while others presented for a trial of labor (i.e., planned vaginal delivery).

Patients were considered eligible for the study if they were 18 years or older, were planning or had the potential to undergo cesarean delivery, and were able to consent to participate. Patients were excluded if there was a planned tubal ligation, infertility resulting in two or more years of treatment to achieve (current) pregnancy, medical or other serious conditions that could interfere with either compliance or ability to complete study protocol, or known allergy to modified sodium hyaluronic acid or carboxymethylcellulose. Once a patient met eligibility criteria, she was offered enrollment in the study. Upon providing consent, she was considered a candidate for randomization. If and when the patient subsequently underwent a cesarean delivery, she was randomized to either placement of HA-CMC adhesion barrier prior to abdominal closure or to routine closure without placement of an adhesion barrier.

The chance of being assigned to either group was equal (i.e., 1:1 randomization). Randomization was done in permuted blocks of varying sizes (6–14) with the randomization code generated using SAS software (SAS Institute, Cary, NC; version 9.1). Enrollment was stratified by primary and repeat cesarean deliveries using separate randomization sequences. A statistician not involved in enrollment, data collection or analysis performed the randomization allocation. The randomization code was not accessible to those enrolling patients. Assignments were kept in sequentially numbered, sealed, opaque envelopes readily accessible to the operating room. Most patients undergoing cesarean delivery were under regional anesthesia. Thus, communication regarding randomization was performed nonverbally in an effort to keep the patient blinded. The randomization card was shown to the operating physician. If the adhesion barrier was to be placed, the circulating nurse placed the product onto the sterile field and recorded the number of sheets used.

The goal of the adhesion barrier placement was to cover the hysterotomy site, bladder flap (if created) and the midline anterior surface of the uterus. This was usually accomplished

with one sheet of HA-CMC product, which was cut into smaller pieces to facilitate placement. However, if the surgeon felt that additional sheets were indicated, this was permitted under the protocol. Prior to the study beginning at each institution, Department-wide presentations were made about the study protocol and the placement of the HA-CMC barrier. Physician training on HA-CMC placement was provided prior to the beginning of the study and at any time during the study period at their request.

The primary outcome was the prevalence of adhesions at the time of the subsequent cesarean delivery. Secondary outcomes (assessed at the time of subsequent delivery) included incision to delivery time, total operative time, estimated blood loss, and the rate of complications (bowel or bladder injury, hysterectomy, blood transfusion, and uterine rupture or dehiscence). We also sought to examine the short-term safety of HA-CMC at the time of placement (immediately following randomization) as measured by post-operative complications (fever, ileus, abscess formation, wound complication), post-operative white blood cell count, narcotic pain medication use, length of stay, readmission, and the frequency of postpartum office visits).

Sample size calculation for the primary endpoint of the study (adhesion formation) was performed with the following assumptions: type I error (α) of 0.05, a background risk of adhesion of 50% in the no treatment group, and a 25% risk of adhesion in the treated group (i.e., a 50% reduction in adhesion formation). A sample size of 65 (of patients who returned for a subsequent cesarean delivery) in each arm would be required to detect the above difference with 80% power. Using existing hospital data on rates of subsequent pregnancy after cesarean, we anticipated the need to randomize approximately 900 patients to obtain our final sample size to be able to assess our primary outcome (adhesion formation seen at the following cesarean), assuming 12–24 months of enrollment and a desire to be able to report the primary outcome within 3 years of completing enrollment.

Data collection involved the antepartum course, intra-operative events, and post-operative course of the patients. There were no additional tests or procedures ordered or performed during the hospital stay as part of this study, either at the time of enrollment or at the subsequent delivery. The operative and post-operative care of the patients were managed by the patient's physician and with hospital-specific standard policies and procedures. After delivery, all inpatient and outpatient electronic records, and hospital admission records were reviewed. We performed a telephone follow-up (two attempts) at 6–8 weeks following delivery to capture the post-operative course and complications. The definitions used for post-operative complications are shown in Table 1.

Both primary and repeat cesarean deliveries, as well as patients with previous abdominal surgery were eligible for enrollment. Therefore, adhesions were assessed at the time of randomization utilizing a previously validated adhesion assessment tool by Lyell et al. This tool was modified to include assessment of adhesions in the area of the bladder, as this site was previously reported by Lyell et al to be commonly included in the "other location" area in their experience (19). Documentation of the adhesion score was completed immediately following conclusion of the procedure. To calculate the score, we assigned a value of "1" to each location where filmy adhesions were noted and "2" to each location where dense

adhesions were noted. Therefore, the score could range from 0–12 based on the location and severity of adhesion formation. In addition, each participating institution agreed to modify the Labor and Delivery medical record to begin assessing adhesions on every patient delivering at the respective institution. With this modification, adhesion data would be collected on enrolled patients who returned for subsequent deliveries and could then be abstracted from the medical record. Other measures included in this analysis (incision-to-delivery time, total operative time, blood loss, etc.) were routinely collected for all patients. The database of enrolled patients was periodically compared to the electronic medical record from each institution to screen for patients that had returned for a subsequent delivery. Once identified, study data was abstracted from their medical record.

All data were analyzed in an intent-to-treat fashion. Differences in continuous variables were assessed by the unpaired t-test or two sample median test. Differences in proportions were evaluated by Fisher's exact probability test. All analyses were performed using SAS 9.2 for Windows (SAS Institute, Inc., Cary, NC). Risk ratios (RR) and 95% confidence intervals (CI) are reported as appropriate. No interim analyses were planned or performed.

With regard to the financial support for this project, the funding organizations (including the product manufacturer) had no role in study design, data collection, analysis, or interpretation, or in the decision to publish results. The authors designed the project and funding was then sought to support its execution through investigator-sponsored grants and other available sources (including the product manufacturer).

Results

A total of 1,670 patients were assessed for eligibility. Of the 1,226 eligible patients, 808 (65.9%) consented for participation and 753 patients were randomized. There were 55 nonrandomized individuals (50 underwent a vaginal delivery, 3 revoked consent and 2 underwent a hysterectomy). There were 380 randomized to the HA-CMC adhesion barrier treatment group and 373 to the no treatment group. Enrollment was discontinued before the target sample of 900 was reached due to lack of additional funding. However, the target of 130 subsequent cesarean deliveries was exceeded (N=172), which satisfied the intent of the original sample size calculation. The recruitment flow diagram is shown in Figure 1. There were no deviations between randomization and actual intervention received. There were no differences in patient demographics or pre-operative characteristics at the time of randomization (Table 2).

Intraoperative characteristics, including urgency of cesarean delivery, total operative time, anesthesia characteristics, operative procedures, operative complications, adhesion formation, and estimated blood loss for randomized patients are shown in Table 3. Again, there were no significant differences between the two groups. There was one patient who's randomization envelope was opened during the case (randomized to no treatment), but ultimately underwent a cesarean hysterectomy due to an intraoperative findings of placenta accreta. With regard to adhesion formation at the time of randomization, we observed adhesions (in any location) in 8.7% of patients undergoing a primary cesarean delivery (n=2), in 61.7% of patients with 1 prior cesarean (n=358), in 80.9% of patients with 2 prior

cesarean deliveries (n=89), and in 75.0% of patients with 3 or more prior cesarean deliveries (n=8). We observed a 0.51 ($P<0.01$) correlation between the adhesion score and skin-to-delivery time and a -0.27 ($P<0.01$) correlation between the adhesion score and total operative time.

Table 4 contains data on post-operative laboratory characteristics including hematocrit and white blood cell count, with no significant difference between the groups at randomization. Similarly, there were no differences in post-operative fever, infectious morbidity, wound or other complications, or length of stay. From the HA-CMC treatment group, 103 patients (27.1%) could be contacted for a telephone interview to determine the number of post-operative visits; 100 patients (26.8%) from the non-intervention group were contacted. Again, there was no difference between the two groups.

There were 5 patients in the treatment arm who required readmission after delivery vs. 2 patients in the no treatment arm ($P=0.45$). Reasons for readmission in the treatment group included appendicitis, gallstone pancreatitis, delayed postpartum hemorrhage, wound infection and pelvic abscess. Reasons for readmission in the no treatment group included seizure disorder and pelvic abscess.

Of the enrolled patients, 80 from the HA-CMC group and 92 controls returned for subsequent deliveries. Table 5 contains these patients' characteristics, operative, and post-operative course at the time of randomization. There were no differences between the two groups in any of the variables analyzed.

At the time of their subsequent delivery, delivery was accomplished at a mean gestational age of 38.6 ± 1.3 weeks for the HA-CMC group versus 38.4 ± 2.0 for the control ($P=0.42$). There was similarly no difference in BMI between the two groups (32.9 ± 8.7 for HA-CMC versus 33.0 ± 6.9 for control group, $P=0.97$).

Table 6 contains data on the surgical characteristics of the patients who returned for a subsequent delivery, with no significant differences between the two groups. Notably, there was no difference in skin-to-delivery time, total operative time, or estimated blood loss. Of note, there were six patients in our cohort who were classified as having a bowel injury at the time of subsequent delivery. All of these were serosal injuries, none of which required reanastomosis.

Table 7 contains the primary outcome (adhesion data) at the time of subsequent delivery. Adhesions in any location were reported in 75.6% of the HA-CMC group and 75.9% of the controls ($P=0.99$). The location and proportion of patients with filmy and dense adhesions are also presented in Table 7, again with no statistical differences between the groups. There was no significant difference in the median adhesion score; 2 (range 0–10) for the HA-CMC group vs. 2 (range 0–8) for the control group ($P=0.65$). The distribution of the adhesion score is represented graphically in Figure 2. We also examined the change in the adhesion score from the time of randomization and at the subsequent delivery. For the control group, the median change was -1 (range -6 to $+4$). In the HA-CMC group, the median change was also -1 (range -8 to $+4$) ($P=0.74$; two sample median test). There were no significant differences in the time from incision to delivery ($P=0.56$).

We looked to see if the incidence of severe adhesions was different between the groups. We arbitrarily defined “severe adhesions” as the upper quartile for the adhesion score. This translated to a score of 4. One third of the HA-CMC patients met the definition for severe adhesions compared to 15.5% in the control group. Although there was a trend for more cases of severe adhesion in the HA-CMC group, it did not reach statistical significance ($P=0.052$).

We also examined the impact of peritoneal closure and rectus muscle approximation on adhesion formation. Of 59 and 106 patients with and without peritoneum closure, subsequent adhesion formation was seen in 71.2% and 78.3%, respectively ($P=0.31$). Of 74 and 91 patients with and without the rectus muscle approximated, subsequent adhesion formation was seen in 73.0% and 78.0%, respectively ($P=.45$).

Post-operatively, hematocrits (%) were similar (30.4 ± 3.1 for HA-CMC versus 30.0 ± 3.5 for the control, $P=0.44$). There was also no difference in the length of stay (days) following the subsequent delivery (median 3, range 1–9 for HA-CMC vs. median 3, range 1–5 for controls, $P=0.51$).

Comment

This is the first study to report data from a multicenter, single blinded, randomized trial evaluating the short-term safety of a modified sodium hyaluronic acid-carboxymethylcellulose when used to prevent adhesions after cesarean delivery. Routine use of a HA-CMC adhesion barrier did not reduce the incidence of adhesions at the time of subsequent cesarean delivery. Similarly, no differences in operative times or the incidence of complications were identified. This study is important given the frequency of cesarean delivery and the possibility of an associated rise in adhesion-related complications.

The strengths of this study lie primarily in its randomized controlled design, with no other management interventions other than the use of the HA-CMC barrier. We were able to obtain a representative population from several suburban sites, and used a pragmatic approach to application of the adhesion barrier. We also used a standardized formal adhesion assessment tool at randomization and at follow-up.

Limitations of the study are that we did not reach our intended enrollment target, but we did have sufficient patients return for subsequent cesarean births to address the primary outcome. Secondly, nearly two-thirds of our patients presented for a scheduled repeat cesarean birth at the time of enrollment. Therefore, we were unable to determine if any subgroup of women (ex. no previous cesarean) having a cesarean would benefit from its use. Our cohort also prohibited evaluation of whether other factors, such as labor, infection, or indication for cesarean had an impact on HA-CMC effectiveness.

Our data are consistent with recently reported retrospective cohort study of the HACMC barrier of patients assessed during repeat cesarean. While the authors did not have specific adhesion data, they also found no differences in delivery or total operative time, or the rate of surgical complications (20).

One concern that our data present is the trend toward an increased incidence of severe adhesions in patients who received HA-CMC (Table 7). While it did not reach statistical significance, there was a trend toward more dense adhesions located between the uterus/bladder, as well as dense adhesions of the uterus to the anterior abdominal wall/fascia when compared to the control group. The trend should be noted since these are the areas that where the barrier should have ideally been placed, and therefore should have benefited the most from an effective adhesion barrier. There is the possibility of a Type 2 error with regard to this finding (where there may be worse adhesion formation by using the HA-CMC barrier) given the sample size.

There are several explanations for the negative results in this study, especially in light of other randomized studies showing benefit of HA-CMC when placed during laparotomy (21–23). First, it is possible that factors influencing adhesion formation following cesarean delivery differ in non-pregnant patients having laparotomy. Cesareans have amniotic fluid and often have increased residual blood left intraabdominally compared to many other surgeries. It is possible those factors impact HA-CMC and limits its ability to maintain a barrier to adhesions. Rapid change in uterine size in the immediate post-operative period may also alter adhesion formation or performance of the adhesion barrier following cesarean delivery (24, 25).

Second, placement of the HA-CMC barrier can be difficult at times. The product formulation is a thin, clear film that is somewhat brittle when dry. When moistened, it quickly becomes gelatinous and sticky. Therefore, accidental contact with the abdominal wall or moist surgical instruments can hamper proper placement. To assess the impact of a possible learning curve of product placement on effectiveness, we performed a regression analysis of HA-CMC patients who returned for a subsequent delivery. The date of randomization did not have an impact on subsequent adhesion formation. Each of the institutions involved in the study are teaching institutions and the degree of participation in the surgery by physicians-in-training varied depending on the specific case and the attending physician. We did not have the resources to monitor who actually placed the HA-CMC barrier, nor did we collect data on how successfully the surgeon felt they placed the product. When designing this study, we considered having specific surgeons who were comfortable with placement of the HA-CMC barrier assist at the time of randomization. We decided against that as we wanted the trial to reflect “real world” usage of the product. Similar to any other surgeon who would decide to use this product in their practice, we provided education and made representatives available to provide additional instruction as needed.

With regard to the safety of HA-CMC, we did not identify any short-term safety concerns. While not specifically powered for safety data, the large number of enrolled patients, the lack of adverse events, and similar post-operative course for both groups are reassuring (26, 27). In earlier studies, the HA-CMC barrier was associated with an increased incidence of anastomotic leaks when placed directly over a gastrointestinal anastomosis site (26). A concern we hoped to address in this study was whether the product can somehow hamper immediate wound healing, which could lead to an increased risk of uterine dehiscence or rupture in subsequent pregnancies. Other investigators have also raised this concern. However, there was no increased rate of rupture or dehiscence in our cohort. We

acknowledge that the size of this study prohibits definitive conclusion regarding uncommon surgical complications that may be related to HA-CMC adhesion barrier placement.

In summary, we could not identify any short-term safety concerns with the use of HACMC at the time of cesarean delivery. However, it does not seem to reduce adhesion formation. Before incorporating an adhesion barrier (and its associated cost) into routine practice, it is important to vigorously test its ability to achieve the desired goal (28). The results of this randomized trial do not support routine use of HA-CMC at the time of cesarean delivery.

Acknowledgments

FINANCIAL SUPPORT:

1. Investigator-Sponsored Trial Grant, Sanofi Biosurgery
2. PhRMA Foundation Post-doctoral Fellowship in Clinical Outcomes Research Grant
3. GCRC Grant #MO1RR10710
1. Sean Keeler, M.D. (Study Design)
 - a. Desert Perinatal Associates, No compensation
2. Martin Feuerman, M.S. (Study design)
 - a. Winthrop University Hospital, Salaried employee
3. Robert Kirshoff (Study design and implementation)
 - a. Winthrop University Hospital, Salaried employee
4. David Cyrille and Firat Koskun (Database design and management)
 - a. Stony Brook University General Clinical Research Center, Salaried employees
5. Denise Knittle, R.N., Sharon Agonis, and Anita Kurt, Ph.D., R.N. (Research Staff)
 - a. Lehigh Valley Health Network, Salaried employees

References

1. Hamilton BEMJ, Ventura SJ. Births: Preliminary Data for 2011. Natl Vital Stat Rep. 2012 Oct 3; 61(5):1–20.
2. Gregory KD, Fridman M, Korst L. Trends and patterns of vaginal birth after cesarean availability in the United States. Semin Perinatol. Aug; 34(4):237–43. [PubMed: 20654773]
3. Ananth CV, Smulian JC, Vintzileos AM. The association of placenta previa with history of cesarean delivery and abortion: a metaanalysis. American journal of obstetrics and gynecology. 1997 Nov; 177(5):1071–8. [PubMed: 9396896]
4. Getahun D, Oyelese Y, Salihu HM, Ananth CV. Previous cesarean delivery and risks of placenta previa and placental abruption. Obstetrics and gynecology. 2006 Apr; 107(4):771–8. [PubMed: 16582111]
5. Wood SL, Chen S, Ross S, Sauve R. The risk of unexplained antepartum stillbirth in second pregnancies following caesarean section in the first pregnancy. Bjog. 2008 May; 115(6):726–31. [PubMed: 18410656]
6. Makoha FW, Felimban HM, Fathuddien MA, Roomi F, Ghabra T. Multiple cesarean section morbidity. Int J Gynaecol Obstet. 2004 Dec; 87(3):227–32. [PubMed: 15548394]
7. Nisenblat V, Barak S, Griness OB, Degani S, Ohel G, Gonen R. Maternal complications associated with multiple cesarean deliveries. Obstetrics and gynecology. 2006 Jul; 108(1):21–6. [PubMed: 16816051]
8. Clark EA, Silver RM. Long-term maternal morbidity associated with repeat cesarean delivery. American journal of obstetrics and gynecology. Dec; 205(6 Suppl):S2–10. [PubMed: 22114995]

9. Gregory KD, Jackson S, Korst L, Fridman M. Cesarean versus vaginal delivery: whose risks? Whose benefits? *Am J Perinatol.* Jan; 29(1):7–18. [PubMed: 21833896]
10. Morales KJ, Gordon MC, Bates GW Jr. Postcesarean delivery adhesions associated with delayed delivery of infant. *American journal of obstetrics and gynecology.* 2007 May; 196(5):461, e1–6. [PubMed: 17466702]
11. Martens MG, Kolrud BL, Faro S, Maccato M, Hammill H. Development of wound infection or separation after cesarean delivery. Prospective evaluation of 2,431 cases. *The Journal of reproductive medicine.* 1995 Mar; 40(3):171–5. [PubMed: 7776298]
12. Lutomski JE, Morrison JJ, Greene RA, Lydon-Rochelle MT. Maternal morbidity during hospitalization for delivery. *Obstetrics and gynecology.* Mar; 117(3):596–602. [PubMed: 21343763]
13. Tran TS, Jamulitrat S, Chongsuvivatwong V, Geater A. Risk factors for postcesarean surgical site infection. *Obstet Gynecol.* 2000; 95(3):367–71. [PubMed: 10711546]
14. Weed S, Bastek JA, Sammel MD, Beshara M, Hoffman S, Srinivas SK. Comparing postcesarean infectious complication rates using two different skin preparations. *Obstet Gynecol.* 2011; 117(5): 1123–9. [PubMed: 21508751]
15. Phipps MG, Watabe B, Clemons JL, Weitzen S, Myers DL. Risk factors for bladder injury during cesarean delivery. *Obstet Gynecol.* 2005; 105(1):156–60. [PubMed: 15625157]
16. GenzymeBiosurgery. Seprafilm Adhesion Barrier [package insert]. 2008. [cited February 19, 2013]; Available from: www.seprafilm.com
17. Fushiki HIT, Kobayashi H, et al. Efficacy of Seprafilm® as an Adhesion Prevention Barrier in Cesarean Sections. *Obstetric and Gynecologic Treatment [Japanese].* 2005; 91(5):557–61.
18. Kim THKJ, Lee HH. Prevention of vesicouterine adhesion after cesarean with Interceed. *Korean Society of Fetal Medicine.* 2006; 2:194. abstract only.
19. Lyell DJ, Caughey AB, Hu E, Daniels K. Peritoneal closure at primary cesarean delivery and adhesions. *Obstetrics and gynecology.* 2005 Aug; 106(2):275–80. [PubMed: 16055575]
20. Edwards RK, Ingersoll M, Gerkin RD, Bodea-Braescu AV, Lin MG. Carboxymethylcellulose Adhesion Barrier Placement at Primary Cesarean Delivery and Outcomes at Repeat Cesarean Delivery. *Obstet Gynecol.* 2014; 123:923–8. [PubMed: 24785841]
21. Becker JM, Dayton MT, Fazio VW, Beck DE, Stryker SJ, Wexner SD, et al. Prevention of postoperative abdominal adhesions by a sodium hyaluronate-based bioresorbable membrane: a prospective, randomized, double-blind multicenter study. *Journal of the American College of Surgeons.* 1996 Oct; 183(4):297–306. [PubMed: 8843257]
22. Diamond MP. Reduction of adhesions after uterine myomectomy by Seprafilm membrane (HAL-F): a blinded, prospective, randomized, multicenter clinical study. *Seprafilm Adhesion Study Group. Fertility and sterility.* 1996 Dec; 66(6):904–10. [PubMed: 8941053]
23. Vrijland WW, Tseng LN, Eijkman HJ, Hop WC, Jakimowicz JJ, Leguit P, et al. Fewer intraperitoneal adhesions with use of hyaluronic acid-carboxymethylcellulose membrane: a randomized clinical trial. *Annals of surgery.* 2002 Feb; 235(2):193–9. [PubMed: 11807358]
24. Bates GW Jr, Shomento S. Adhesion prevention in patients with multiple cesarean deliveries. *American journal of obstetrics and gynecology.* Dec.2015 (6 Suppl):S19–24.
25. Salamonsen LA. Tissue injury and repair in the female human reproductive tract. *Reproduction.* 2003 Mar; 125(3):301–11. [PubMed: 12611594]
26. Beck DE, Cohen Z, Fleshman JW, Kaufman HS, van Goor H, Wolff BG. A prospective, randomized, multicenter, controlled study of the safety of Seprafilm adhesion barrier in abdominopelvic surgery of the intestine. *Diseases of the colon and rectum.* 2003 Oct; 46(10): 1310–9. [PubMed: 14530667]
27. Diamond MP, Burns EL, Accomando B, Mian S, Holmdahl L. Seprafilm((R)) adhesion barrier: (2) a review of the clinical literature on intraabdominal use. *Gynecol Surg. Sep;* 9(3):247–57. [PubMed: 22837733]
28. Albright CM, Rouse DJ. Adhesion barriers at cesarean delivery: advertising compared with the evidence. *Obstetrics and gynecology.* Jul; 118(1):157–60. [PubMed: 21691174]

Figure 1.
CONSORT Patient flow diagram

Figure 2.
Boxplot of the adhesion score at the time of subsequent cesarean delivery

Table 1**Serious Adverse Event Definitions**

Event	Definition
<i>Ileus/bowel obstruction</i>	Nausea/vomiting that necessitates reduction in diet (ex. Regular to clear liquids or NPO status), inability to advance diet, insertion of a nasal-gastric tube, administration of IV fluids, or re-operation. Radiologic evidence of obstruction of ileus or obstruction would be supportive, but not necessary.
<i>Fever</i>	Temperature 100.4°F (>38°C) occurring > 24 hours post-operatively, regardless of suspected cause
<i>Abscess</i>	Evidence of abdominal-pelvic fluid collection with signs of inflammation/infection requiring intervention including, but not limited to, antibiotic administration or drainage
<i>Wound Cellulitis</i>	Evidence of superficial infection (redness, warmth, fever, etc.) necessitating intervention (e.g., Antibiotic administration, wound exploration)
<i>Wound Separation</i>	Separation of the superficial layers of the surgical site requiring any intervention (including debridement, packing, primary closure, healing by secondary intention, or additional patient visits)
<i>Wound Dehiscence</i>	Separation of the deep layers of the surgical site including fascia
<i>Deep Venous Thrombosis</i>	Radiologic evidence of new-onset deep venous thrombosis
<i>Pulmonary Embolism</i>	New-onset radiologic evidence (CT, angiography, V-Q scan) of pulmonary embolism in the appropriate clinical setting (oxygen desaturation, chest pain, tachycardia, etc.)
<i>Antibiotic Administration</i>	The need for initiation of therapeutic antibiotic administration for any reason (e.g., endometritis, urinary tract infection, pneumonia, etc.) during hospital stay or upon discharge. Does not include continuation of pre-hospital antibiotics.
<i>Readmission</i>	Hospital admission within 6 weeks following delivery for any reason

Table 2**Patient Demographics and Peri-operative characteristics**

Patient characteristics	HA-CMC (N=380)	No treatment (N=373)
Maternal age (years) [†]	30.4 ± 5.1	30.9 ± 5.3
Gravidity [‡]	2 (1, 20)	2 (1, 11)
Parity [‡]	1 (0, 4)	1 (0, 4)
Race/Ethnicity, % (n)		
Caucasian	68.2 (259)	70.6 (264)
African-American	10.3 (39)	10.2 (38)
Asian	3.7 (14)	4.8 (18)
Latino	15.2 (59)	11.5 (43)
Other race/ethnicity	2.4 (9)	2.7 (10)
Gestational age (weeks) [†]	38.7 ± 1.9	38.7 ± 3.9
Body-mass index (kg/m ²) [†]	33.3 ± 6.6	33.2 ± 7.8
Number of previous cesareans [‡]	1 (0, 3)	1 (0, 3)
Indication for cesarean, % (n)		
Planned repeat cesarean	70.0 (266)	67.0 (250)
Non-reassuring fetal heart rate	2.6 (10)	3.0 (11)
Arrest of labor	5.5 (21)	3.2 (12)
Failed induction	1.8 (7)	3.2 (12)
Previous uterine surgery	1.8 (7)	2.4 (9)
Malpresentation	14.2 (54)	13.9 (52)
Abnormal placentation	1.3 (5)	2.7 (10)
Multiple gestation	4.5 (17)	6.7 (25)
Maternal infection	0.8 (3)	1.3 (5)
Diabetes (any), % of arm (n)	9.8 (37)	11.8 (44)
Type I	0.8 (3)	0.5 (2)
Type II	1.0 (4)	0.5 (2)
Gestational Diabetes, A1	4.5 (17)	4.8 (18)
Gestational Diabetes, A2	3.4 (13)	5.6 (21)
Pre-operative hematocrit [†]	34.8 ± 4.3	34.4 ± 5.0
Pre-operative WBC count [†]	10.3 ± 3.4	10.7 ± 4.6
Pre-operative T _{max} [†] (°F)	97.8 ± 1.0	97.9 ± 0.9

[†]Data are presented as mean (standard deviation) and compared between groups using the student's t-test based on unequal between-group variances

[‡]Data are presented as median (range), and compared between groups based on the two-sample median test

Table 3

Intra-operative characteristics (Randomization delivery)

Surgical characteristics	HA-CMC (N=380)	No treatment (N=373)	P-value
Urgency, % (n)			0.69
Elective	86.1 (327)	85.2 (317)	
Non-elective	12.6 (48)	14.0 (52)	
Emergent	1.3 (5)	0.8 (3)	
Total operative time (minutes) [‡]	55 (13, 190)	55 (18, 321)	0.86
Anesthesia, % (n)			
Spinal	92.9 (353)	94.1 (351)	0.56
Epidural	6.3 (24)	4.6 (17)	0.34
Combined Spinal-Epidural	1.1 (4)	1.1 (4)	0.99
General	0.3 (1)	1.6 (6)	0.07
ASA classification, % (n)		0.07	
Class I	12.4 (46)	9.0 (33)	
Class II	70.6 (262)	74.9 (264)	
Class III	17.0 (63)	15.9 (58)	
Class IV	0.0 (0)	0.3 (1)	
Procedure type, % (n)			
Low Transverse	97.1 (369)	95.4 (356)	0.25
Classical	1.8 (7)	1.9 (7)	0.99
Other	1.3 (5)	3.2 (12)	0.09
Rectus Muscle Approximation, %(n)	40.9 (155)	42.2 (157)	0.77
Peritoneum closure, %(n)	28.5 (108)	33.6 (125)	0.13
Uterine Closure, %(n)			1.0
Single Layer	67.1 (253)	66.9 (247)	
Double Layer	32.9 (124)	33.1 (122)	
Estimated blood loss (ml) [‡]	800 (400, 2000)	800 (500, 3000)	0.58
Adhesion score [‡]	0 (0, 10)	0 (0, 11)	0.714
Adhesion at any location, % (n)	43.7 (166)	42.4 (158)	0.769
Bowel adhesions	3.4 (13)	4.3 (16)	0.574
Uterus to Fascia	12.6 (48)	12.3 (46)	0.913
Omentum to Fascia	12.9 (49)	15.0 (56)	0.462
Omentum to Uterus	12.9 (49)	13.1 (49)	0.999
Bladder to Uterus	34.5 (131)	33.0 (133)	0.700
Other location	5.5 (21)	5.4 (20)	0.999
Complications, % (n)			
Bladder injury	0.0 (0)	0.0 (0)	—
Bowel injury	0.0 (0)	0.3 (1)	0.50
Hysterectomy	0.0 (0)	0.5 (1)	0.50
Intra-operative transfusion	0.0 (0)	0.8 (3)	0.12
Placenta accreta	0.0 (0)	0.3 (1)	0.50

Surgical characteristics	HA-CMC (N=380)	No treatment (N=373)	P-value
Uterine rupture	0.0 (0)	0.0 (0)	—
Uterine dehiscence	0.0 (0)	0.3 (1)	0.50

[‡]Data are presented as median (range), and compared between groups based on the two-sample median test

Key: American Society of Anesthesiologists (ASA)

Table 4**Post-operative Course**

Post-operative course	HA-CMC (N=380)	No treatment (N=373)	P-value	Risk Ratio (95% CI)
Post-operative hematocrit [†]	29.9 ± 4.1	30.2 ± 3.6	0.22	
Post-operative WBC count [†]	11.3 ± 6.4	11.0 ± 3.3	0.61	
Post-operative T _{max} (>24 hours after delivery) [†]	98.2 ± 1.0	98.2 ± 0.9	0.59	
Intravenous narcotic use, %(n)	77.0 (292)	78.2 (291)	0.73	0.9 (0.6, 1.6)
Number of oral narcotic pills [‡]	10 (0, 54)	10 (1, 43)	0.51	
Post-operative antibiotics to treat infection, %(n)	8.2 (31)	5.2 (19)	0.11	1.6 (0.9, 3.0)
Post-operative complications, %(n)	6.3 (24)	4.0 (15)	0.19	1.5 (0.7, 3.0)
Fever	4.5 (17)	3.0 (11)	0.34	1.5 (0.7, 3.3)
Ileus obstruction	0.0 (0)	0.0 (0)	—	
Abscess	0.0 (0)	0.3 (1)	0.99	
Any wound complication	2.1 (8)	0.8 (3)	0.22	2.8 (0.7, 11.0)
Wound separation	5.1 (6)	1.7 (2)	0.17	3.2 (0.6, 16.0)
Wound cellulitis	1.7 (2)	0.0 (0)	0.25	
Wound dehiscence	0.0 (0)	0.3 (1)	0.50	
Pulmonary embolus-DVT	0.0 (0)	0.3 (1)	0.50	
Length of stay [‡] , days	3 (2, 62)	3 (2, 65)	0.42	
Readmission (6 weeks postpartum), % (n)	1.3 (5)	0.5 (2)	0.45	2.5 (0.5, 13.3)
Number of office visits (8 weeks postpartum), %			0.96	
None	2.9 (3/103)	2.0 (2/100)		
1	38.8 (40/103)	39.0 (39/100)		
2	43.7 (45/103)	46.0 (46/100)		
3	14.6 (15/103)	13.0 (13/100)		

[†]Data are presented as mean (standard deviation) and compared between groups using the student's t-test based on unequal between-group variances

[‡]Data are presented as median (range), and compared between groups based on the two-sample median test

Table 5

Patient Demographics and Pre-operative characteristics (at randomization) among patients that returned for subsequent delivery

Patient characteristics	HA-CMC (N=80)	No treatment (N=92)
Maternal age (years) [†]	29.9 ± 4.3	30.0 ± 5.6
Gravidity [‡]	2 (1, 7)	2 (1, 9)
Parity [‡]	0 (0, 2)	1 (0, 4)
Race/Ethnicity, % (n)		
Caucasian	78.8 (63)	71.7 (66)
African-American	10.0 (8)	8.7 (8)
Asian	1.3 (1)	3.3 (3)
Latino	8.8 (7)	13.0 (12)
Other race/ethnicity	1.3 (1)	3.3 (3)
Gestational age (weeks) [†]	38.6 ± 2.3	39.0 ± 4.2
Body-mass index (kg/m ²) [†]	33.6 ± 6.7	33.1 ± 9.3
Number of previous cesareans [‡]	0 (0, 2)	1 (0, 4)
Indication for cesarean, % (n)		
Planned repeat cesarean	66.3 (53)	57.6 (53)
Non-reassuring fetal heart rate	2.5 (2)	1.1 (1)
Arrest of labor	3.8 (3)	2.2 (2)
Failed induction	2.5 (2)	5.4 (5)
Previous uterine surgery	1.3 (1)	3.3 (3)
Malpresentation	17.5 (14)	22.8 (21)
Abnormal placentation	1.3 (1)	2.2 (2)
Multiple gestation	2.5 (2)	3.3 (3)
Maternal infection	0.0 (0)	2.2 (2)
Diabetes (any), % of arm (n)	9 (11.7)	6.6 (6)
Type I	22.2 (2)	0.0 (0)
Type II	22.2 (2)	0.0 (0)
Gestational Diabetes, A1	22.2 (2)	50.0 (3)
Gestational Diabetes, A2	33.3 (3)	50.0 (3)
Pre-operative hematocrit [†]	35.0 ± 4.0	33.5 ± 5.7
Pre-operative WBC count [†]	10.6 ± 4.1	11.4 ± 5.7
Pre-operative T _{max} [†] (°F)	97.9 ± 0.9	97.9 ± 0.9
Surgical characteristics		
Urgency, % (n)		
Elective	82.5 (66)	79.4 (73)
Non-elective	17.5 (14)	19.6 (18)
Emergent	0.0 (0)	1.1 (1)
Total operative time (minutes) [‡]	52 (16, 124)	48 (22, 129)

Patient characteristics	HA-CMC (N=80)	No treatment (N=92)
Anesthesia, % (n)		
Spinal	95.0 (76)	94.6 (87)
Epidural	5.0 (4)	4.4 (4)
Combined Spinal-Epidural	0.0 (0)	1.1 (1)
General	0.0 (0)	0.0 (0)
ASA classification, % (n)		
Class I	12.7 (10)	9.0 (8)
Class II	72.3 (57)	74.2 (66)
Class III	15.2 (12)	16.9 (15)
Class IV		
Procedure type, % (n)		
Low Transverse	98.7 (79)	96.6 (89)
Classical	1.3 (1)	2.2 (2)
Other	0.0 (0)	2.2 (2)
Rectus muscle approximation, % (n)	45 (36)	43.5 (40)
Peritoneum closure, % (n)	31.3 (25)	38.0 (35)
Uterine Closure		
Single layer	71.3 (57)	70.7 (65)
Double layer	28.8 (23)	29.3 (27)
Estimated blood loss (ml) [‡]	800 (500, 2000)	800 (600, 1500)
Post-operative course		
Post-operative hematocrit [‡]	30 (14, 38)	31 (19, 39)
Post-operative WBC count [‡]	10 (7, 28)	11 (6, 29)
Post-operative T _{max} (>24 hours after delivery) [‡]	98.3 ± 1.0	98.1 ± 0.9
Intravenous narcotic use, % (n)	5.1 (4)	8.7 (8)
Number of oral narcotic pills [‡]	10 (1, 54)	10 (1, 38)
Post-operative antibiotics to treat infection, % (n)	7.6 (6)	7.8 (7)
Post-operative complications, % (n)	6.3 (5)	4.4 (4)
Fever	3.8 (3)	3.3 (3)
Ileus obstruction	0.0 (0)	0.0 (0)
Abscess	0.0 (0)	0.0 (0)
Any wound complication	3.8 (3)	1.1 (1)
Wound separation	6.7 (2)	3.7 (1)
Wound cellulitis	3.3 (1)	0.0 (0)
Wound dehiscence	0.0 (0)	0.0 (0)
Pulmonary embolus-DVT	0.0 (0)	0.0 (0)
Length of stay [‡] , days	4 (2, 24)	3 (2, 17)
Readmission (6 weeks postpartum), % (n)	3.3 (1)	0.0 (0)
Number of office visits (8 weeks postpartum), % (n)		
None	3.9 (1)	0.0 (0)
1	42.3 (11)	35.0 (7)

Patient characteristics	HA-CMC (N=80)	No treatment (N=92)
2	42.3 (11)	55.0 (11)
3	11.5 (3)	10.0 (2)

[‡]Data are presented as mean (standard deviation) and compared between groups using the student's t-test based on unequal between-group variances

[‡]Data are presented as median (range), and compared between groups based on the two-sample median test

Table 6

Delivery Surgical Characteristics at Follow-up

Patient characteristics	HA-CMC (n=80)	Control (n=92)	P-value
Urgency of cesarean, %			0.793
Scheduled	78.8	76.1	
Non-emergent	20.0	20.7	
Emergent	1.3	3.3	
Labor prior to operation, %	20.0	21.7	0.852
Rupture of membranes, %	6.3	8.7	0.579
Skin to delivery time (minutes)	13 (3, 70)	13 (4, 55)	0.973
Total operative time (minutes)	51 (23, 175)	54 (26, 157)	0.540
Cesarean procedure type, %			
Low transverse	98.8	96.7	0.624
Classical	1.3	2.2	0.999
Estimated blood loss (ml)	800 (500, 2,000)	800 (600, 1,500)	0.745
Overall complications, % (n)	7.5 (6)	4.3 (4)	0.665
Bladder Injury	0.0	0.0	—
Bowel injury	5.2 (4)	2.3 (2)	0.423
Hysterectomy	0.0	0.0	—
Intra-operative transfusion	1.3 (1)	1.1 (1)	0.999
Placenta accreta	0.0	0.0	—
Uterine rupture	0.0	0.0	—
Uterine dehiscence	2.5 (2)	1.1 (1)	0.598

Table 7

Subsequent delivery adhesion data (Primary Outcome)

Adhesion characteristics	HA-CMC (n=80)	Control (n=92)	P-value
Adhesion score [†]	2 (0, 10)	2 (0, 8)	0.647
Change in adhesion score [‡]	-1 (-8, 4)	-1 (-6, 4)	0.742
Any adhesion (any location), % *	75.6	75.9	0.999
Bowel adhesions, %	5.2	2.3	0.455
Uterus to fascia, %	36.4	26.7	0.096
Omentum to fascia, %	32.5	27.9	0.508
Omentum to uterus, %	18.2	23.3	0.713
Bladder to uterus, %	65.4	62.1	0.243
Other location, %	5.2	10.5	0.501
Filmy adhesions (any location), %			
Bowel adhesions, %	2.6	2.3	
Uterus to fascia, %	7.8	11.6	
Omentum to fascia, %	15.6	17.4	
Omentum to uterus, %	11.7	14.0	
Bladder to uterus, %	34.6	42.5	
Other location, %	1.3	2.3	
Dense adhesions (any location), %			
Bowel adhesions, %	2.6	0	
Uterus to fascia, %	28.6	15.1	
Omentum to fascia, %	16.9	10.5	
Omentum to uterus, %	6.5	9.3	
Bladder to uterus, %	30.8	19.5	
Other location, %	3.9	8.1	
Severe adhesions (adhesion score >4), %	33.3	15.5	0.052

[†]Data are presented as median (range), and compared between groups based on the two-sample median test

[‡]Difference in adhesion score from randomization compared to the subsequent delivery

* Proportions were compared using the Fisher's Exact test