Chapter

Biologic Hemostatic Agents in Obstetrics and Gynecology

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Abstract

In Obstetrics and Gynecology, the practice of biologic hemostatic agents in the field are generally used to augment the basic tenets of hemostasis to decrease the morbidity and mortality of such procedures. These hemostatic agents work along with the body's physiology to rapidly aid in platelet plug formation, activation of the clotting cascade, the creation of fibrin, and to form a stable clot. The four main sub-categories of hemostatic agents include mechanical, biological, flowable, and fibrin sealants. Mechanical agents act as scaffolding for platelet aggregation to form a platelet plug. Biological agents activate clotting factors in the coagulation cascade to aid in hemostasis. Flowable agents combine biologic with mechanical agents to stabilize clot formation while also providing mechanical tamponade. Fibrin sealants combine high levels of fibrin and thrombin that when combined, form a fibrin clot at an accelerated speed. Hemostatic agents in obstetrics are often used in the setting of postpartum hemorrhage, cesarean delivery and postpartum hysterectomy to decrease the rate of morbidity most commonly seen with abnormal placentation and uterine atony. With gynecologic surgery, hemostatic agents are more commonly used then in obstetrics. They aid in hemostasis with common gynecologic procedures including hysterectomies, ovarian cystectomies, myomectomies, endometriosis cases, incontinence procedures and malignant debulking procedures. Also, with the increase in minimally invasive surgical techniques, topical hemostasis can aid in fewer transfusions, improved visualization in the surgical field decreased operative time and reduction in the risk of conversion to laparotomy.

Keywords: obstetrics, gynecology, postpartum hemorrhage, cesarean delivery, hysterectomy, ovarian cystectomies, myomectomies, endometriosis, malignant debulking, minimally invasive gynecology, hemostasis, mechanical hemostasis, platelet plug formation, biologic agents, thrombin, gelatins, oxidized regenerated cellulose, collagen, microporous polysaccharide spheres, fibrin sealants

1. Introduction

Intraoperative hemostasis is primarily achieved through knowledge of anatomy and good surgical technique. Technology has augmented the basic tenets of surgical hemostasis since 1926 and has continued to evolve. In addition to applying pressure and using suture, there are now a wide variety of hemostatic options available to gynecologic surgeons including monopolar/bipolar cautery, harmonic technology, hemoclips, laser, argon beam coagulation, tacks, and topical hemostatic agents. Like any other trade, it is important to have the right tool for the job. If there is bleeding

in a sensitive anatomic location in the pelvis, mechanical and thermal techniques may not be practical given the risk to adjacent tissues. Topical hemostatic agents have been available since the mid 20th century and can act as an adjunct to provide both active and passive hemostasis in situations where bleeding is difficult or impractical to be controlled by conventional methods. Topical hemostatic agents work by augmenting specific parts of physiologic hemostasis. Of the four phases of hemostasis [1, 2], topical hemostatic agents primarily affect formation of the platelet plug and propagation of the coagulation cascade. Topical hemostatic agent use is common practice in many surgical procedures, and has been utilized across all surgical specialties [3]. Likely due to marketing, usage of topical hemostatic agents has increased by 10–21% since 2000 [4]. This chapter will focus on use of topical hemostatic agents in obstetrics/gynecological surgeries with a focus on postpartum hemorrhage, myomectomy, hysterectomy, endometriosis surgery, oncologic debulking, and ovarian cystectomy.

2. Hemostatic mechanisms

In order to understand the mechanism of action of topical hemostatic agents, it is important to understand the basic physiology of hemostasis. There are four main phases of hemostasis: endothelial injury and platelet plug formation, activation of the clotting cascade, termination of the clotting, and fibrinolysis [3]. Hemostasis represents a delicate and regulated balance between thrombosis and thrombolysis. Formation of a stable hemostatic clot relies on a complex interaction between vasoconstriction, circulating clotting factors, and platelet factors. In a surgical patient, the inciting event is endothelial damage from trauma. Injury to the endothelium exposes blood to subendothelial elements that promote platelet adhesion and activation. Endothelial injury also activates both the extrinsic and intrinsic coagulation pathways through increased expression of tissue factor and exposure to negatively charged surfaces respectively.

After vessel injury, there is temporary vasoconstriction which facilitates platelet adhesion and subsequent activation. This forms a fragile platelet plug which requires stabilization during secondary hemostasis to form a clot. Initiation of the coagulation cascade occurs through both extrinsic and intrinsic pathways. This involves multiple plasma proteins, calcium ions, and platelets. At the end of the cascade, thrombin ultimately converts fibrinogen to fibrin leading to a stable clot [5]. This is critical as thrombin can be applied alone or in combination with other hemostatic agents, bypassing the intrinsic and extrinsic pathways as long as there is adequate circulating fibrinogen present.

3. Hemostatic agents

There are four sub-categories of hemostatic agents utilized. These include mechanical, biological, flowable, and fibrin sealant. They each have different properties and associated cost [6]. Although there are different mechanisms of action, these topical hemostatic agents act by augmenting the first phase of coagulation (platelet plug formation) and/or stimulating the production of fibrin for clot stabilization. Agents that both stimulate platelet plug formation and contain thrombin are the most effective at creating hemostasis but are the most costly. **Table 1** provides a summary of the agents discussed in this chapter. The four sub-categories of hemostatic agents will be discussed individually followed by their usage in common obstetric/gynecologic procedures.

Biologic Hemostatic Agents in Obstetrics and Gynecology
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Agent	Source	How supplied	Trade name	Mechanism of Action	Absorption time [7]	Adverse effect * [8]	Relative Expense ¶ [7, 9]
Oxidized Regenerated Cellulose	Plant	Powder, cloth, foam, and sponge	Surgicel, Surgicell Fibrillar, Nu-Knit	Creates a scaffolding for platelet aggregation, lowers pH to activate clotting cascade	1–2 weeksΔ	Foreign body reaction, infection, adhesions [3]	$
Gelatins	Porcine Collagen	Powder, Foam, sponge	Gelfoam, Surgifoam	Expands to provide a matrix for clot formation, can act as a sponge to absorb blood, some contain thrombin to activate clotting cascade.	4–6 weeks	Infection, abscess or granuloma formation, fibrosis, clot disruption if sponge is removed [3]	$
Microfibrillar Collagen	Bovine Collagen	Sheet, powder, sponge	Avitene, Avitene Ultrafoam, Avitene Ultrawrap, Helitene, Helistat	Acts as scaffolding for platelet aggregation	2–3 months	Difficult to handle, Granuloma formation, infection	$$
Microporous Polysaccharide spheres	Plant	Powder	Arista, Vitasure, Hemostase	Absorbs water to concentrate platelets and accelerate clot formation	< 48 hours	Can alter glucose loads in diabetic patient if used excessively	$
Fibrin Sealants◊	Pooled human plasma, Pooled human and equine collagen, Individual human plasma with bovine collagen and thrombin	Liquid	Tisseel, Evicel, Tachosil, Vitagel	Contain high levels of fibrinogen and thrombin separately that when combined form a fibrin clot at an accelerated speed	Immediate	Potential exposure to blood borne viruses	$$$

**Severe hypersensitivity reactions and antibody formation can occur with use of protein-containing topical hemostatic and fibrin sealants; more evident with repeated application.*
¶Price range (US dollars): $:50 to 100 dollars, $$ 101 to 300 dollars, $$$: 301 to 500 dollars; Cost is highly variable and subject to institutional contractual agreements.
ΔDelayed resorption can occur with oxidized regenerated cellulose due to the low pH which inhibits proteases and elastases. May delay for more than 2 weeks.
◊Fibrinogen concentration are higher for commercial preparations (Tisseel 70 mg/mL and Evicel 55 to 85 mg/mL) as compared to unmanipulated cryoprecipitate (2.5 to 25 mg/mL) [10, 11].

Table 1.
Biologic hemostatic agents.

3.1 Mechanical

When normal mechanical techniques for maintaining hemostasis such as pressure, sutures, clips, gauze sponges fail or cannot be used due to sensitive anatomic location, mechanical topical hemostatic agents can be used alone or in combination (not all mechanical products) with thrombin. Mechanical agents act as a scaffold for platelet aggregation and can dehydrate the injury bed allowing for a local increase in clotting factors. This type of hemostatic agent when used alone acts passively to control hemostasis which means that an intact clotting cascade is necessary for adequate clot stabilization. The properties of the most common topical mechanical hemostatic agents are listed below and included in **Table 1**. Clinically, these agents are useful with heavier bleeding (especially if combined with an active hemostatic agent like thrombin) because they can absorb multiple times their weight in fluid [12]. Given expansion of these agents, caution should be exercised when applying them in anatomic locations where there is risk for nerve injury. If these agents are needed near nerves, it is recommended that after hemostasis is achieved, residual agent is removed [13]. Although it is not possible to conduct randomized trials with topical hemostatic agents, one study evaluated many of these mechanical agents in vitro and found that microfibrillar collagen was the most effective followed by collagen sponge, gelatin sponge and oxidized regenerated cellulose [14].

Use of mechanical hemostatic agents can mimic abcess formation on postoperative imaging [15]. Interpretation as to whether its abscess versus normal degeneration of topical hemostatic agents may be aided by informing radiologist that topical hemostatic agents have been used [16]. An abscess typically has rim enhanced and air-fluid levels. Topical hemostatic agent degeneration usually has tightly packed gas bubbles which remain unchanged on serial exams with no rim enhancement or air-fluid levels [16]. Often, as mechanical hemostatic agents degenerate over time, they may be mistaken as granulomas or malignancy [17, 18].

1. Oxidized Regenerated Cellulose (ORC) (Surgicel, Surgicell Fibrillar,Nu-Knit)

   This type of mechanical agent is used in cases of relatively light venous bleeding. Minimal preparation is required, and it is the least expensive of hemostatic agents utilized. ORC can be used in heparinized patients although efficacy in thrombocytopenic patients is limited [19].
   When applied directly to tissue, oxidized regenerated cellulose creates a scaffold for platelet aggregation. By decreasing tissue pH, it works to further hemostasis by activating the clotting cascade. The decreased pH may have an additional benefit: bactericidal activity [5]. This agent, however, should not be used with biologic agents (Thrombin) [3].
   Oxidized Regenerated Cellulose comes in different forms: Powder, cloth, foam, and sponge. These are absorbed in 14 days but can persist up to 1 year [14]. The cloth form of ORC is easily rolled and can be placed through a laparoscopic trocar. These agents may also help to prevent development of adhesions although evidence to support this is limited [20] It should be noted that ORC has been associated with abscess formation.

2. Gelatins (Gelfoam,Surgifoam)

   Made from porcine collagen, gelatin hemostatic agents, comprised of powder or foam, can be saturated with normal saline to form a paste [9]. These agents provide a matrix for clot formation and can expand up to 200%. When applied directly to tissue, these agents can act as a sponge to absorb blood. Clotting oc-

curs through contact activation as the gelatin particles restrict blood flow and provide a stable matrix for a clot to form [21]. Pressure is necessary for several minutes for optimal hemostasis. Pressure will also keep the gelatin from dislodging [19].

Gelatins are absorbed within 4–6 weeks. These agents can also be passed through laparoscopic trocars. Because these agents have a neutral pH they can be used with biologic agents [7]. Gelatins are frequently (and easily) combined with activated thrombin to augment hemostasis if there is brisk bleeding.

3. Microfibrillar Collagen (bovine collagen) –Avitene, Avitene Ultrafoam,Avitene Ultrawrap, Helitene,Helistat)

   Microfibrillar collagen is applied directly to tissue and acts as a scaffolding for platelet aggregation [3]. These agents are available as a sheet, powder, or sponge. They can be difficult to handle, however, because they tend to stick to gloves and instruments [14]. These agents are absorbed in 2–3 months. Combining microfibrillar collagen with thrombin or saline may reduce the hemostatic efficacy of the microfibrillar collagen. It is important to note that granulomatous reactions with microfibrillar collagens have been linked to bowel obstruction and surgical re-exploration.

4. Microporous Polysaccharide spheres (Arista, Vitasure, Hemostase)

   These agents are made from potato starch and are available in powder form for laparoscopic application [3]. By absorbing water, these agents work to concentrate platelets to accelerate clot formation. It can be applied to the surgical field with gentle pressure. These agents are absorbed within 48 hours limiting potential for lasting complications such as abscess formation or bowel obstruction [3]. These agents are not meant to be combined with activated thrombin as adding liquid will impair the ability of the starch to absorb water in the field. Laparoscopic applicators are available to spray the starch intraabdominally during laparoscopic surgery. As these agents are made from potato starch, they are inexpensive.

3.2 Biological

Bovine thrombin (Thrombin-jmi), Pooled human thrombin (Evithrom), Recombinant thrombin (Recothrom).

Biological hemostatic agents are active agents that work to provide hemostasis by activating clotting factors in the final stages of the coagulation cascade. Thrombin is activated by calcium and as noted previously acts to convert fibrinogen to fibrin, stabilizing the clot. Although activated thrombin does not require circulating clotting factors to work, it will not be effective if there is hypofibrinogenemia which is often seen in cases of disseminated intravascular coagulation (DIC). Bovine thrombin has been approved for use since the 1970s. Thrombin alone is indicated for localized, minor bleeding and is dispersed as a liquid spray. Thrombin can be reconstituted from a powder or thawed from frozen formulations to form a liquid or paste which can then be applied alone or in conjunction with absorbable gelatin [22–24]. In obstetrical and gynecological surgery, thrombin is rarely used alone. Fibrinogen was combined with concentrated plasma thrombin in the late 1990s creating a fibrin sealant [25]. Fibrin sealants can also contain a matrix to support platelet aggregation and activation. From a biologic perspective, fibrin sealants are more likely to provide hemostasis in case of coagulopathy/DIC because fibrinogen is supplied with thrombin. Combining active (thrombin or thrombin with fibrinogen)

with a passive hemostatic agent can significantly improve hemostasis. In vitro and clinical studies have demonstrated faster hemostasis with the use of active hemostatic agents [26, 27]. Active hemostatic agents are uniformly more costly than mechanical (passive) hemostatic agents. The risks of using human or bovine products is low **Flowable**-Floseal, Gelfoam.

When thrombin is combined with gelatin granules, hemostasis can be achieved on wet, actively bleeding tissue. As gelatin capsules swell, this leads to mechanical tamponade (passive). Thrombin then converts patients' fibrinogen to fibrin further stabilizing the clot. These agents require intraoperative preparation and are applied with paste like consistency [24]. Flowable agents may contribute to adhesive disease and may be associated with small bowel obstruction [28, 29]. They are typically absorbed in 6–8 weeks and can sometimes be mistaken for abscess on postoperative imaging. Products like floseal are available with a laparoscopic applicator to facilitate placement of the agent during complicated laparoscopic surgery.

3.3 Fibrin sealants

Pooled human plasma (Tisseel, Evicel), Pooled human and equine collagen (Tachosil), Individual human plasma with bovine collagen and thrombin (Vitagel).

Fibrin sealants provide high levels of fibrinogen and thrombin separately that when combined form a fibrin clot at an accelerated speed. Fibrin sealants are comprised of 2 parts: a sealer protein solution containing aprotinin, factor XII, and fibrinogen, and a second component containing thrombin. Concentration of fibrinogen determines strength of sealant, and thrombin determines speed of clot formation [14]. Fibrin sealants are very effective and are best used for bleeding from large surfaces such as diffuse peritoneal bleeding after removal of a mass/malignancy. In a randomized trial of 224 patients comparing fibrin sealant to ORC for bleeding after liver resection, 81% acquired hemostasis in 3 mins versus 50% with ORC [30]. Fibrin sealants have also been used off-label as an adhesion barrier, but this is controversial and expensive.

4. Practical usage of topical hemostatic agents in obstetrics and gynecology

Selection of a particular topical hemostatic agent in Ob/Gyn depends entirely on the clinical situation, local availability of agents, and cost considerations. There is no "one size fits all" agent. The ideal topical hemostatic agent will control hemostasis rapidly, have a low risk of adverse events, be easy to prepare and handle, and be compatible with any patient factors [12]. Examples of practical usage of topical hemostatic agents in Ob/Gyn are provided in the following sections.

4.1 Obstetrical usage

In obstetrics, topical hemostatic agents are most often used to control postpartum hemorrhage in the setting of postpartum hysterectomy. Hemorrhage at time of cesarean section is the leading cause of morbidity. Eight percent of maternal deaths are due to postpartum hemorrhage in the United States [31]. Common indications for postpartum hysterectomy include abnormal placentation and uterine atony. Abnormal placentation has replaced uterine atony as the most common indication leading to emergency postpartum hysterectomy [31]. Placenta accreta now occurs in as many as 1 in 553 pregnancies. Topical hemostatic agents may be applied if traditional techniques for controlling postpartum hemorrhage such as: uterotonic

agents, vessel ligation, packing, balloon tamponade, over–sewing the placental bed, compression sutures, or uterine artery embolization are not successful. Topical hemstatic agents may be particularly helpful in cases of placenta previa with lower segment and implantation site bleeding. Bleeding can be brisk and present over large surfaces in these cases. Additionally, patients with hemorrhage can have factor and fibrinogen deficiencies. Therefore, fibrin sealants and agents that have both mechanical and biological properties are preferred. Hemorrhage at time of cesarean section is the leading cause of morbidity. 8% maternal deaths are due to postpartum hemorrhage in the United States [31]. With the statistics provided above, excellent hemostasis has become imperative for the safety and well being of obstetrical patients.

In 2007, Moriarty, et al. [32], presented a case reporting the use of topical hemostatic agents in massive postpartum hemorrhage. In this case the patient had a cesarean section for placental abruption. Due to persistent uterine atony and hemorrhage unresponsive to typical management techniques, she underwent a total abdominal hysterectomy. This was complicated by DIC with persistent bleeding from venous plexus at vaginal vault. FloSeal, a flowable hemostatic agent, was applied and hemostasis was achieved [32]. FloSeal was also used to control persistent postpartum hemorrhage from implantation site with success [33, 34]. In a case series, by Chung et al. in 2017, of 11 patients with obstetrical hemorrhage, 10 were controlled with intrauterine Floseal, with only 1 failure that required hysterectomy [35].

Fibrin sealants have also been used as an adjunct to control hemostasis at the placental implantation site. In 2010, Fuglsang and Petersen [36], published a series of 15 cases in which all cases were complicated by placenta previa and delivered by cesarean section. All were complicated by persistent bleeding from the lower uterine segment. Hemostasis was controlled with the topical application of Tachosil [36].

Although most applications of topical hemostatic agents occur at the time of cesarean section or hysterectomy, they have also been used to control hemostasis from vaginal and vulvar lacerations that occur following traumatic vaginal deliveries [37].

4.2 Gynecologic usage

Use of topical hemostatic agents is far more common in gynecologic surgery than in obstetrics. Common cases that may require use of topical hemostatic agents include hysterectomies, ovarian cystectomies myomectomy, endometriosis resection/ablation, incontinence procedures, and malignant debulking procedures. In these cases, advantages to use of topical hemostasis include fewer transfusions, improved visualization of the surgical field, and decreased operative time which can all potentially decrease morbidity and mortality [12].

There has been a trend over the past two decades towards application of minimally invasive surgical approaches [38]. At our institution, for example, more than 84% of hysterectomies are performed laparoscopically. If there is diffuse small vessel bleeding, bleeding near the ureter or adjacent to major vessels (such as in the parametrium), using a topical hemostatic agent may reduce the risk of conversion to laparotomy. A systematic review of topical hemostatic agents used in minimally invasive gynecologic surgery (MIGS) concluded that application of topical hemostatic agents in MIGS procedures can decrease operative time, blood loss, and may ameliorate damage to ovarian function. However, more data is needed on usage of hemostatic agents during other procedures like myomectomy, hysterectomy, and adnexal surgery [39]. In cases whereressure, electrosurgery, suturing, or stapling, may not be feasible during minimally invasive procedures such as with diffuse small

vessel bleeding, bleeding near ureter or major vessels, usage of topical hemostatic agents may be another option before converting to laparotomy.

4.3 Hysterectomy

Hysterectomy is the most common major gynecological procedure. More than 430,000 hysterectomies are performed in the United States every year. Most are performed for benign reasons [39].

Usage of hemostatic agents during laparoscopic or robotic hysterectomies has increased since introduction of fibrin sealants in the 1990's. Minimally invasive hysterectomy typically has less blood loss than open hysterectomy, so indications for topical hemostatic use may be less clear [4]. Evidence suggests that use of topical hemostatic agents at the time of hysterectomy is controversial. A study by Kakos, et al. [40], evaluated factors associated with the usage of hemostatic agents during traditional laparoscopic or robotic hysterectomies. Findings from this study revealed that the usage of hemostatic agents at the time of traditional laparoscopic or robotic hysterectomy was not associated with aggregate differences in intra-operative or postoperative bleeding metrics. Length of stay was also unchanged relative to similar hysterectomies performed without the routine use of hemostatic agents. Their findings supported the idea that surgeon's usage of these products was for prophylaxis rather than treatment [40]. Similar findings were published by Obermair, et al. [41], who compared adverse events and surgical outcomes of hysterectomy with or without usage of gelatin –thrombin matrix (Surgiflo). Surgiflo neither prevented nor caused additional adverse events in women undergoing hysterectomies [41].

Watrowski,et al. [42], studied the impact of the use of intraoperative hemostatic gelatin –thrombin matrix (FloSeal, Baxter healthcare) on transfusion rates and short-term perioperative outcomes in gynecological surgery. They found that usage of these hemostatic agents was associated with significantly better short- term perioperative outcomes including, shortened surgical and hospital times, less post-operative anemia, fewer blood transfusions, and reduced number of reoperations and ICU stays [42].

Despite the dogma that improved hemostasis can lead to improved clinical outcomes, there is evidence demonstrating the potential harms of topical hemostatic agents if used inappropriately. Harris, et al. [43], performed a retrospective cohort study of hemostatic agents used during hysterectomy and risk of postoperative complications. Women who received a hemostatic agent (N = 4659) were compared to women who did not receive a topical hemostatic agent (N = 9316). Hemostatic agent usage was associated with an increased rate of hospital readmission. Among all hysterectomy approaches, hemostatic agents used during robotic- assisted laparoscopic hysterectomy associated with an increased predicted rate of blood transfusions, and increase predicted rate of pelvic abscess diagnosis, and increased predicted rate of hospital readmission, and increased predicted rate of re-operation Their conclusion was that hemostatic agents should be used carefully owing to associations with increased postoperative re-admissions and re-operations when used during hysterectomy [43]. This study, however, did not control for diagnosis, making malignancy a cofounder and limiting strong conclusions regarding risks of hemostatic agent use in hysterectomy for benign indications [22]. Harris et al., in a second large retrospective study, compared postoperative outcomes between cohorts of patients undergoing hysterectomy for benign indications that fulfilled a perioperative bundle of four criteria. These included a minimally invasive approach, appropriate preoperative antibiotics, operative duration of less than 2 hours, and absence of intraoperative hemostatic agent use. Of all cohorts missing

only one of the four criteria, there was an association with a greater risk of post-operative complications in hyterectomies for benign indications in which hemostatic agents were used [44].

4.4 Myomectomy

Leiomyomas are the most common benign gynecologic tumor, with an estimated instance of 70–80% in women by the age 50 years [45, 46]. Most patients with leiomyomas are asymptomatic. For those with symptoms related to bulk, abnormal uterine bleeding, or infertility, there are typically multiple management options. These include: observation, medical management, uterine artery embolization, ablative procedures, and surgical resection. Surgical resection (in the absence of hysterectomy) is inclusive of hysteroscopic, laparoscopic, and open myomectomy. A variety of different medical techniques have been used to diminish blood loss during the myomectomy. These include vaginal prostaglandins, vasopressin, bupivacaine with epinephrine, oxytocin, fibrin sealant coated suture, IV tranexamic acid, and GnRH analogs. The evidence presented here will focus on topical hemostatic agents used during myomectomy.

A retrospective study by Barakat, et al. [47], found that 6.5% of patients undergoing an abdominal approach and 1.1% of patients undergoing a minimally invasive approach will require a blood transfusion. Approximately 2% would be converted to a laparotomy [47].

A variety of different medical techniques have been used to diminish blood loss during the myomectomy. These include vaginal prostaglandins, vasopressin, bupivacaine with epinephrine, oxytocin, fibrin –sealant coated suture, IV tranexamic acid, GnRH analogs. For the purpose of this chapter review, the focus will be on hemostatic agents during myomectomy.

Raga, et al., did a review of Floseal compared to placebo in a randomized cohort of 50 women undergoing myomectomy. Estimated blood loss (EBL) was significantly decreased in the treatment group. Length of stay and intraoperative blood transfusions were also less in the treatment group. Postoperative hemoglobin was significantly higher in the treatment group [48]. Fibrin sealants have also been studied in myomectomy. Tisseel has been shown to decrease mean time to achieve hemostasis, operative time, EBL, and post-operative HgB change [49].

4.5 Endometriosis resection

Endometriosis is a benign chronic disease associated with pain, dyspareunia, and infertility. Surgical options for conservative treatment include electrocauterization of cyst wall, cystectomy, and laser vaporization of cyst wall. Laparoscopic ovarian cystectomy has a significantly reduced rate of recurrence and an increased pregnancy rate when compared to coagulation and laser ablation methods [50, 51]. The goals of endometriosis resection in reproductive aged women are pain control and enhancement of fertility. Topical hemostatic agents have been investigated as an alternative to bipolar cautery and suturing to control hemostasis during ovarian cystectomy. The rationale is that there will be less trauma to the ovary and less impact on ovarian reserve [52–54]. A meta-analysis concluded that use of hemostatic agents was associated with significantly less decline in ovarian reserve over bipolar dissection [55]. Choi, et al. [56], investigated the impact of topical hemostatic agents and bipolar coagulation during laparoscopic ovarian endometriotic cyst resection on ovarian reserve by comparing the postoperative anti-mullerian hormone (AMH) levels. AMH was significantly decreased in both groups 3 months postoperatively. However, the rate of decrease in the bipolar coagulation group was

greater than that of the hemostatic sealant group [56]. These findings were further supported by a multi -centered, randomized controlled trial that showed no difference in operative outcomes, operative time, estimated blood loss or perioperative complications between the bipolar and topical hemostatic agent groups. Similarly, in both groups, postoperative AMH levels were lower than pre-operative AMH levels, but the rate of decline of AMH levels was greater in the bipolar group than in the hemostatic sealant group [57–59].

When peritoneal endometriosis is resected or ablated, there can be diffuse bleeding from multiple sites. Peritoneal endometriosis is frequently found in the deep pelvis on the surface of the uterosacral ligaments and over the path of the ureter. Controlling bleeding during these often complicated peritoneal resections can be challenging with conventional methods and application of topical hemostatic agents may be helpful [60]. There is not strong evidence for or against use of topical hemostatic agents for this particular indication.

5. Risks of topical hemostatic agent use

Several case reports have discussed risks of hemostatic agent use in gynecologic surgery including abscess formation, mimickry of abscess or malignant disease, small-bowel obstruction, blood –borne disease transmission, thrombus formation, and allergic reactions [3, 17, 19, 22, 24, 61–63].

Abscesses, or mimickry of abscesses, on imaging, is the most commonly reported complications of topical hemostatic agents. Mechanical agents being the most frequently associated. Fagotti, et al., demonstrated a statistically significant association between oxidative regenerating cellulose (ORC) (Surgicel) and pelvic abscess formation (11.8% with ORC verses 1.7% without) [15].

Anderson, et al., in a retrospective cohort study examined all malignancy related hysterectomies, and hysterectomies for benign indications through all routes except vaginal. Gelatin-thrombin matrix (GTM) was used in 40% of cases. 3% developed abscess. Based on this, their recommendation was that liberal use of GTM should be used with caution in clean contaminated cases [15].

A large retrospective cohort study of over 17,000 patients, by Harris et al., examined the use of hemostatic agents during all routes of hysterectomy and evaluated risks of post-operative complications. Among all hysterectomy approaches, and after adjusting for demographic and surgical factors, hemostatic agent use during robotic assisted laparoscopic hysterectomy was associated with an increased predicted rate of blood transfusions, and increased predicted rate of pelvic abscess diagnosis, and increased predicted rate of hospital readmission, and an increased predicted rate of reoperation. Their conclusion was that hemostatic agent should be use carefully owing to associations with increased postoperative re-admissions and re-operations when use during hysterectomy [43].

Collections seen postoperatively on imaging may be misinterpreted as an abscess [15]. Interpretation as to whether its abscess versus normal degeneration of topical hemostatic agents may be aided by informing radiologist that topical hemostatic agents have been used [16]. An abscess typically has rim enhanced and air-fluid levels. Topical hemostatic agent degeneration usually has tightly packed gas bubbles which remain unchanged on serial exams with no rim enhancement or air-fluid levels [16]. Often, as mechanical hemostatic agents degenerate over time, they may be mistaken as granulomas or malignancy [17, 18].

The next most common complication associated with topical hemostatic agents is small-bowel obstruction secondary to inflammatory foreign body giant cell reaction. Symptoms may present on postoperative days 5–9 [29, 64]. To decrease the

chances of this occurring, as per package insert, excess topical hemostatic agents should be gently irrigated and removed.

Another concern regarding usage of biological agents is the potential for immunological risks. Agents that contain bovine thrombin have been associated with antibody –mediated reactions that have resulted in bleeding diatheses [65].

Donor pool human derived thrombin, approved in 2007 by the FDA, may potentially carry risk of viral disease transmission including HIV, hepatitis, parvovirus B19.

Recombinant thrombin may eliminate the risk of disease transmission and decreased immunologic response. However, allergic reactions to animal proteins have been reported [23].

6. Conclusion

Topical hemostatic agents should be used as an adjunct to good surgical technique. There are many potential applications of topical hemostatic agents in obstetrics and gynecology. Choice of topical hemostatic agent is at the discretion of the clinician and subject to hospital availability and cost. Mechanical hemostatic agents are passive and augment endemic clotting factors. Biologic hemostatic agents are active because they contain thrombin allowing better clot stabilization. Combining mechanical and biologic hemostatic agents (often done at the product level) can improve efficacy at a higher price point. Although the goal of these agents is to improve postoperative outcomes, there is limited evidence to support their widespread use in obstetrics and gynecology. In-depth knowledge of the risks and benefits of these agents is important because appropriate use has the potential to improve clinical outcomes. Since hemostatic agents have been introduced, they have been applied across many subspecialties, including Obstetrics and Gynecology. Knowledge of their mechanisms of actions, potential complications from their use, and limited and often conflicting data behind case-specific applications, warrants judicious usage of these agents. Larger studies, specifically on case- specific usage, along with focus on value-based applications, need to be done before empiric recommendations on routine usage of these agents can be made. At this point they should only be used as an adjunct to traditional means of achieving hemostasis.

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