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Use of Monsel's Solution to Treat Obstetrical Hemorrhage: A Review and Comparison to Other Topical Hemostatic Agents

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Abstract

Peripartum hemorrhage accounts for 8% of maternal deaths in the United States, and nearly 27% worldwide. A growing need exists for tactics to spare morbidity given a rise of abnormal placentation that contributes to excessive blood loss at the time of delivery. Approaches such as compression sutures, balloon tamponade, and pelvic artery embolization are not without side effects and potential implications for future fertility. The use of topical hemostatic agents has become widespread in gynecologic and obstetric surgery despite a paucity of distinct studies in the field, and may allow providers to increasingly avoid cesarean hysterectomy. A variety of topical hemostatic agents exist along a wide cost continuum, each characterized by specific efficacy, advantages, drawbacks, and often gaps in long-term data to support safety and impact on future fertility. Herein, we comprehensively review these agents and illustrate a non-traditional use of Monsel's solution applied directly to the placental bed in a case of focal placenta accreta. This ultimately contributed to successful uterine preservation with no known adverse sequelae. Monsel's solution may have a role in establishing hemostasis in the setting of abnormal placentation, and may be a particularly attractive alternative in resource-poor nations.

Keywords

hemostatic agent; peripartum hemorrhage; placenta accreta; Monsel's solution

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CONDENSATION: We review topical hemostatic agents for intrauterine use and comment on a case in which Monsel's solution contributed to uterine preservation despite placenta accreta.

INTRODUCTION

The use of topical hemostatic agents is widespread in gynecologic surgery despite a paucity of distinct studies in the field, and has increased by 10-21% between 2000-2010 [1]. This approach represents a very effective tool in the control of intra-operative bleeding, however, most data regarding topical hemostatic agents must be extrapolated from other specialties. Given the increasing incidence of abnormal placentation secondary to prior cesarean delivery, a critical role for topical hemostatic agents for obstetric indications has emerged. Placenta accreta now occurs in as many as 1:553 pregnancies [2]. Hemorrhage at the time of cesarean delivery remains a leading cause of morbidity. In the United States, peripartum hemorrhage still accounts for 8% of maternal deaths [3]; worldwide it accounts for nearly 27% and resulted in 661,000 deaths from 2003-9 [4]. The importance of this complication, risk factors, maneuvers and therapeutic interventions has been the subject of multiple recent reports [5-10]. Several interventions may be employed to control bleeding, including various surgical approaches (e.g., oversewing of the site of hemorrhage; placement of B-lynch, Hayman, and Cho sutures) [11-13], systemic uterotonics, restoration of coagulation pathways through activated factor VII [14-15], uterine or hypogastric artery ligation or embolization, and intrauterine tamponade [16]. When conservative approaches fail, hysterectomy can be life-saving. A case is presented below in which topical hemostatic agents, including Monsel's solution, were applied directly on the endometrium to avoid cesarean hysterectomy.

CASE

A 23-year-old gravida 3 para 0020 at 35 and 1/7 weeks gestational age presented to labor and delivery two hours after loss of fluid per vagina. Her history was significant for a posterior placenta previa diagnosed at 23 weeks gestational age and followed by ultrasound every four weeks during her pregnancy. An ultrasound performed 3 days prior to her presentation showed persistent marginal placenta previa with a leading edge < 9 mm from the os. The patient was counseled at that time to undergo cesarean delivery. Her history was notable for two first trimester terminations by dilation and curettage. The remainder of her prenatal course was uncomplicated.

On initial speculum examination, the patient was noted to have approximately 500 cc of blood in the vagina and on the surrounding perineum. The fetus was cephalic on ultrasound with an amniotic fluid index of 15 cm. External fetal monitoring revealed a category 1 tracing. Intravenous access was established. Pre-operative hematocrit was 38.6%. Three units of blood were requested prior to proceeding to the operating room for cesarean delivery. Maternal vital signs remained stable with pulse 90-110 beats/minute and blood pressure 110-116/65-80 mm Hg. Vaginal bleeding ceased spontaneously.

Non-emergent primary low transverse cesarean delivery was performed and a viable male infant was delivered with Apgar scores of 9/9 at 1 and 5 minutes, respectively. The placenta delivered spontaneously from the posterior endometrium. At this time, hemorrhage was noted arising from the bed of the placenta. Several 0-Vicryl figure-of-eight sutures were placed in the bed with no resolution of bleeding. Pitocin 30U was given intravenously.

Bleeding persisted heavily and an intra-operative consult to the Gynecologic Oncology service was requested. Severe additional stitches were placed in the endometrium without resolution of bleeding. The fundus was noted to be intermittently atonic. Intramuscular methylergonovine (200 mcg) and intrauterine carboprost tromethamine (250 mcg) were ordered, however the patient's blood pressure rose precipitously to 200/100 mm Hg and prevented administration of more than 75% of the proposed doses. With a total intraoperative estimated blood loss of 1700 cc, three units of packed red blood cells and 1 unit of FFP were infused. Given the patient's age and desire for future pregnancy, topical hemostatics were applied beginning with approximately 16 mL of Monsel's solution impregnated in a uterine pack. Bleeding dramatically slowed after application for a few minutes of the pack on the placental bed. Surgicel® SNoW™ (Structure Non-Woven material; Ethicon, Blue Ash, OH) and Evicel® sealant (Ethicon) were subsequently prophylactically applied on the now hemostatic placental bed. The hysterotomy and abdomen were closed and the patient was transferred directly to the Interventional Radiology Suite in preparation for potential uterine embolization. Angiography was performed immediately and was unremarkable for active bleeding (**Figure 1**). The patient was transferred back to labor and delivery for further management, and ultimately discharged with her infant on post-operative day 4 without further bleeding. Hematocrit on discharge was stable and had equilibrated to 27.4%. She remained afebrile throughout her course.

Pathologic analysis revealed a 600g placenta (> 90th percentile for gestational age) with intervillous fibrin and calcification; there were increased syncytial knots within the chorionic villi but no evidence of inflammatory changes within the chorionic plate or amnion.

The patient began depo provera for contraception at 1 month postpartum. A CT of the abdomen and pelvis at 4 months postpartum showed a normal-appearing uterine scar and no evidence of sequelae in the endometrium or peritoneal cavity (**Figure 2**). A transabdominal and transvaginal ultrasound at 11 months post-partum was also unremarkable with no complications at 1 year from the procedure. The patient plans to delay future conception for over 2 years from the time of her cesarean delivery.

BACKGROUND AND HISTORY

We report our experience with use of Monsel's solution (20% aqueous ferric subsulfate) as the primary hemostatic to control hemorrhage during cesarean delivery secondary to marginal placenta previa and suspected focal placenta accreta. Leon Monsel, a French pharmacist, pioneered use of ferric subsulfate for its styptic qualities as early as 1852 during the Crimean War [17]. Initially, Monsel's solution was used primarily for disruptions of the epithelium, which were numerous in times of war [18]. In 1859, W. Proctor published the formula for the solution in the *American Journal of Pharmacology*, which led to wider usage, though little research was conducted about its effects on tissue until the mid-twentieth century [17-18]. In 1880, during a conference on postpartum hemorrhage, Dr. Aug. F. Erich advocated "mopping the cavity with a styptic, the most effectual being Monsel's solution"... "the uterus may be contracted to a considerable degree, and yet a vexatious oozing may

continue... a sponge may be saturated with the styptic, carried into the uterus and the whole cavity thoroughly swabbed with it" [19]. There is very little subsequent mention of ferric subsulfate in the medical literature until a study was published in the *Archives of Dermatology*, which compared it to ferrous chloride for hemostasis. The authors concluded that the hemostatic effect of Monsel's solution was due to mechanical sealing of small vessels rather than the acidic background. Monsel's solution subsequently gained popularity [20], and since that time has remained useful to gynecologists mostly during cervical biopsies and excisional procedures [21], and to dermatologists for punch biopsies. Modern intrauterine use of Monsel's solution is not well documented, and to date only one case report regarding its application during hemorrhage following dilation and evacuation exists in the English literature [22].

MECHANISM OF ACTION

Monsel's solution is a brown fluid which is prepared by reacting ferric sulfate with sulfuric acid and nitric acid, and thus remains very acidic (pH approaching 1) [23]. Hemostasis as a result of Monsel's solution is believed to be due to denaturation and agglutination of proteins such as fibrinogen by ferric ions, which is augmented by the low pH and subsulfate group [23]. Uptake and tissue effects of Monsel's solution have been studied extensively in the dermatologic and dermatopathology literature. Monsel's solution may lead to deposition of ferric salts (i.e., ferrugination) within fibrin, dermal collagen and striated muscle, which may cause refractory pigmentation of skin following its usage and an inflammatory reaction that may persist for weeks at the site of damage. When Monsel's is used on epithelium after dermatologic biopsies there is often evidence of a "tattoo" effect with extended pigmentation of tissue. Ferrugination can also be seen with trauma from an iron-coated instrument [24-25] [26]. In muscle, ferrugination may cause damage and inflammation, but cross-striations are preserved and sometimes accentuated [26].

EFFICACY

Most evidence for the efficacy of Monsel's solution is anecdotal. It is generally accepted that Monsel's solution is an ideal hemostatic for small amounts of bleeding, particularly on the cervix or epithelium. No studies have determined its efficacy with larger amounts of hemorrhage, however, resultant coagulation may be so effective that some authors advocate application completely in lieu of sutures following cone biopsy [21] [27]. Most commercial preparations achieve hemostasis in < 20 seconds [28-29].

CONCERNS AND COMPLICATIONS

Critics have noted that Monsel's solution can seep into tissues and cause iron-protein precipitate formation, trapping calcium ions and causing denaturing of the sarcolemma in muscle, ultimately causing necrosis [24-25]. Most practitioners agree that Monsel's solution should be used with caution in the intraperitoneal setting given limited data [24-25][29,30]. The histologic effect of Monsel's may persist for up to 3 weeks in tissue [31]. Monsel's applied to biopsy sites specifically in the cervix has been associated with local tissue necrosis, impediment of re-epithelialization, and formation of granulation tissue around the iron-containing solution which can then persist in siderophages for up to 3 months. If

Monsel's solution is applied to a pathological specimen it is recommended that the physician inform the pathologist [32]. In certain instances, atypical histiocytic reactions to Monsel's solution in the skin have been confused with malignant melanoma [24-25], have obscured interpretation of depth of melanoma invasion [33], or have impaired interpretation of cone biopsy specimens if performed less than 3 weeks from use of Monsel's at the time of cervical biopsy [31]. Though not apparent in animal models [23], Armstrong and colleagues (1986) found in human subjects that the agent caused less rapid wound healing and also inferior cosmesis compared with collagen matrix product [26]. Despite these pathological findings, most clinicians agree cervical and vaginal tissue to which Monsel's solution has been applied generally appears grossly normal within several weeks of application.

Several critics have proposed that Monsel's solution may be a nidus of infection, particularly nosocomial micro-organisms given its nonsterile usage in most clinics and storage over long periods of time with several uses across multiple patients. A study from Brigham and Women's Hospital, however, failed to show growth in cultures after 5 days using Monsel's solution inoculated with nosocomial bacteria, including *Clostridium* sp. and *P. aeruginosa*. Furthermore, cultured Monsel's solution from open clinic samples failed to grow bacterial colonies [34]. Epidemiological literature and biochemical properties moreover suggest that Monsel's solution may inhibit bacterial growth [35], thereby evoking its safety for usage in obstetrics.

In gynecologic literature, it has been reported that only 50% of operative reports correctly noted the usage of topical hemostatic agents when used intraoperatively [36]. Inclusion of this information is essential when considering possible surgical complications and when interpreting post-operative imaging, as intra-abdominal topical hemostatics may resemble abscesses [37-38].

COMPARISON TO OTHER TOPICAL HEMOSTATIC AGENTS

Other topical hemostatic agents include chelating agents, polysaccharide matrices, exogenous coagulation pathway proteins (i.e., fibrinogen, thrombin), and combination preparations (**Table 1**). Use of these agents for gynecologic and obstetric indications is under-reported. There are no objective comparisons of Monsel's solution to other available hemostatic agents.

a. CHELATING AGENTS: *chitosan-covered gauze and aluminum silicate*

Deacetylated chitin harvested from the exoskeletons of crustaceans exploits the electrostatic interaction of negatively charged erythrocyte membranes and positively charged carbohydrate to form clot. Chitosan (HemCon, Portland, OR; CELOX, Medtrade products, UK) is non-toxic, degradeable, antimicrobial, and has even been considered as a mucoadhesive medium for vaginal drug delivery [39]. Schmid and colleagues (2013) used chitosan-impregnated gauze as uterine packing in 19 consecutive cases of post-partum hemorrhage following vaginal (n=8) or cesarean (n=11) delivery. Rate of hysterectomy was reduced by 75% relative to an equivalent time period prior to the introduction of the product, and no adverse side effects were noted [40]. Quikclot® (Z-Medica, Wallingford, CT) is a chelating agent consisting of aluminum silicate which concentrates clotting factors and

platelets. This product was originally designed for external use in combat settings. Intra-abdominal use should generally be reserved for life-threatening penetrating trauma given an exothermic reaction with blood that may cause local tissue damage [41]. Accordingly, there are no reports of its use for obstetric or gynecologic indications.

In animal models, comparisons of these two products for external use show no superiority of either agent [42].

b. NON-FLOWABLE MATRIX: microporous polysaccharide spheres, gelatin, oxidized regenerated cellulose, collagen

Microporous polysaccharide spheres represent a proprietary preparation of potato starch granules irradiated for sterility (Arista, Bard Davol, Warwick, RI). Via osmosis, the carbohydrate spheres concentrate clotting factors and platelets. Microporous polysaccharide spheres have been shown to perform equivalently compared to other non-flowable hemostatic agents, but inferiorly to thrombin and gelatin combinations (e.g., FloSeal), regardless of conditions of hypothermia, hypocoagulability, and hemodilution [43-44]. Use in gynecologic/obstetric surgery is lacking, but good outcomes were achieved in robotic-assisted athermal nerve-sparing prostatectomy; mean decrease in post-operative hemoglobin was nearly double in patients who did not receive the agent (3.2 g/dL versus 1.2 g/dL) [45].

Gelatin sponges (Gelfilm, Pfizer, NY, NY; Surgifoam-sponge, Ethicon, Blue Ash, OH) and powder (Surgifoam-powder, Ethicon) provide tamponade with expansion upon absorption of as much as 45 times their dry weight in fluid [46], as well as minor mechanical activation of the clotting cascade. Unfortunately, the neutral pH affords no anti-microbial properties, but the squares may be easily moldable for insertion through a laparoscopic port.

Oxidized regenerated cellulose serves as a scaffold for platelet adherence and thromboplastin release, and was introduced for surgical use in 1943 [47]. Like Monsel's solution, a low pH provides antimicrobial benefits and causes local vasoconstriction [48-49]. Sharma & Malhotra (2006) employed it successfully across hysterotomy sites that exhibited persistent oozing despite oxytocin, ergometrine, intramyometrial prostaglandin, and local hemostatic sutures [50]. This same group reported successful hemostasis with laparoscopic placement for uterine perforation during termination of pregnancy [51] and tubal sterilization [52]. In a cross-sectional study of 41 pregnant women who developed post-partum hemorrhage following cesarean section 2006-12 at a single institution, the rate of hysterectomy was 5% versus 66% in women who did and did not have application of 2-3 Fibrillar™ (Ethicon) gauzes to the lower uterine segment [53]. Rates of transfusion, admission to the intensive care unit, and length of hospitalization were also reduced ($p<0.001$). Surgicel® (Ethicon) has been used in combination with abdominal packing with good effect in cases of hemorrhage following cesarean hysterectomy or tumor debulking [54]. No post-marketing contraindications have been identified for the use in obstetrics and gynecology. Though in most instances degradation occurs within 4 weeks, there have been reports of material discovered as many as 15 months from placement upon repeat laparotomy for gynecologic malignancy [55]. Oxidized regenerated cellulose may also prevent formation of peritoneal adhesions, and is marketed under a separate entity

(Gynecare Interceed, Ethicon) for this purpose and varies slightly by degree of oxidization and weave [56].

c. Collagen attracts and aggregates platelets. Bovine collagen has been used laparoscopically to avoid laparotomy by controlling bleeding as a result of perforation during dilation and curettage [57]. Karagiannis and colleagues (2008) reported good outcomes with use of type I collagen in 5 obstetric and 3 gynecologic cases [58]. Use of microfibrillar collagen has shown to reduce blood loss more effectively relative to oxidized regenerated cellulose [59]. One industry-sponsored porcine study found equal efficacy of collagen alone (Ultrafoam, Bard Davol) and gelatin matrix with thrombin (Gelfoam hemostasis kit, Baxter, Deerfield, IL) [60]. Though mostly innocuous, in rare instances patients may develop intense allergic reactions to this substance, as manifested by eosinophilia, fever, hepatic dysfunction and verified by skin testing [61]. Occasionally, granulomas may form. After application during total abdominal hysterectomy and bilateral salpingo-oophorectomy for a mucinous cystadenoma, a patient experienced formation of a large granuloma that prompted re-operation 3 months post-operatively [62]. In some cases, these granulomas have led to bowel obstruction requiring operative intervention [63].

d. FLOWABLE MATRIX, BIOLOGIC DERIVATIVES, & COMBINATION PREPARATIONS: spray gelatin, thrombin, fibrinogen + thrombin, gelatin + thrombin, collagen + fibrin + thrombin, collagen + fibrin + autologous plasma

Exogenous biologic derivatives such as fibrinogen or thrombin augment the coagulation cascade (**Figure 3**). Intraoperative use of fibrin sealants was conceptualized as early as 1909 [64], with growing popularity after initial investigations during repair of peripheral nerves as early as 1940 [65]. Fibrin glue was utilized in conjunction with polyglycolic mesh by Jaraquemada and colleagues (2004) in a protocol for uterine repair in the setting of placenta percreta [66]. This was successful in 50 patients, though an additional 19 ultimately progressed to hysterectomy. Interestingly, thrombin may double as a potent uterotonic due to stimulation of membrane receptors [67], and thrombin-soaked uterine packs have been used to produce hemostasis of the lower uterine segment after 8 hours of tamponade [68].

A number of combination preparations have evolved. Tisseel™ (Baxter) is a proprietary spray sealant composed of human fibrin and thrombin. Tisseel™ has been used successfully for hemostasis of complex obstetric lacerations [69], postpartum hemorrhage from obstetric trauma [70], and life-threatening gynecologic hemorrhage as early as 1989 [71]. Notably, use with oxidized cellulose matrix can reduce efficacy. Anaphylaxis to the protease inhibitor aprotinin component has been reported and gas embolism can occur when administered at higher-than-recommended pressures [72]. Tachosil® (Baxter) is a patch coated with human fibrinogen and thrombin coated onto an equine collagen sponge; it is a refinement of the bovine analog TachoComb® and does not contain aprotinin. Fuglsang & Petersen (2010) reported outcomes of 15 women with peripartum hemorrhage at time of repeat cesarean section in the setting of placenta previa. There were no instances of hysterectomy or post-operative endometritis [73]. Tinelli (2011) described use of Tachosil® to control hemorrhage from the hysterotomy site at time of re-operation following cesarean section

[74]. Laparoscopic application of TachoComb® successfully controlled vaginal cuff bleeding during laparoscopic or vaginal hysterectomy [75]. A randomized trial of Tachosil® versus Surgicel® for secondary treatment of local bleeding in hepatic resection in ongoing [76]. CoStasis (Cohesion Technologies, Palo Alto, CA) is another permutation consisting of collagen, thrombin, and autologous plasma obtained from the patient.

FloSeal™ (Baxter) is a proprietary combination of flowable gelatin available with or without bovine thrombin. The gelatin granules and lead to constriction of blood flow while thrombin catalyzes fibrin polymerization across this matrix. Gelatin with thrombin has been found to be superior to gelatin sponge alone [77]. Cessation of hemorrhage has been described upon application of FloSeal™ to the vaginal cuff bed following cesarean hysterectomy [78], to hysterotomy sites [79], in conjunction with pressure upon re-laparotomy following cesarean delivery in the setting of placenta previa [80], to the endometrium following vacuum-assisted vaginal delivery complicated by acute fatty liver of pregnancy [81], to the placental implantation site in the case of placenta previa [82-83], to vaginal lacerations, and as an adjunct to hysterectomy and laparoscopic endometrioma resection [84-85]. As with collagen-based preparations, severe pelvic inflammatory responses [86], caseating granulomas [87], obstruction [88], and abscess [89] pursuant to placement have been documented.

Biologic derivatives are not without risk. Instances of auto-immunity prompted by exposure to bovine factor V found in commercial thrombin preparations have led to coagulopathy [90-91]. Biologically derived sealants carry potential for transmission of microbials [92], though residual risk of pathogen transmission per vial has been calculated to be less than 1 in 10^{15} [93]. A case of parvovirus infection following fibrin glue application during laparoscopic hysterectomy has been reported [94]. Recombinant human preparations may circumvent this [95]. Concerns have also been raised regarding increased risk of abscess formation. In a study of 413 women undergoing hysterectomy, 51% in the setting of malignancy, multivariate analyses revealed an OR of 7.0 (95% CI 1.5-32.9, $p=.013$) for development of abscess as defined as defined by fever $> 38^{\circ}\text{C}$, presence of a walled-off collection on CT imaging, and leukocytosis $> 11,000/\mu\text{L}$ in the setting of gelatin-thrombin versus no hemostatic agent [89]. Lastly, these agents have been implicated in abdominopelvic adhesive disease. Hoffmann et al (2009) studied adhesion formation after laparotomy, peritoneal excision, and application of various hemostatic agents (e.g., activated starch microspheres (Arista), thrombin-coated collagen microspheres (FloSeal), thrombin-activated fibrin polymer (Tisseel), polyethylene glycol polymer (CoSeal, Baxter), and oxidized cellulose (Surgicel). Adhesion formation at 7 days correlated with amount of residual material; Arista and CoSeal showed significantly lower adhesion formation than controls ($p < 0.05$) [96].

COST IMPLICATIONS

Monsel's solution is highly cost-effective, especially relative to most other hemostatic agents. Some sources quote an average price per 15 cc quantity of \$2.50, which remains more economical even compared to chitosan and aluminum silicate gauzes [97]. At most institutions, the most expensive preparations (e.g., flowable combination biologic

derivatives) may cost in excess of \$400-\$1000 per use. Non-flowable matrix (e.g., oxidized regenerated cellulose, collagen, microporous polysaccharide spheres) and single-agent biologic derivatives (e.g., thrombin) tend to be intermediate to this in cost [98].

FUTURE FERTILITY

The effect of Monsel's on smooth muscle or uterine endometrium and future fertility are unknown. Monsel's has been used extensively for localized cervical and vaginal bleeding without future adverse outcomes. While there is minimal data regarding use of intrauterine Monsel's and future pregnancy, in the existing report by Disu and colleagues (2006), the patient went on to deliver a full term infant in her next pregnancy [22].

Fertility outcomes following application of other topical hemostatic agents are also inadequately described. One Swedish study examined the effects of application of the topical hemostatic fleece placed during postpartum hemorrhage in the setting of placenta accreta. While the sample size was small (n=11), at time of hysteroscopy or transvaginal ultrasound at a mean of 9.4 months following cesarean delivery, most patients were found to have only a small amount of the agent undergoing resorption; normal endometrium was present and no intrauterine adhesions were found. All patients were found to have healed cesarean scars [99].

In contrast, pelvic artery embolization has been associated with subsequent placental disorders leading to fetal growth restriction and pre-eclampsia, (reviewed in [100]; [101-102]). Patients who undergo placement of square compression sutures may experience late post-partum hemorrhage as far as 37 days post-operatively [103], and as many as 18.5% of patients (5/27) who undergo placement of compression sutures demonstrate intrauterine synechiae on hysteroscopic examination [104]. While tamponade by Bakri balloon (Cook Medical, Bloomington, IN) placement may offer less blood loss, shorter operative times [105], and fewer sequelae for future fertility relative to compression sutures, in rare instances, the device may migrate intra-abdominally through uterine perforation [106].

In cases where the alternative may be cesarean hysterectomy, use of topical hemostatics including Monsel's solution on the endometrium should be strongly considered. The intrauterine use of topical hemostatics warrants continued examination. The limited data presently available suggest that it is unlikely for topical hemostatics to negatively impact future fertility, however given ferric subsulfate's mechanism of action and potential tissue effects, research and long-term follow-up is needed.

CONCLUSIONS

Topical hemostatic agents have distinct utility in management of hemorrhage in the setting of abnormal placentation. Careful application of Monsel's solution to the bleeding placenta bed with a swab or impregnated pack and avoiding any peritoneal exposure may have an under-recognized role in treatment of peripartum hemorrhage due to abnormal placentation during cesarean delivery. Well-designed, specialty-specific trials regarding use of topical hemostatic agents remain lacking, but a growing body of anecdotal support exists in the literature. Presently, data to support use in gynecologic and obstetric surgery is largely

extrapolated from other surgical subspecialty literature. Monsel's solution may represent a feasible and cost-effective adjunct to reduce maternal hemorrhage and cesarean hysterectomy in the setting of abnormal placentation, especially for focal accreta, particularly in resource-poor nations. Long-term follow-up is required to uncover any unanticipated negative repercussions on maternal safety and future fertility.

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Figure 1.

The patient was transferred directly from the operating room to the Interventional Radiology suite following abdominal closure in preparation for possible uterine artery embolization. Angiography performed immediately after surgery revealed no active bleeding.

Figure 2. CT performed 4 months following delivery showed no sequelae from intrauterine application of Monsel's solution for hemostasis at the site of focal placenta accreta.

Figure 3.
Schematic representation of the interactions between various hemostatic agents and the coagulation pathway.

Table 1

Comparison and classification of various topical hemostatic agents by mechanisms of action, disadvantages, time to resorption, and salient successful applications in obstetrics and gynecology.

SUBSTANCE	US TRADE NAME / MANUFACTURER	DERIVATIVE	MECHANISM	DISADVANTAGES	OUTCOMES IN INTRA-ABDOMINAL/OB/GYN SURGERY	TIME TO ABSORPTION
FERRIC SUBSULFATE	- Monsel's Solution (e.g., Premier, Plymouth Meeting, PA among others)	chemical	agglutination of coagulation factors	<ul style="list-style-type: none"> ■ acidic ■ may cause 'tattooing effect' 	present case	3 weeks
CHITOSAN (DEACETYLATED CHITIN)	-ChitoFlex (HemCon, Portland, OR) -CELOX (Medtrade Products, UK)	shellfish exoskeleton	positive charge attracts red blood cells and provides scaffold for clot formation	<ul style="list-style-type: none"> ■ caution in individuals with shellfish allergy, though no hypersensitivity reactions have been described in such individuals 	[40]	must be removed within ~48 hours of application
KAOLIN (ALUMINUM SILICATE)	- Quikclot (Z-Medica, Wallingford, CT)	mineral	hydrophilic nature concentrates clotting factors and platelets	<ul style="list-style-type: none"> ■ contact with blood produces an exothermic reaction reaching temperatures as high as 90° C [41] 	not recommended by manufacturer for intrathoracic or intra-abdominal use; reserved for external wounds or salvage of life-threatening penetrating trauma	must be removed within ~48 hours of application
MICROPOROUS POLYSACCHARIDE SPHERES	- Arista (Bard Davol, Warwick, RI) [107]	plant	osmotic nature concentrates clotting factors and platelets	<ul style="list-style-type: none"> ■ caution with use > 50g in diabetic patients as starch may influence glucose load ■ compatible with cell saver if 40 micron filter used 		48 hours via amylases
GELATIN SPONGE / POWDER	- Gelfilm (Pfizer, NY, NY) - Surgifoam sponge and powder (Ethicon, Blue Ash, OH)	porcine	expansion by as much as 200% <i>in vivo</i> provides scaffold for clot; thromboplastin is also released from platelets after contact, which interacts with prothrombin and calcium	<ul style="list-style-type: none"> ■ neutral pH does not provide antimicrobial effects 		4-6 weeks

SUBSTANCE	US TRADE NAME / MANUFACTURER	DERIVATIVE	MECHANISM	DISADVANTAGES	OUTCOMES IN INTRA-ABDOMINAL /OB/GYN SURGERY	TIME TO ABSORPTION
			to produce thrombin			
OXIDIZED REGENERATED CELLULOSE	- Surgicel family (Ethicon; Nu-Knit, Fibrillar, SNoW) [108]	plant	provides scaffold for clot formation; low pH induces vasoconstriction [49]; may also prevent adhesion formation [56]	■ may mimic abscess on post-operative imaging [37]	[50-52]	1-4 weeks, though in rare instances material has been identified up to 15 months post-operatively [55]
COLLAGEN	- Avitene / Actifoam (Bard Davol, Warwick, RI) - Helistat / Helitene (Integra Lifesciences, Plainsboro, NJ) [109]	bovine	activation of the intrinsic coagulation pathway	■ granulomatous reactions have been linked to bowel obstruction and surgical re-exploration [62-63] ■ systemic allergic reactions have been described [61] ■ may mimic abscess of post-operative imaging [38] ■ caution with concurrent use with cell salvage given inability to filter	[57-58]	> 8 weeks
GELATIN	- Gelfoam (Pfizer) - Surgifoam (Ethicon, Blue Ash, OH) - Spongostan (Ethicon, Blue Ash, OH) [110]	porcine	expansion by as much as 200% <i>in vivo</i> provides scaffold for clot; thromboplastin is also released from platelets after contact, which interacts with prothrombin and calcium to produce thrombin	■ caution with concurrent use with cell salvage given inability to filter		4-6 weeks
THROMBIN	Thrombin-JMI (Pfizer, NY, NY)	bovine	augmentation of coagulation cascade; may promote uterine contractility [67]	■ the acidity of oxidized regenerated cellulose can inactivate thrombin therefore the two products should not be used in conjunction	[68]	Immediate
	Evithrom (Ethicon, Blue Ash, OH)	human				
	Recothrom (Medicines Company, Parsippany, NJ)	recombinant human				

SUBSTANCE	US TRADE NAME / MANUFACTURER	DERIVATIVE	MECHANISM	DISADVANTAGES	OUTCOMES IN INTRA-ABDOMINAL /OB/GYN SURGERY	TIME TO ABSORPTION
FIBRIN + THROMBIN	- Artiss (Baxter, Deerfield, IL) - Tisseel (Baxter, Deerfield, IL) - Evicel (Ethicon, Blue Ash, OH) [111]	human	augmentation of coagulation cascade	■ the acidity of oxidized regenerated cellulose can inactivate thrombin therefore the two products should not be used in conjunction ■ injection into medium/large vessels may cause thromboembolism	[69-71]	Immediate
GELATIN + THROMBIN	- FloSeal (Baxter, Deerfield, IL) - Surgiflo (Ethicon, Blue Ash, OH) [112]	bovine porcine	as above	■ may contribute to adhesive disease linked to small bowel obstruction [88] ■ auto/cross - immunity against factor V may cause paradoxical bleeding diathesis [90] ■ injection into medium/large vessels may cause thromboembolism ■ severe pelvic inflammatory responses [86] and caseating granuloma [87] formation may occur ■ use may be linked to increased risk of abscess formation [89]	[78-85]	6-8 weeks
COLLAGEN + FIBRIN + THROMBIN	- TachoComb (Baxter, Deerfield, IL)	bovine	as above	■ auto/cross - immunity against factor V may cause paradoxical bleeding diathesis [90]	[73-75][99]	< 20 weeks
	- TachoSil (Baxter, Deerfield, IL)	human				
COLLAGEN + THROMBIN + AUTOLOGOUS PLASMA	- CoStasis / Dynastat (Cohesion Technologies, Palo Alto, CA)	bovine	as above	■ auto/cross - immunity against factor V may cause paradoxical bleeding diathesis [90]		4 weeks