

# Systematic Review of Topical Hemostatic Agent Use in Minimally Invasive Gynecologic Surgery

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## ABSTRACT

**Background and Objectives:** To perform a systematic review of articles evaluating hemostatic effectiveness and peri-operative outcomes when topical hemostatic agents (HA) are used in minimally invasive gynecologic surgeries (MIGS) for benign conditions.

**Methods:** Studies published through March 31, 2017 were retrieved through PubMed, EMBASE, Cochrane, and ClinicalTrials.gov to identify all eligible studies. No studies were excluded based on publish date. All comparative studies or case series with >10 participants reporting use of at least one topical HA in MIGS for benign conditions were included as long as full-text articles were available and written in English. Studies were excluded if surgery was done for malignancy or completed via an open approach. Articles that included multiple surgical subspecialties were excluded if data related to MIGS was unable to be isolated. Evaluation for eligibility and data extraction was performed by three independent reviewers. Quality of evidence was also assessed by each reviewer.

**Results:** From 132 articles, a total of 8 studies were included in this systematic review. We found that use of fibrin sealant decreased time to hemostasis, postoperative hemoglobin drop, and estimated blood loss (EBL) com-

pared with bipolar energy and reduced the overall operative time in laparoscopic myomectomy. When fibrin sealant use at time of myomectomy was compared to bipolar energy there was no significant difference in the rate of postoperative complications. Furthermore, there was less of a decrease in anti-Mullerian hormone (AMH) level when a thrombin-gelatin matrix was used compared to bipolar energy on ovarian tissue.

**Conclusion:** Application of topical HA in MIGS can reduce operative time, blood loss, and ameliorate damage to ovarian function. However, more data needs to be gathered for use of HA during different types of gynecologic procedures (adnexal surgery, myomectomy, and hysterectomy) to provide better quality evidence to guide their use.

**Key Words:** Gynecology, Hemostatic Agents, Hemostasis, Minimally Invasive Surgery, Topical Agents.

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## INTRODUCTION

There has been a major shift in gynecology in the last two decades towards increasing rates of minimally invasive laparoscopic surgeries compared to open procedures.<sup>1</sup> While more complicated cases can be completed using a minimally invasive approach, inability to maintain hemostasis can potentially lead to longer operating times and possible conversion to a laparotomy.<sup>2,3</sup> In some cases, application of pressure, electrosurgery, and suturing alone may be sufficient or safe to achieve hemostasis. However, in situations with diffuse small vessel bleeding or bleeding near vital structures, like larger vessels or ureters, these techniques may not be suitable. Topical hemostatic agents (HA) could serve as an alternative option to reduce thermal damage, devascularization, and tissue necrosis while also reducing blood loss<sup>4,5</sup>. The use of topical HA have also been shown to reduce time to hemostasis, and potentially prevent conversion to laparotomy during surgery.<sup>4,6,7</sup> Studies in specialties outside gynecology have shown that HA can effectively achieve hemostasis, reduce blood loss, shorten operative times, and reduce peri-operative transfusion.<sup>8-10</sup>

Although literature shows widespread use and efficacy of HA in several sub specialties,<sup>5,9,11</sup> the use and role of HA in minimally invasive gynecologic surgery (MIGS) has not been clearly defined in specific benign gynecologic procedures. The aim of this study is to conduct a systematic review to evaluate the surgical outcome when topical HA are used in MIGS. For the purposes of this review, the outcomes of interest are hemostatic effectiveness, impact on blood loss, postoperative bleeding, time in the operating room, postoperative complications and length (LOS). A secondary objective of this study is to determine short and long term adverse complications and impact on ovarian reserve, if any, as a result of the use of the HA. For a brief review, the commonly used agents, their brand names, and mechanism of action are displayed in **Table 1**.

## MATERIALS AND METHODS

### Search Strategy

A systematic literature review was performed using a PICO (Patient or Population, Intervention, Control or Comparison, Outcome and Study design) framework. All studies included in this review evaluated the intra-operative use of HA in women undergoing minimally invasive gynecologic procedures for benign conditions. We analyzed the impact of HA on hemostasis, need for peri-operative transfusion, impact on ovarian reserve, and other postoperative complications (such as infections, conversion to laparotomy, prolonged hospital stay, transfusion, etc.). We performed an electronic search using the National Library of Medicine database (Medline) through its online site (PubMed), EMBASE, Cochrane, and ClinicalTrials.gov to identify all studies reporting HA use in laparoscopic gynecologic surgery. MeSH terms used included “hemostatic matrix” or “topical hemostatic agent” or “hemostatic sealant” or “Oxidized Cellulose” or “TachoSil” or “gelatin-thrombin matrix” or “FloSeal” and “tubal” or “uterine” or “ovarian cystectomy” or “endometriosis” or “endometrioma” or “myomectomy” or “hysterectomy” or “laparoscopic endometrioma surgery” or “gynecology” or “gynecologic surgery” and “Humans [MeSH] AND English[lang]”. Text terms as well as MeSH keywords specific to each part of the question were used for the searches. Initial and follow-up search in the same databases were performed in March 2017 and again in June 2017. Of note, no date restrictions were applied.

### Selection Criteria

Only comparative studies and case series with >10 participants evaluating intra-operative use of at least one topical HA in a minimally invasive gynecologic procedure for benign indications were included. Only studies written in English were included. No studies were excluded based on date published.

Studies were excluded if surgery was done for malignancy or completed via an open approach. This was done to ensure extracted data was applicable to minimally invasive benign gynecologic cases. Excluding open cases allowed the focus to be on data for HA that can be applied through laparoscopic trocars. Articles including cases done for malignancy often include lymphadenectomy, which is often the portion of the procedure associated with increased bleeding and complications.<sup>12</sup> Additionally, patients with malignancy are more likely to need blood products secondary to disease progression.<sup>13</sup> Thus, measurements for hemostatic efficacy and postoperative complications from both benign and malignant cases would be difficult to combine. For these reasons, malignant cases were excluded. Articles that included both open and minimally invasive procedures were excluded if specific data for use of topical HA in MIGS for benign indications were unable to be extracted. Similarly, articles that included multiple surgical subspecialties were excluded if data related to MIGS was unable to be isolated.

### Data Extraction

Three independent observers (TI, AM, and EH) analyzed the titles and abstracts of all identified reports. For the studies that appeared to meet the inclusion criteria or for which there was insufficient data in the titles and the respective abstracts to make a clear decision, the full texts of the articles were retrieved for further analysis. The final inclusion of the relevant full text articles for evaluation was decided by consensus of the three observers. Data on relevant outcomes was catalogued using standardized data extraction tables to track outcomes and quality of outcomes.

### Quality Assessment

The Study Quality Assessment Tools provided by the National Institutes of Health (NIH) (<https://www.nhlbi.nih.gov/health-pro/guidelines/in-develop/cardiovascular-risk-reduction/tools>) were used to assign each study a quality rating of either good, fair, or poor. The quality ratings assigned by each reviewer for each study were pooled and the most common quality rating was used. Criteria for assessment of controlled intervention studies included randomization, blinding, similarity of groups at baseline regard-

**Table 1.**  
Summary of Topical Hemostatic Agents

Type	Class	Brand Name(s)	Mechanism of Action	
Absorbable Agents	Oxidized Regenerated Cellulose (ORC)*	Surgicel®	Creates scaffold for platelet aggregation	
		Original®	Bactericidal properties	
		NuKnit®		
		Fibrillar™		
	Microfibrillar Collagen (MFC)		SNoW®	
			Avitene®	Creates scaffold for platelet aggregation
			Avitene Ultrafoam	
			Avitene UltraWrap	
			Endo-Avitene	
	Microporous Polysaccharide		Helistat	
Helitene®				
Gelatin		Arista™	Absorbs water and other low molecular weight compounds from the blood and concentrates these component to form platelet plug	
		Gelfoam®	Gelatin matrix:	
Biologic Agents	Topical Thrombin	Surgifoam®	Absorbs surrounding blood, increasing the agent's size and weight	
		Thrombin-JMI®	Topical thrombin:	
		Evithrom®	Converts fibrinogen to fibrin	
	Topical Thrombin + Gelatin		Recothrom®	Activates platelets, aiding in formation of platelet plug
			Thrombi-Gel®	Topical thrombin: Converts fibrinogen to fibrin Activates platelets, aiding in formation of platelet plug Gelatin matrix: Absorbs surrounding blood, increasing the agent's size and weight
	Topical Thrombin + Gelatin		Floseal®*	Topical thrombin:
			Surgiflo®	Converts fibrinogen to fibrin Activates platelets, aiding in formation of platelet plug Gelatin matrix: Absorbs surrounding blood, increasing the agent's size and weight
	Fibrin Sealant*		Tisseel®	Comprised of two components:
			TachoSil®	Sealer protein solution
			Evicel®	Contains aprotinin, factor XIII and fibrinogen Thrombin solution Converts fibrinogen in protein solution to fibrin Contains calcium chloride

\*These agents are discussed in the included articles.

ing characteristics that may affect outcomes, proper assessment of outcome measures, and power and sample size calculation.

The quality of case control and case series studies were assessed based on the presence of a clear statement of research question, sample size calculation, use of control group, clear definition of patient population, use of appropriate outcome measures, and assessment of potential confounders. Studies rated “good” had the least risk of bias and results are considered valid. Studies rated “fair” were deemed susceptible to some bias but not enough to invalidate their results. This category is broad and can encompass a wide variety of studies with their inherent strengths and weaknesses. A “poor” rating indicated significant risk of bias. Therefore, risk of bias was individually assessed by each reviewing author.

We were unable to perform a meta-analysis due to heterogeneity of the research methods and measured outcomes of the included studies.

## RESULTS

### Study Selection

Using the search strategy above, 127 articles were identified and citation chasing yielded 5 additional studies for a total of 132 articles. Eighty-eight unique articles were identified after duplicates were removed. Of these, 48 titles indicated that the articles did not meet our inclusion criteria. Abstracts of the remaining 40 articles were reviewed and 17 full-text articles were screened for consideration. The other 23 articles were excluded after the abstracts were screened for inclusion criteria. Of the 17 full-text articles that were screened, 11 were excluded for reasons including: inability to isolate data for MIGS vs. open procedures or procedures done by other specialties, small sample size, article was a case report, included malignant cases, or if the article was a systematic review. References of the final list of included articles were manually searched to ensure inclusion of all pertinent studies. This revealed two additional articles that fit the inclusion criteria (**Figure 1**).

### Study Characteristics

We identified a total of 8 studies that met inclusion criteria. These included 2 randomized control trials, 1 case-control study, and 5 prospective cohort studies.

The use of HA during laparoscopic gynecologic procedures was evaluated in 1 study involving myomectomy, 5 studies

in adnexal procedures (including cystectomy, sterilization, and salpingotomy for ectopic pregnancy), 1 study during sterilization, and 1 study for repair of uterine perforation.<sup>14–21</sup> No studies evaluating HA use at time of laparoscopic hysterectomy for benign indication were found.

### Quality Assessment and Risk of Bias

Out of the 8 included studies, 2 were rated as good, 4 fair, and 2 poor. The justification for quality assessment ratings are addressed in **Table 2**.

### Surgical Outcomes

Primary surgical outcomes commonly encountered when HA were used in MIGS were hemostatic effectiveness, total operative time, length of stay, and postoperative complications. Methods used to describe hemostatic effectiveness varied and included subjective achievement of hemostasis (yes or no), time to hemostasis (in seconds or minutes), postoperative decrease in hemoglobin (difference between preoperative and postoperative hemoglobin), estimated blood loss (subjectively measured in studies that evaluated this variable), and need for postoperative transfusion. A portion of the included studies also included the impact on ovarian reserve when HA was used at the time of ovarian cystectomy. Major findings from the included studies are summarized in **Table 2**.

There were two studies that evaluated use of a fibrin sealant at the time of surgery. A case control study of 30 women assessed efficacy of fibrin sealant Tisseel (Baxter Healthcare Corporation, Deerfield, IL, USA) at the time of laparoscopic myomectomy over the suture line for single isolated leiomyoma  $\leq 6$  cm and  $\geq 4$ cm. The group that used Tisseel showed reduced intraoperative blood loss ( $p < .05$ ), decreased time to intraoperative hemostasis ( $p < .0005$ ), and less decrease in postoperative hemoglobin ( $p < .05$ ) with statistical significance when compared to bipolar energy. The same study observed a significant reduction in operative time when the fibrin sealant was used ( $p < .05$ ).<sup>14</sup> Another type of fibrin sealant, Tachosil (Baxter Healthcare Corporation, Deerfield, IL, USA), was evaluated in a prospective cohort study of 129 with respect to potential benefits on ovarian reserve during laparoscopic ovarian cystectomy. Floseal (Baxter Healthcare Corporation, Deerfield, IL, USA), a thrombin-gelatin matrix, was another agent of interest in this article. Findings included statistically significant less decline of AMH with use of either of these HA when compared to bipolar energy ( $p = .003$ ). However, there was no significant difference in AMH when comparing the fibrin sealant to

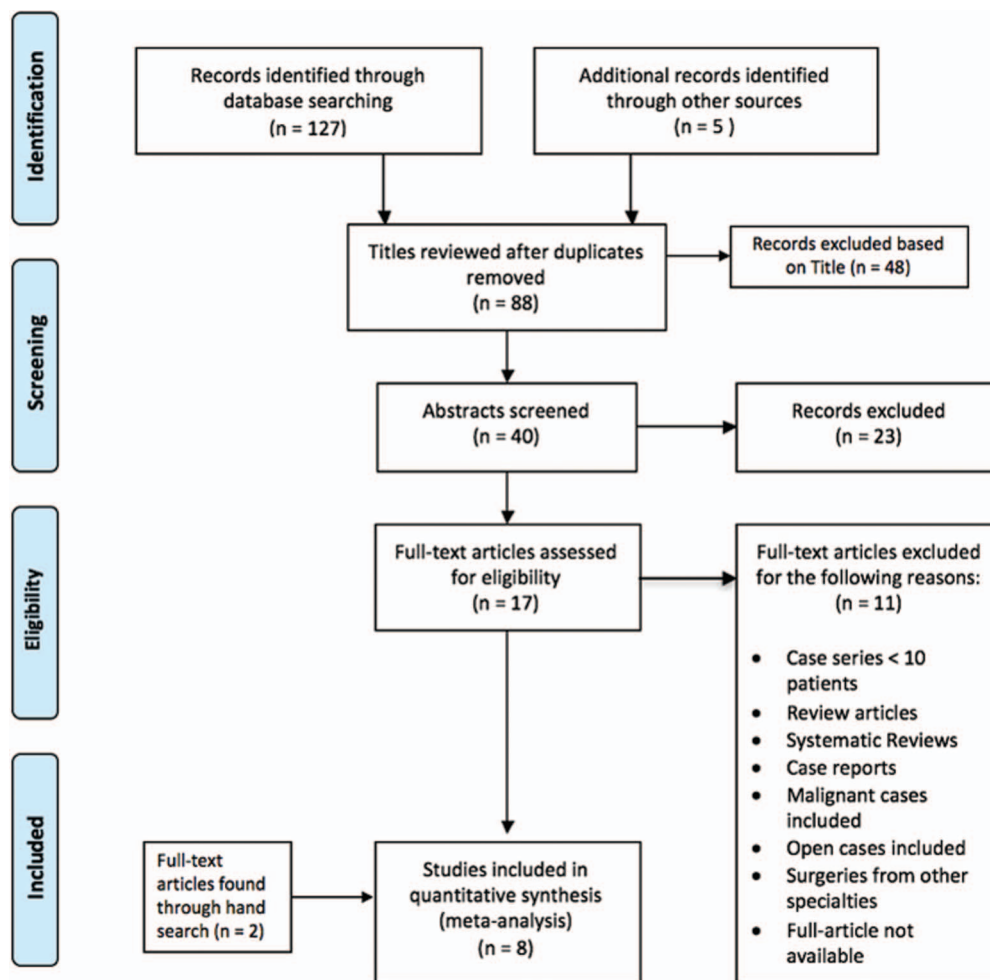


Figure 1. PRISMA Flowsheet.

the thrombin-gelatin matrix ( $p = .962$ ).<sup>16</sup> Of note, in groups where HA was used there was no subsequent use of bipolar energy.

Application of fibrin sealant at the time of laparoscopic myomectomy revealed no significant postoperative complications nor did it impact patients' length of stay in the hospital.<sup>14</sup> Data regarding postoperative complications when fibrin sealant was used at the time of laparoscopic ovarian cystectomy was not reported.<sup>16</sup>

Use of a thrombin-gelatin matrix and associated outcomes was also assessed in other types of gynecologic procedures. Two studies investigated the potential benefits when thrombin-gelatin matrix Floseal was used at the time of laparoscopic excision of ovarian endometrioma. A prospective cohort study showed that time to hemostasis was shorter but not statistically significant with use of Floseal

when compared with bipolar energy. Additionally, average blood loss was less but not statistically significant in the Floseal group ( $p = .373$ ). Operative time, was not significantly longer in the Floseal either ( $p = .334$ ) nor decreased nor was operative time improved by using Floseal.<sup>15</sup> A separate prospective randomized pilot study did not assess hemostatic efficacy of the Floseal, but estimated the effect of its use on serum AMH as a measure of ovarian reserve. The mean serum AMH in the Floseal group after one month was higher than the bipolar energy group ( $2.72 \pm 1.49$  vs.  $1.64 \pm 0.93$  ng/mL). However, percentage changes between preoperative and postoperative month 3 serum AMH values were not statistically different among the HA group and the bipolar energy group ( $p = .467$ ).<sup>21</sup> Again, in these studies that used thrombin-gelatin matrix, no bipolar energy was ever used in the HA groups.

**Table 2.**  
Summary of Key Information from Included Studies Categorized by Type of Topical Hemostatic Agent

Type of Product	Type of Study	Number of Patients	Type of Procedure	Major Findings ( <i>p</i> value)	Quality
Fibrin Sealant	Case-Control (Angioli et al., 2012)	<i>N</i> = 30	Laparoscopic myomectomy	Reduction in blood loss with fibrin sealant (Tisseel®) was significant ( <i>p</i> < .05) Less decrease in post-operative hemoglobin with fibrin sealant (Tisseel®) was significant ( <i>p</i> < .05) Decreased time to hemostasis with fibrin sealant (Tisseel®) was significant ( <i>p</i> < .0005) Reduction in operative time with fibrin sealant (Tisseel®) was significant ( <i>p</i> < .0005)	Fair Potential confounders not addressed Specific inclusion criteria stated Good follow-up
	Prospective Cohort* (Kang et al., 2015)	<i>N</i> = 129	Laparoscopic ovarian cystectomy	Significantly less decline in AMH with use of fibrin sealant (TachoSil®) or thrombin/gelatin matrix (FloSeal®) vs. bipolar energy ( <i>p</i> = .003) No significant differences in AMH when comparing fibrin sealant(TachoSil®) vs.thrombin/gelatin matrix (FloSeal®) ( <i>p</i> = .962)	<u>Fair</u> Good sample size No sample size calculation No discussion of how patients were divided among treatment arms
Thrombin Gelatin Matrix	Prospective Cohort (Angioli et al., 2009)	<i>N</i> = 20	Laparoscopic excision of ovarian endometrioma	Time of hemostasis in thrombin/gelatin matrix (FloSeal®) group was shorter but not statistically significant when compared with bipolar energy ( <i>p</i> = .19)	Fair
				Average blood loss in thrombin/gelatin matrix group was less but not statistically significant ( <i>p</i> = .373)	Small sample size
				Operating time was not significantly longer in thrombin/gelatin matrix group ( <i>p</i> = .334) No post-operative transfusions needed	Potential confounders not addressed

*Continued*

**Table 2.**  
Continued

Type of Product	Type of Study	Number of Patients	Type of Procedure	Major Findings ( <i>p</i> value)	Quality
	Prospective Cohort* (Kang et al., 2015)	<i>N</i> = 129	Laparoscopic ovarian cystectomy	Less decline in AMH with use of thrombin/gelatin matrix (FloSeal®) or fibrin sealant (TachoSil®) vs. bipolar energy was significant ( <i>p</i> = .003)	Fair
	Prospective Cohort (Song et al., 2014)	<i>N</i> = 20	Laparoscopic salpingotomy for tubal pregnancy	Achievement of hemostasis in 95% of cases	Good sample size No sample size calculation No discussion of how patients were divided among treatment arms Poor No sample size calculation Single surgeon experience Concomitant use of vasopressin for hemostasis One case excluded with conversion to salpingectomy Lack of fertility follow-up Lack of comparison/control group
	Randomized Control Trial (Song et al., 2014)	<i>N</i> = 100	Laparoscopic ovarian cystectomy via single-site approach	Significantly less decline in AMH with use of thrombin/gelatin matrix (FloSeal®) vs. bipolar energy ( <i>p</i> = .004)	Good Appropriate Randomization Outcomes assessed reliably Good sample size Multicenter study Standardized surgical approach (SS) Good follow-up
	Prospective Randomized, Pilot Study (Sonmezer et al., 2013)	<i>N</i> = 30	Laparoscopic excision of ovarian endometrioma	The mean serum AMH in the thrombin/gelatin matrix group after one month was higher than in the bipolar energy group (2.72 ± 1.49 vs. 1.64 ± 0.93 ng/mL)	Good

*Continued*

**Table 2.**  
Continued

Type of Product	Type of Study	Number of Patients	Type of Procedure	Major Findings ( <i>p</i> value)	Quality
				Percentage changes in serum AMH b/w pre-operative and post-operative month 1 higher in bipolar energy group compared to thrombin/gelatin matrix ( <i>p</i> = .001)	Appropriate randomization
				Percent changes between preoperative and post-operative month 3 serum AMH was not significantly different among the two groups ( <i>p</i> = .467)	Outcomes assessed reliably Good follow-up Addressed other studies investigating AMH levels and ovarian damage
Oxidized Regenerated Cellulose	Prospective Cohort (Sharma et al., 2003)	<i>N</i> = 28	Laparoscopic sterilization	Achievement of hemostasis in 92.8% of patients	Poor Small sample size Potential confounders not addressed Lack of control/comparison group
	Prospective Cohort (Sharma et al., 2003)	<i>N</i> = 30	Surgical termination of pregnancy and laparoscopic sterilization	Achievement of hemostasis in 93.3% of patients	Fair Small sample size Lack of control/comparison group No follow-up for potential complications associated with HA

\*Same study, but included more than one hemostatic agent. *N* = sample size; AMH = anti-Mullerian hormone.

Outcomes on ovarian reserve were further examined in a randomized control trial for laparoscopic ovarian cystectomy via a single-site approach. Again, thrombin-gelatin matrix Floseal was the agent of choice. This was applied after ovarian cystectomy for hemostasis and showed significantly less decline in AMH when compared to bipolar energy 3 mo postoperatively (*p* = .004).<sup>20</sup> All studies investigating ovarian reserve are summarized in **Table 3**.

A small prospective cohort study analyzed hemostatic benefits of thrombin-gelatin matrix at the time of laparoscopic salpingotomy for tubal pregnancy.<sup>19</sup> The HA achieved hemostasis in 95% of cases and prevented salpingectomy. It should be noted that vasopressin was injected in the mesosalpinx for all cases prior to salpingotomy.

Of the four included articles that investigated thrombin-gelatin matrix, three measured postoperative complications. These studies reported that there were no postoperative complications among participants of either the control group or the thrombin-gelatin matrix group.<sup>15,16,19,20</sup>

The last type of HA to be addressed among the included studies is oxidized regenerated cellulose (ORC). Two prospective cohort studies published by the same author used the ORC Surgicel Original (Ethicon, Inc., San Lorenzo, Puerto Rico) at the time of each respective procedure. When laparoscopic sterilization was performed, 92.8% of cases established hemostasis with Surgicel.<sup>17</sup> Patients who underwent procedure for pregnancy termination and laparoscopic sterilization who were noted to have uterine perforation had Surgicel® placed over the perforation site



and achieved hemostasis in 93.3% of cases.<sup>18</sup> The only mention of postoperative complications among these studies was conversion to laparotomy for control of bleeding during the procedure. A total of 58 patients participated in these studies, and 4 ultimately underwent laparotomy following failure of ORC to control bleeding from either fallopian tubes or uterine perforation. Notably, control of bleeding with laparoscopic techniques was not pursued and the surgeons converted to laparotomy immediately following failure of hemostatic agent and placed sutures via open approach. Statistical significance was not calculated for these cases of conversion by the authors.

## **DISCUSSION**

### **Main Findings**

In a Cochrane review of HA, fibrin sealants have shown success in reducing postoperative blood loss and perioperative transfusions in minimally invasive surgeries among other specialties such as general surgery, cardiothoracic, urology, and orthopedics.<sup>10</sup> In the realm of gynecology, a case control study evaluating fibrin sealant Tisseel® during laparoscopic myomectomy for a single fibroid exhibited a favorable hemostasis profile and decreased overall operative time.<sup>14</sup> These findings are consistent with a prospective randomized trial evaluating thrombin-gelatin matrix Floseal® over the suture line during open myomectomy in compared to traditional methods of bipolar energy and suture. This study also found a significant reduction in EBL and postoperative hemoglobin decrease. However, there was no significant effect on operative time unlike study included in this review.<sup>22</sup> Although these studies used different HA and approach to myomectomy, findings suggest that HA use over the suture line at the time of myomectomy can improve measures of outcome pertaining to hemostasis. In addition, hemostatic agent use may have the potential benefit of shortening operative time during minimally invasive procedures.

Recently, Liu et al. reported their experience with fibrin sealant use at the time of laparoscopic cystectomy for endometrioma and their benefits in terms of blood loss and operative times.<sup>23</sup> While this study fit the inclusion criteria for this review, it was published outside of the time frame of original literature search. No conclusive statements can be made regarding fibrin sealant use during the time of endometrioma for hemostatic benefit.

Use of HA at the time of adnexal surgery may better preserve serum AMH levels when compared to bipolar energy.<sup>24,25</sup> A systematic review investigating thrombin-gelatin matrix Floseal use at the time of laparoscopic cystectomy for endometrioma provided moderate quality evidence that hemostatic methods other than bipolar energy better preserve serum AMH levels.<sup>25</sup> Subsequent studies investigating thrombin/gelatin matrix Floseal or fibrin sealant TachoSil for hemostasis showed less decline of AMH than use of bipolar energy when measured postoperative at 1 mo. However, when subgroup analysis was performed based on ovarian cyst type (endometrioma vs. nonendometrioma) there was no significant difference in the rate of serum AMH decline regardless of the hemostatic method.<sup>16</sup> These same agents were analyzed by Choi et al. and showed less decrease in AMH with use of either Floseal or Tachosil compared to bipolar energy group 3 mo postoperatively, without superiority of one agent over the other.<sup>26</sup>

In women concerned with fertility there is good evidence to consider use of thrombin-gelatin matrix or fibrin sealant at the time of laparoscopic ovarian cystectomy for hemostasis in effort to ameliorate damage to ovarian function.<sup>27</sup>

ORC, Surgicel, is another HA that is easily applied laparoscopically which makes it an attractive option for minimally invasive gynecologic surgeons.<sup>4</sup> Surgicel was found to be effective for controlling tubal hemorrhage and uterine perforation in two separate prospective studies. Based on the available data, ORC can be applied in procedures where control of bleeding is needed on the tubes or uterus.<sup>17,18</sup> However, given the lack of control groups and the potential for bias in these studies no strong recommendations can be made for ORC use in MIGS.

Several case reports and case series highlight potential postoperative complications that may be encountered with the various hemostatic agents. These include reports that ORC, microfibrillar collagen, and gelatin may cause postoperative abscess or pelvic infection.<sup>28-33</sup> Some studies also report HA causing small bowel obstruction and HA mimicking cancer on imaging.<sup>34-39</sup> Additionally, a large retrospective study with 17,960 women who underwent hysterectomy assessed 4,659 cases where HA was used. Of those hysterectomies, the data for benign pathology using a minimally invasive approach was not reported separately. The study demonstrated statistically significant postoperative complications where HA was used including: increased rate of blood transfusions, increased rate of pelvic abscess diagnosis, increased hospital readmission,

**Table 3.**  
Effect on Ovarian Reserve

Author, Year, Sample Size	Agent	Rate of AMH Decline (%)
Kang et al., 2015 <i>N</i> = 129	Floseal or TachoSil	15.4 IQR 5.2–41.9
	Bipolar energy	41.2 IQR 16.7–52.4
	<i>p</i> value	<i>p</i> = .003
	Floseal	15.4 IQR 7.8–44.6
	TachoSil	15.9 IQR 0.7–41.1
Song et al., June, 2014 <i>N</i> = 100	<i>p</i> value	<i>p</i> = .003 (BC vs HA)
	Floseal	16.1 IQR 8.3–44.7
	Bipolar energy	41.2 IQR 17.2–54.5
Sonmezer et al., 2013 <i>N</i> = 30	<i>p</i> value	<i>p</i> = .004
	Floseal	19
	Bipolar energy	23
	<i>p</i> value	<i>p</i> = .467

*N* = sample size; IQR = interquartile range.

and increased predicted rate of reoperation.<sup>40</sup> Postoperative complications were limited amongst the included articles. In our systematic review of the literature, no statistically significant postoperative complications were reported. Moreover, of the studies that noted complications, none were related to infection, abscess, or small bowel obstruction as cited in the literature. It should be noted that of the included studies that reported postoperative complications, only one recorded follow-up 3 mo after the initial surgery<sup>20</sup> while the other studies only reported complications if observed in the immediate postoperative period. As a result, no conclusions can be made regarding postoperative complications secondary to hemostatic agent use in MIGS as data that includes longer periods of follow-up is lacking.

Interestingly, hysterectomy was not a procedure that was performed in any of the included articles. A retrospective study by Kakos et al. explored factors associated with hemostatic agent use during minimally invasive hysterectomy.<sup>27</sup> However, data was collected for women undergoing laparoscopic hysterectomy for any indication. As a result, we were not able to determine if cases of malignancy were included in the study population and the study did not qualify for our review. There are no well-designed randomized control trials in the literature that observe variables of hemostatic effectiveness specific to minimally invasive hysterectomy for benign indication and this should be pursued.

Length of stay amongst studies was difficult to compare given the heterogeneity in type of procedures performed. However, when reported there was no statistically significant difference between the HA group and the control group.

### Study Heterogeneity

The results observed in the included studies were heterogeneous making comparison of outcomes difficult. For example, several types of gynecologic procedures were included: myomectomy, surgery for ectopic pregnancy, ovarian cystectomy, and uterine perforation. Moreover, studies varied in outcomes measured. Evaluation of hemostasis itself was not measured by one standard measurement but rather by one, or a combination of, variable(s): EBL, time to hemostasis, change in hemoglobin, and transfusion. Some studies omitted measurements of hemostasis and focused on evaluation of AMH as a reflection of ovarian reserve as the primary outcome.

Operative time, length of stay, and postoperative outcomes were difficult to compare due to the variability of the types of procedures performed in the included studies.

Due to small sample numbers of participants and lack of power analyses in some studies comparisons among the studies could not be performed.

### Study Strengths and Limitations

This systematic review addresses use of hemostatic agents specific to minimally invasive gynecologic surgery for benign conditions. Studies were not excluded based on date allowing for a comprehensive review of the existing literature. The focused question, which only returned a limited number of articles, helped to identify gaps in the current literature.

A limitation of this study is possible deletion of pertinent studies despite a thorough search of the literature. The search strategy was repeated 3 mo after the initial search and similar results were found. A manual review of references from included full-text articles was also performed to ensure all pertinent articles were found to the best of our ability. A final search one year after was performed to identify any additional literature and 2 articles meeting our inclusion criteria were found.

Another limitation is the variety of procedure types. Included studies investigated HA in very distinct gynecologic procedures such as myomectomy, cystectomy, salpingotomy for ectopic pregnancy, and uterine perforation. Therefore, there was difficulty drawing meaningful comparisons from the data extracted from included studies.

### Future Directions

This systematic review helps identify the gaps in the literature pertaining to hemostatic agent use at the time of minimally invasive gynecologic surgeries. Many other subspecialties such as orthopedics, cardiothoracic, urology, and general surgery have randomized control trials or multicentre studies looking at hemostatic success of various agents.<sup>8,10</sup> These results have not yet been replicated for minimally invasive gynecology. No studies were found regarding HA use during minimally invasive hysterectomy for benign indications which is one of the most common procedures performed by gynecologic surgeons. More well-designed studies are needed to explore the hemostatic effectiveness specific to each type of gynecologic procedure. As more complex gynecologic surgeries are being completed in a minimally invasive fashion, it is important to be familiar adjuncts to traditional methods of hemostasis that can be used when there may be concern for thermal damage, devascularization, and tissue necrosis near vital structures. Furthermore, when designing a study for hemostatic agent use, follow-up needs to be extended to allow adequate assessment of potential postoperative complications that may result.

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