Limited Efficacy and Adverse Effect of Sodium Hyaluronic Acid-Carboxymethylcellulose and Oxidized Regenerated Cellulose at Primary Cesarean Delivery

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Abstract

Introduction: Adhesion is associated to delayed delivery of the neonate and higher incidence of intraoperative and postoperative complications. Currently, there is no definite consensus regarding the use of adhesion barriers at cesarean section. Objective: To analyze the postoperative outcomes among two adhesion barrier groups and control group at the primary and the secondary cesarean section. Methods: This retrospective study includes 199 Asian women undergoing primary and secondary cesarean section between January1, 2011, and September 31, 2019. We used regression to analyze risk factors of postcesarean fever at primary cesarean section. Further we used interaction analysis to examine the effect of surgical site infection risk factors and use of adhesion barrier on postcesarean fever rates at the primary cesarean section. Results: We found that use of adhesion barrier at the primary cesarean section is associated with a significantly higher incidence of postcesarean fever (p=0.045). The risk factor for postcesarean fever is the use of anti-adhesion filmduring emergency cesarean section (p=0.041). In the subgroup of labor before operation and emergency cesarean section, adhesion barrier user had significant higher risk of postcesarean fever than nonuser ($p<0.05$). Conclusion: The patients used of anti-adhesion films during emergency cases and when a woman has labor before operation is associated with a significantly higher risk of postcesarean fever which potentially means increased risk of surgical site infection.

Tweetable abstract

Currently, there is no conclusive consensus regarding usage of adhesion barriers at cesarean section. Previous studies of HA-CMC were performed by different surgeons which affect background adhesion incidence, and studies of ORC were limited to one small study. We are interested in the adhesion rates under the minimal effect of confounding factors and the postoperative outcome of different adhesion barriers. We found the use of adhesion barrier at cesarean delivery didn't improve adhesion formation but had significantly higher rates of postcesarean fever. Our result does not support application of anti-adhesion films during cesarean deliveries especiallyin emergency cesarean section or in a woman having labor before operation.

Introduction

Repeat cesarean section (CS) has led to more difficult surgeries, secondary to adhesion found at delivery. The more often the abdomen is entered, the more extensive and dense adhesion may be encountered. Previous research reported prevalence of adhesion in 11.5–46% of women at their second CS and 26–75% of women during their third CS [1-11]. Adhesion has been linked in the delayed delivery of the neonate, higher incidence of bladder or bowel injury, excessive bleeding, and increased operative time during repeat CS [10-13]. There are several adhesion prevention barriers approved by the U.S. Food and Drug Administration

(FDA) for the prevention of postoperative adhesion. Two commercially available barriers for CS such as HA-CMC (Seprafilm®) or ORC (Interceed®) have been studied, and some retrospective and prospective studies suggest that these barriers reduce the amount and severity of adhesion formation and blood loss [14-21]. In our experience, adhesion after the primary CS is generally minimal or nonexistent. One randomized trial and two retrospective researches demonstrated that HA-CMC applied during CS did not reduce adhesion formation and affect operative outcome at repeat CS [22-24]. However, these studies of HA-CMC reported the data were from a multicenter and CS were performed by different surgeons with varying experience and surgical techniques (e.g., rectus muscle approximation, uterine or peritoneal closure, packing the gutters) [3, 4, 25-30]. Second, they did not exclude the patient with history of uterine incision or laparoscopy. These confounding factors affect background adhesion incidence. Third, data regarding the use of ORC for adhesion prevention during CS were limited to one small study. So we executed a CS retrospective chart review performed by three physicians with profound experience and similar surgical techniques. We evaluated clinical efficacy of placement of the HA-CMC and ORC during primary CS and assess surgical outcomes at primary and secondary CS.

Patients and Methods

We conducted a retrospective study between January1, 2011, and September 31, 2019. The study was reviewed and approved by the institutional ethics committee of the MacKay Memorial Hospital (18MMHIS155e). The study included all Asian women undergoing primary CS performed by the three experienced surgeons (at least more than 20 years as an obstetrician) at MacKay Memorial Hospital, a quaternary care referral hospital at Taipei. Most patients received secondary CS by the same surgeon, while a minority received the secondary operation by the other two surgeons at or less than five years interval. Additional inclusion criteria included the following: both deliveries were live neonates at 23–42 weeks of gestation, delivered through Pfannenstiel incisions, intraperitoneal CS, and both hysterotomy with low transverse incision. Exclusion criteria included the following: (a) American Society of Anesthesiologists (ASA) score >3; (b) medical records mentioning history of pelvic inflammatory disease or endometriosis; (c) uterine incision (e.g., myomectomy, cesarean), open abdominal or laparoscopic pelvic surgery before the primary or the secondary CS; (d) tubal sterilization, ovarian cystectomy or myomectomy during CS.

Operative notes and electronic medical records on labor and delivery of patients concerning the primary and the secondary surgical procedures were used to obtain data on demographic data (maternal age, parity, gestational age, body mass index (BMI), ASA score) and relevant data from their medical and surgical history. We also collected the basic characteristics and complications at each surgery, including preoperative and postoperative laboratory data, estimated blood loss, visceral organ injury, the description of adhesion, operative times, and skin-to-delivery time.

Adhesion reduction agent in CS is the indication of HA-CMC or ORC in Taiwan. Our pregnant women could choose to use anti-adhesion material or not before undergoing operation. Preoperative skin preparation was done and prophylactic and therapeutic antibiotics were given according to local standards. After delivery, all uterus were closed in two layers, and closure of the bladder flap and peritoneum and rectus muscle approximation were also done. Abdominal irrigation or packing of bowel was avoided during operation. HA-CMC or ORC was placed over the incisional site and the midline anterior surface of the uterus. This was usually completed with 1 sheet or cut into smaller pieces to facilitate placement. Because there has not been a validated adhesion scoring system to be used for cesarean deliveries, we evaluated adhesion that was in the field of manipulation. Adhesion was scored as severe or mild, if the operative summary contained the words *severe* ,*extensive* , *vascular* , and *dense* or if the operative notes used words such as *mild* , *few* , *filmy,* and*some* . The outcome measures were the incidence of adhesion, skin-to-delivery time (defined as the time from skin incision to the first neonate delivery), operative time (defined as the time from skin incision to skin closure) during the secondary CS, estimated blood loss, and rates of intraoperative (e.g., bladder or bowel injury, hysterectomy, injury to uterine vessels, postpartum hemorrhage, or drop of Hb) and postoperative complications (e.g., fever, ileus, incisional wound infection, metritis, UTI, hospital length, readmission for SSI, and the frequency of postpartum clinic visits) related to the repeat CS. We also examine the short-term

postoperative outcome (as repeat CS) of the adhesion barriers placement at the primary CS as measured by postoperative complications (e.g., postoperative white blood cell count).

Sample size at each group was calculated based on studies performed by Fushiki et al. [16] and Chapa et al. [19] for the endpoint of adhesion formation. We estimated that a minimum of 20 patients in HA-CMC group and 14 patients in ORC group would be required to detect these differences with 80% power.

Statistical analysis was performed with R software, version 3.3.1 (R Project for Statistical Computing, Vienna, Austria). Differences in demographics among the three groups were assessed with the Student's t-test or chi-square as appropriate and the results for continuous variables were given as the mean ± SD. Multiple logistic regression was used to evaluate for SSI risk factors of postcesarean fever at the primary CS. An interaction term analysis was performed to examine the impact of SSI risk factors and use of adhesion barrier on postcesarean fever rates at the primary CS. The magnitude of statistical significance was expressed with Adj-HR and 95% CI. Statistical significance was defined at the 95% level ($P<0.05$).

Results

A total of 236 patients were included in this study and 37 were excluded due to one or more exclusion criteria. Finally, 99 women received the HA-CMC, 26 women received the ORC, and 74 did not receive adhesion barrier at the primary CS. There were no differences in patient demographics or preoperative characteristics at the time of the primary CS except for gestational age and preoperative white blood cell count, which was highest in the nonuser group (Table 1). Table 2 shows intraoperative characteristics including skin-to-delivery time, total operative time, adhesion condition, intraoperative complications or estimated blood loss, and neonatal birth weight, and there were no significant differences among the 3 groups. It also contained postoperative laboratory data includinghematocrit, drops of hematocrit and white blood cell count, with no significant difference among the groups. Similarly, there were no differences in the need of additional therapeutic antibiotic, hospital length, readmission for SSI, and the frequency of postpartum clinic visits. However, two patients who received the HA-CMC adhesion barrier were readmitted to the hospital for postpartum metritis. But both groups that used adhesion barrier had significantly higher rates of postoperative fever compared with the control group (HA-CMC 17.2% vs. ORC 15.4% vs. nonuse 5.4%,p =0.045).

Demographic data at the time of the secondary CS are shown in Table 3. There were no significant differences among the groups except for gestational age and the percentage of adhesion barrier use at the secondary CS. Around 63% of nonuser at the primary CS chose to use adhesion barrier at the secondary CS and 97% and 96.2% of the other two groups chose to use adhesion barrier at repeat CS. There were less than 40% of patients in labor and less than 20% of patients with membrane rupture before operation in either group at secondary CS, while there were50–70% of patients in labor and 40–60% with membrane rupture before the primary CS. Table 4 shows adhesion and intraoperative and postoperative outcomes at the secondary CS. Notably, there were no differences as regards skin-to-delivery time, total operative time, adhesion formation, bladder or bowel injury, hysterectomy, injury to uterine vessels, estimated blood loss, or drop of Hb.

Since the use of adhesion barrier user at the primary CS had significantly higher rates of postcesarean fever, the following SSI risk factors relating to postcesarean fever were evaluated using logistic regression: use of the adhesion barrier, labor or membrane rupture before operation, emergency operation, total operative time, estimated blood loss [?]500 cc, BMI [?]30 kg/m2, diabetes mellitus, hypertension, or preeclampsia. All nine risk factors were entered in a multiple regression and we found the use of adhesion barrier at the primary CS as an independent risk factor of postcesarean fever (p= 0.045, Adj-HR=3.53, 95% CI=1.03–10.24) (Table 5). An interaction term analysis was performed to examine the impact of SSI risk factors and use of adhesion barrier on postcesarean fever at the primary CS (Table 6). The strongest risk factor for postcesarean fever is the use of anti-adhesion filmduring emergency CS (p= 0.041). Borderline interaction between labor before operation and use of anti-adhesion filmmay play some role for postcesarean fever (p= 0.054).In the subgroup of labor before operation and emergency CS, adhesion barrier use had significantly higher risk of postcesarean fever (labor before operation: user 21.2% vs. nonuser 2.2%,p= 0.018, Adj-HR=12.12, 95% CI=1.53–95.78; emergency CS: user 20.3% vs. nonuser 2.0%, p= 0.016, Adj-HR=12.71, 95% CI=1.62–99.62).

Discussion

Our result demonstrates that the incidence of adhesion at the secondary CS is minimal or nonexistent and use of adhesion barrier did not reduce skin-to-delivery time and the likelihood of intraoperative or postoperative complications at the secondary CS. However, use of adhesion barrier films at the primary CS associated with a higher incidence of postcesarean fever which potentially means increased risk of SSI.

Existing similar study [23]reported adhesion rates of 18% vs. 17% in use and nonuse of HA-CMC and 20% vs. 83% in use and nonuse of ORC, respectively, at the repeat CS [19]. Our data reported minimal adhesion rates which are obviously lower than existing data [23]. We believe that is reliable because we minimize the effect of confounding factors such as history of pelvic inflammatory disease, endometriosis, and open abdominal or laparoscopic pelvic surgery before the primary and the secondary operations. Second, operations were performed by three physicians with profound experience and had minimal blood loss during operation. Third, all CS were operated with the same techniques that reduce adhesion (e.g., rectus muscle approximation, closure of the bladder flap and peritoneum) [3, 4, 26-30]. There were also many proposed mechanisms to explain why adhesion formation following CS was less than laparotomyin nonpregnant woman: (a) greater tissue perfusion in pregnancy is associated with less tissue hypoxia; (b) the lower segment incision is covered by the bladder which is constantly being filled and emptied during the healing process and this movement disrupts fibrinous formation between the uterus and the bladder and between the lower segment and the anterior abdominal wall; (c) one single incision in the lower segment at CS is less than myomectomy which associated with more tissue handling; (d) less hematoma developed in the low transverse incision at CS; (e) rapid change inuterine size in the postoperative period disrupts adhesion formation. In fact, evidence in the literature suggests that the consequences of postoperative adhesion such as bowel obstruction, urinary tract injury, infertility, ectopic pregnancy, and chronic pain may be less following CS compared with gynecological surgery [31].

Reported studies of the HA-CMC barrier found no differences in the incidence of adhesion, skin-to-delivery time, and total operative time which were consistent with our result except for higher rates of postcesarean fever after the primary CS [22-24]. However, only one of them mentioned about postoperative complications and most CS were elective in this study [22]. To date, cases of chemical peritonitis (inflammation) associated with adhesion barrier following emergency CS have been reported in Japan [32, 33]. The mechanisms leading to chemical inflammation associated with adhesion barrier have not been clear but the hyaluronan-based membrane has been observed to be associated with an increased adhesion in an animal model of bacterial peritonitis [34, 35]. These studies implied postcesarean peritonitis in patients who received the adhesion barrier films was associated with wound classification which reflects the degree of contamination of the wound during operation. A recent study showed the percentage of class III and class IV in emergency CS was 22.3% and the metritis rates of patients who received the HA-CMC barrier with contaminated or dirty/infected wound was much higher than cases using 4% Icodextrin solution (32.0% vs. 10.3%, p =0.048) [36]. It was mentioned that contaminated or dirty/infected wound with placement of anti-adhesion films may form occlusive barrier that prevents omentum to absorb the microabscess and serve as a culture medium to nourish bacteria.

Our concern is that patients who used adhesion barrier at the primary CS had significantly higher rates of postcesarean fever and therefore it is an independent risk factor of postcesarean fever. So we performed interaction term analysis to examine the impact of SSI risk factors [37] and use of adhesion barrier on postcesarean fever. And we found the strongest risk factor for postcesarean fever is the use of anti-adhesion film during emergency CS (p=0.041) as well as in cases where women have labor before operation (p=0.054). We think that it is because at least half of the primary CS in our study were conducted in emergency or having labor before operation. Most of them (e.g., prolonged labor, fetal distress) had long duration of labor or membrane rupture and they also received more digital vaginal examinations before operation. Thus, a contaminated wound with anti-adhesion films means more chances of having SSI.

Based from our data, the incidence of adhesion at the secondary CS is minimal or nonexistent and use of adhesion barriers at primary CS don't significantly reduce adhesion, shorten the time needed for neonate

delivery, and improve surgical outcome at repeat CS. Furthermore, use of adhesion barrier films during emergency cases and when a woman has labor before operation is associated with a significantly higher risk of postcesarean fever which potentially means increased risk of SSI. Unlike our study, analysis of SSI risk factors and use of adhesion barrier has not been available previously. Collectively, our study adds new information regarding impact of adhesion barrier on postcesarean fever.

There was only one phase IV prospective trial that has reported the effectiveness of HA-CMC at the repeat CS but there is no prospective trial for safety of use in specific condition such asemergency operation or labor before operation. There is also no prospective trial reporting the effectiveness and safety of ORC. Prospective studies comparing the effectiveness and safety of all adhesion barriers extensively used in primary CS can help in evaluating the cost-effectiveness of these products and developing evidence-based decision-making.

Strengths and Limitations

Like all retrospective studies, our study is limited by its nature and the limitations inherent in such a design. Besides, there were fewer patients in the ORC group compared with nonusers. Although residents noted the electronic medical records as detailed as possible, we might have underestimated the adhesion rates because assessment and description of adhesion is subjective and there has not been a validated adhesion scoring system to be used for the two procedures. Our study has several strengths. The inclusion criteria were designed to minimize the effect of confounding factors as possible such as previous pelvic operations on the outcomes, and the CSs were performed by three physicians in the same hospital with profound experience and similar surgical techniques.

Conclusions

Our result shows the incidence of adhesion at the secondary CS is minimal or nonexistent and use of adhesion barriers at primary CS does not significantly reduce adhesion, shorten the time needed for neonate delivery, and improve surgical outcome at repeat CS. In contrast, use of adhesion barrier films during emergency CS or in a woman having labor before operation is associated with a significantly higher risk of postcesarean fever which potentially means increased risk of SSI. Therefore, we don't suggest routine application of adhesion barrier films during cesarean deliveries especially in emergency CS or in a woman having labor before operation.

Abbreviations: CS (cesarean section), BMI (body mass index), American Society of Anesthesiologists (ASA), surgical site infection (SSI), hyaluronic acid/carboxymethylcellulose (HA-CMC), oxidized regenerated cellulose (ORC), Food and Drug Administration (FDA), urinary tract infection (UTI)

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Authors' contributions

KSL, JPH, JHY were involved in the conception and design of the study; KSL YLW, WCH, JPH were involved in collected clinic patients in MacKay Memorial Hospital; KSL, JHY contributed to data analysis and interpretation; JPH as co-corresponding authors, had the major roles in advising, drafting, and revising the draft. All authors were involved in the writing of the manuscript and provided final approval.

Competing interests

The authors declare that they have no competing interests.

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Table 1. Patient demographics and perioperative characteristics at the primary cesarean delivery.

Variable	Variable	Non-use(n=74)	Non-use(n=74)	HA-C
Age (years)	Age (years)	31.26±4.13	31.26±4.13	31.54±
BMI (Kg/M^2)	BMI (Kg/M^2)	27.47±3.82	27.47±3.82	27.20±
GA (weeks)	GA (weeks)	37.51±3.40	37.51±3.40	38.57±
Systematic or gestational disease	Systematic or gestational disease			
Diabetes mellitus	Diabetes mellitus			
Gestational	Gestational	6(8.1%)	6(8.1%)	5(5.1%
Pregestational	Pregestational	0(0.0%)	0(0.0%)	2(2.0%
Hypertension	Hypertension			
Gestational	Gestational	2(2.7%)	2(2.7%)	2(2.0%
Chronic	Chronic	1(1.4%)	1(1.4%)	0(0.0%
Preeclampsia or superimposed	Preeclampsia or superimposed	3(4.1%)	3(4.1%)	6(6.1%
SLE	SLE	0(0.0%)	0(0.0%)	1(1.0%
HIV	HIV	0(0.0%)	0(0.0%)	2(2.0%
Indication for cesarean	Indication for cesarean	Indication for cesarean		
Prolonged labor	Prolonged labor	21(28.4%)	21(28.4%)	29(29.3
Fetal distress	Fetal distress	18(24.3%)	18(24.3%)	14(14.1
Malpresentation	Malpresentation	21(28.4%)	21(28.4%)	32(32.3
Twins with malpresentation	Twins with malpresentation	0(0.0%)	0(0.0%)	3(3.0%
Elective	Elective	9(12.2%)	9(12.2%)	14(14.1
Macrosomia	Macrosomia	4(5.4%)	4(5.4%)	3(3.0%
Placenta previa	Placenta previa	2(2.7%)	2(2.7%)	7(7.1%
Cephalopelvic disproportion	Cephalopelvic disproportion	1(1.4%)	1(1.4%)	0(0.0%
Condyloma/HIV infection	Condyloma/HIV infection	0(0.0%)	0(0.0%)	3(3.0%
Pre OP Hb	Pre OP Hb	11.62±1.32	11.62±1.32	11.85±
Pre OP WBC	Pre OP WBC	10091.89±3379.42	10091.89±3379.42	9117.1
Pre OP BT[?]38	Pre OP BT[?]38	3(4.1%)	3(4.1%)	5(5.1%
Labor before OP	Labor before OP	46(62.2%)	46(62.2%)	49(49.5
MR before OP	MR before OP	38(51.4%)	38(51.4%)	46(46.5
Urgency	Urgency			
Elective	Elective	23(31.1%)	23(31.1%)	42(42.4
Emergency	Emergency	51(68.9%)	51(68.9%)	57(57.6
ASA	ASA			
Class I	Class I	26(35.1%)	26(35.1%)	40(40.4
Class II	Class II	46(62.2%)	46(62.2%)	57(57.6
Class III	Class III	2(2.7%)	2(2.7%)	2(2.0%
$p < 0.05$				

Table1. Data are mean ± SD or n (%) and compared among groups using Student's t- test or chi-square test for P -value. Significant P -values are emboldened. Abbreviations: HA-CMC, hyaluronic acid/carboxymethylcellulose; ORC, oxidized regenerated cellulose; BMI, body mass index; GA, gestational age; SLE, systemic lupus erythematosus; HIV, human immunodeficiency virus; OP, operative; WBC, white blood cell count; BT, body temperature; MR, membrane rupture; ASA, American Society of Anesthesiologists.

Table 2. Patient intraoperative and postoperative outcome at the primary cesarean delivery

Variable	Non-use(n=74)	HA-CMC(n=99)	ORC(n=26)	p
Skin incision to delivery(min)	4.38±1.76	4.65±2.09	4.00±0.94	0.256
OP time (min)	49.46±10.70	51.54±14.58	47.92±10.28	0.342
Anesthesia				0.840
Spinal	68(91.9%)	92(92.9%)	24(92.3%)	
General	5(6.8%)	7(7.1%)	2(7.7%)	
Skin closure				0.19
Suture	53(71.6%)	75(75.8%)	15(57.7%)	
Staples	21(28.4%)	24(24.2%)	11(42.3%)	
Neonatal BW(g)	2873.58±788.73	3087.05±479.54	3078.92±294.68	0.057
HB POD1	10.51±1.49	10.77±1.53	10.68±1.70	0.551
Hb—POD1	1.11±0.91	1.08±1.00	0.89±0.89	0.582
Blood loss (cc)	321.62±170.23	347.47±198.25	313.46±136.79	0.543
WBC POD1	14100.00±3566.01	14258.59±3714.29	15346.15±3662.48	0.312
Post OP max BT(¿24 hrs after OP)	37.39±0.40	37.53±0.49	37.39±0.41	0.107
Hospital length(Days)	4.77±0.61	4.98±0.74	5.15±2.07	0.171
Readmission[?]1 month for SSI	0(0.0%)	2(2.0%)	0(0.0%)	0.628
Postpartum clinic visits[?]2 months				0.110
None	0(0.0%)	6(6.1%)	0(0.0%)	
1	48(64.9%)	59(59.6%)	13(50.0%)	
2	23(31.1%)	33(33.3%)	12(46.2%)	
Adhesion				1.000
None	74(100%)	99(100%)	26(100%)	
Mild	0(0.0%)	0(0.0%)	0(0.0%)	
Severe	0(0.0%)	0(0.0%)	0(0.0%)	
Intraoperative complication				
Bladder injury	0(0.0%)	0(0.0%)	0(0.0%)	1.000
Bowel injury	0(0.0%)	0(0.0%)	0(0.0%)	1.000
Hysterectomy	0(0.0%)	0(0.0%)	0(0.0%)	1.000
Intraop transfusion	0(0.0%)	1(1.0%)	0(0.0%)	1.000
Injury to uterine vessels	1(1.4%)	3(3.0%)	0(0.0%)	0.793
Postpartum hemorrhage	1(1.4%)	3(3.0%)	0(0.0%)	0.793
Postoperative complication				
Fever	4(5.4%)	17(17.2%)	4(15.4%)	**0.045***
Ileus	0(0.0%)	0(0.0%)	0(0.0%)	1.000
Incisional wound infection	1(1.4%)	2(2.0%)	0(0.0%)	1.000
Postcesarean metritis	0(0.0%)	3(3.0%)	0(0.0%)	0.369
Urinary tract infection	0(0.0%)	0(0.0%)	0(0.0%)	1.000
Therapeutic antibiotics	2(2.7%)	7(7.1%)	1(3.8%)	0.486

* $p < 0.05$

Table2. Data are mean ± SD or n (%) and compared among groups using Student's t- test or chi-square test for P -value. Significant P -values are emboldened. Abbreviations: OP, operative; SSI, surgical site infection; BW, body weight; POD, postoperative day; WBC, white blood cell count; BT, body temperature.

Table 3. Patient demographics and perioperative characteristics at the secondary cesarean delivery

Variable	Variable	Non-use(n=74)	HA-CMC(n=9
Age(years)	Age(years)	33.89±4.37	34.12±3.33

Variable	Variable	Non-use(n=74)	HA-CMC(n=9
BMI(Kg/M^2)	BMI(Kg/M^2)	27.26±3.97	27.15±3.72
GA (weeks)	GA (weeks)	37.64±1.15	37.92±0.82
OP interval (months)	OP interval (months)	32.51±12.55	30.98±10.41
Systematic or gestational disease	Systematic or gestational disease	Systematic or gestational disease	
Diabetes mellitus	Diabetes mellitus		
Gestational	Gestational	5(6.8%)	10(10.1%)
Pregestational	Pregestational	0(0.0%)	2(2.0%)
Hypertension	Hypertension		
Gestational	Gestational	2(2.7%)	3(3.0%)
Chronic	Chronic	1(1.4%)	0(0.0%)
Preeclampsia or superimposed	Preeclampsia or superimposed	2(2.7%)	0(0.0%)
SLE	SLE	0(0.0%)	1(1.0%)
HIV	HIV	0(0.0%)	2(2.0%)
Indication for cesarean			
Prolonged labor	Prolonged labor	0(0.0%)	0(0.0%)
Fetal distress	Fetal distress	1(1.4%)	1(1.0%)
Previous CS	Previous CS	74(100.0%)	99(100.0%)
Malpresentation	Malpresentation	6(8.1%)	8(8.1%)
Twins with malpresentation	Twins with malpresentation	0(0.0%)	0(0.0%)
Elective	Elective	0(0.0%)	0(0.0%)
Macrosomia	Macrosomia	0(0.0%)	2(2.0%)
Placenta previa	Placenta previa	1(1.4%)	0(0.0%)
Cephalopelvic disproportion	Cephalopelvic disproportion	0(0.0%)	0(0.0%)
Condyloma/HIV infection	Condyloma/HIV infection	0(0.0%)	2(2.0%)
Pre OP Hb	Pre OP Hb	11.31±1.41	11.52±1.32
Pre OP WBC	Pre OP WBC	9271.62±2316.91	8783.84±2475.17
Pre OP BT[?]38	Pre OP BT[?]38	0(0.0%)	0(0.0%)
Labor before OP	Labor before OP	20(27.0%)	18(18.2%)
MR before OP	MR before OP	9(12.2%)	7(7.1%)
Urgency	Urgency		
Elective	Elective	48(64.9%)	75(75.8%)
Emergency	Emergency	26(35.1%)	24(24.2%)
ASA	ASA		
Class I	Class I	20(27.0%)	21(21.2%)
Class II	Class II	52(70.3%)	77(77.8%)
Class III	Class III	2(2.7%)	1(1.0%)
Adhesion barrier	Adhesion barrier		
Non-use	Non-use	27(36.5%)	3(3.0%)
HA-CMC	HA-CMC	32(43.2%)	55(55.6%)
ORC	ORC	14(18.9%)	25(25.3%)
Other	Other	1(1.4%)	16(16.1%)

* $p < 0.05$

Table3. Data are mean ± SD or n (%) and compared among groups using Student's t- test or chi-square test for P -value. Significant P -values are emboldened. Abbreviations: HA-CMC, hyaluronic acid/carboxymethylcellulose; ORC, oxidized regenerated cellulose; BMI, body mass index; GA, gestational age; OP, operative; SLE, systemic lupus erythematosus; HIV, human immunodeficiency virus; CS, cesarean section; WBC, white blood cell count; BT, body temperature; MR, membrane rupture; ASA, American Society of Anesthesiologists.

Table 4. Patient intraoperative and postoperative outcome at the secondary cesarean delivery

Variable	Non-use(n=74)	HA-CMC(n=99)	ORC(n=26)	p
Skin incision to delivery(min)	5.26±2.05	5.56±2.50	5.54±2.37	0.687
OP time (min)	57.05±14.90	56.54±15.92	60.04±16.88	0.596
Anesthesia				1.000
Spinal	72(97.3%)	97(98.0%)	26(100.0%)	
General	2(2.7%)	2(2.0%)	0(0.0%)	
Skin closure				0.293
Suture	54(73.0%)	76(76.8%)	16(61.5%)	
Staples	20(27.0%)	23(23.2%)	10(38.5%)	
Neonatal BW(g)	3018.92±391.80	3082.87±379.82	2957.85±500.33	0.302
HB POD1	10.46±1.49	10.59±1.38	10.80±1.39	0.562
Hb—POD1	0.85±0.80	0.92±0.76	0.63±0.76	0.226
Blood loss (cc)	339.86±182.63	339.39±189.29	340.38±179.45	1.000
WBC POD1	12817.57±3689.98	11839.53±2991.95	11446.15±2825.21	0.075
Post OP max BT(¿24 hrs after OP)	37.31±0.39	37.27±0.37	37.14±0.31	0.128
Hospital length(days)	4.68±0.50	4.73±0.47	4.65±0.49	0.692
Readmission[?]1 month for SSI	0(0.0%)	1(1.0%)	0(0.0%)	1.000
Postpartum clinic visits[?]2 months				0.078
None	4(5.4%)	13(13.1%)	1(3.8%)	
1	46(62.2%)	54(54.5%)	12(46.2%)	
2	20(27.0%)	32(32.3%)	11(42.3%)	?¿?
3	4(5.4%)	0(0.0%)	2(7.7%)	
Adhesion				0.703
None	71(95.9%)	92(92.9%)	26(100%)	
Mild	3(4.1%)	5(5.1%)	0(0.0%)	
Severe	0(0.0%)	2(2.0%)	0(0.0%)	
Adhesion site				
Uterus and bladder	0(0.0%)	1(1.0%)	0(0.0%)	1.000
Uterus and peritonium	0(0.0%)	5(5.0%)	0(0.0%)	0.454
Uterus and intestines	0(0.0%)	0(0.0%)	0(0.0%)	1.000
Uterus and omentum	2(2.7%)	0(0.0%)	0(0.0%)	0.382
Non-uterus	1(1.4%)	3(3.0%)	0(0.0%)	0.793
Intraoperative complication				
Bladder injury	0(0.0%)	0(0.0%)	0(0.0%)	1.000
Bowel injury	0(0.0%)	0(0.0%)	0(0.0%)	1.000
Hysterectomy	0(0.0%)	0(0.0%)	0(0.0%)	1.000
Intraop transfusion	2(2.7%)	0(0.0%)	0(0.0%)	0.382
Injury to uterine vessels	5(6.8%)	4(4.0%)	0(0.0%)	0.399
Postpartum hemorrhage	2(2.7%)	1(1.0%)	0(0.0%)	0.723
Postoperative complication				
Fever	7(9.5%)	4(4.0%)	0(0.0%)	0.156
Ileus	0(0.0%)	0(0.0%)	0(0.0%)	1.000
Incisional wound infection	4(5.4%)	2(2.0%)	0(0.0%)	0.415
Postcesarean metritis	1(1.4%)	1(1.0%)	0(0.0%)	1.000
Urinary tract infection	1(1.4%)	1(1.0%)	0(0.0%)	1.000
Therapeutic antibiotics	2(2.7%)	7(7.1%)	1(3.8%)	0.486

* $p < 0.05$

Table 4. Data are mean ± SD or n (%) and compared among groups using Student's t- test or chi-square test for P -value. Significant P -values are emboldened. Abbreviations: HA-CMC, hyaluronic acid/carboxymethylcellulose; ORC, oxidized regenerated cellulose; OP, operative; SSI, surgical site infection; BW, body weight; POD, postoperative day; WBC, white blood cell count; BT, body temperature.

Table 5. Multiple regression analysis to evaluate SSI risk factors of postcesarean fever at the primary cesarean delivery

Variable	Adj-HR (95% CI)	p
Use of adhesion barrier	3.25 (1.03-10.24)	**0.045***
Labor before OP	0.85 (0.33-2.19)	0.742
MR before OP	0.41 (0.15-1.16)	0.094
Emergency OP	0.71 (0.27-1.86)	0.488
OP time (min)#	1.02 (0.98-1.05)	0.335
Blood loss[?]500 c.c.	1.11 (0.39-3.18	0.935
BMI[?]30 kg/m2	0.98 (0.31-3.05)	0.97
Diabetes mellitus	2.42 (0.70-8.33)	0.162
HTN or preeclampsia	0.59 (0.09-3.74)	0.572

* $p < 0.05$# Continuous variablesCategorical variables

Table 5. A total of 125 women in the adhesion barrier group were compared to 74 women in the nonuser group. Linear regression was used to analyze continuous variables and logistic regression was used to evaluate categorical variables. The association of adhesion barrier vs. nonuser was adjusted for preoperative fever and therapeutic antibiotics. Abbreviations: OP, operative; MR, membrane rupture; BMI, body mass index; HTN, hypertension; Adj-HR, adjusted hazard ratio.

Table 6. Interaction-term analysis of the impact of SSI risk factors and use of adhesion barrier on postcesarean fever at the primary cesarean delivery

Variable	Adhesion barrier No.*	Adhesion barrier No.*	Febrile rates	Adj-HR (95% CI)	p
Labor before OP					
No labor	Non-use	3/28	10.7%	1	
	Use	7/59	11.7%	1.12 (0.27-4.71)	0.
Labor	Non-use	1/46	2.2%	1	
	Use	14/66	21.2%	**12.12** (1.53-95.78)	**0.**
MR before OP					
No MR	Non-use	3/36	8.3%	1	
	Use	12/68	17.6%	2.36 (0.62-8.97)	0.
MR	Non-use	1/38	2.6%	1	
	Use	9/57	15.8%	6.94(0.84-57.22)	0.
Urgency of OP					
Elective	Non-use	3/23	13.0%	1	
	Use	6/51	11.8%	0.89 (0.20-3.92)	0.
Emergency	Non-use	1/51	2.0%	1	
	Use	15/74	20.3%	**12.71**(1.62-99.62)	**0.**
Blood loss (cc)					
<500 c.c.	Non-use	3/60	5.0%	1	
	Use	15/94	16.0%	3.61 (1.00-13.05)	0.
500 c.c.	Non-use	1/14	7.1%	1	
	Use	6/31	19.4%	3.12(0.34-28.74)	0.

Variable	**Adhesion barrier No.***	**Adhesion barrier No.***	**Febrile rates**	**Adj-HR (95% CI)**	p
BMI					
<30 kg/m2	Non-use	4/53	7.5%	1	
	Use	16/102	15.7%	2.28 (0.72-7.20)	0.
30 kg/m2	Non-use	0/21	0.0%	1	
	Use	5/23	21.7%	0.00 (0.00-Inf)	0.
Diabetes mellitus					
No Diabetes mellitus	Non-use	4/68	5.9%	1	
	Use	16/112	14.3%	2.67 (0.85-8.34)	0.
Diabetes mellitus	Non-use	0/6	0.0%	1	
	Use	5/13	38.5%	0.00 (0.00-Inf)	0.
HTN or Preeclampsia	HTN or Preeclampsia				
No HTN	Non-use	4/68	5.9%	1	
	Use	19/115	16.5%	**3.17** (1.03-9.74)	**0.**
HTN	Non-use	0/6	0.0%	1	
	Use	2/10	20%	1.00 (0.00-Inf)	0.

* $p < 0.05$

Table 6. The 74 women in the nonuser were compared to 125 women in the adhesion barrier group. Interaction term analysis was used for examination. The associations of labor before OP, MR before OP, and urgency of OP were adjusted for preoperative fever and therapeutic antibiotics. Abbreviations: OP, operative; MR, membrane rupture; BMI, body mass index; HTN, hypertension; Adj-HR, adjusted hazard ratio.