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Topical haemostatics and sealants in gynaecological and obstetric surgery: state of the art

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ABSTRACT

Nowadays a large variety of topical haemostatics and surgical sealants are available and widely used in gynaecology and obstetrics when conventional manoeuvres to treat or prevent haemorrhage or seroma/lymphocele could appear insufficient, but most of publications relate to other surgical specialties. A recent European consensus on the optimal use of haemostatic powders in surgery, has pointed out the value of these agents and the powder formulation of microporous polysaccharide spheres has shown the strongest evidence to support its optimal use. Anyway, it is advisable that specific and appropriate perspective clinical trials on topical haemostatics and surgical sealants are carried out in the future, focused on gynaecological and obstetric surgery, to allow Obgyn specialists to obtain the maximum benefits from the use of these agents in their practice.

INTRODUCTION

Despite the significant development of nonsurgical treatments for gynaecologic diseases, surgery remains the main clinical approach in this clinical field [1].
Nevertheless, all surgical procedures involve risks: complications can arise both intraoperatively or postoperatively following gynaecologic or obstetric surgery and may be related to patients' conditions as well as to surgeon, or surgical procedure [1, 2]. The anatomical proximity of uterus and relevant annexes to ureters, bowels, vessels, and nerves, makes these organs and tissues potentially susceptible to injuries in occasion of gynaecological surgery [2]. In fact, a recent and large retrospective analysis has shown that 75% of iatrogenic urinary tract injuries are due to gynaecologic surgeries and that urinary tract injury complicates 0.2 to 1% of all gynaecologic procedures and pelvic operations [3].
Taking into consideration all the gynaecological and obstetric surgical approaches, haemorrhage and haematoma formation is the most frequent complication, followed in order by infection and abscess, bowel injury, bladder injury, ureteral injury, peritoneal inclusion cyst, lymphocele, pelvic floor dysfunction, wound dehiscence, and abdominal wall endometriosis [1].
The total abdominal hysterectomy appears to be the surgery with the highest risk of complications and the caesarean section the one with the lowest risk [1].
Currently, abdominopelvic surgeries are increasingly being performed with minimally invasive techniques and in the last decades the laparoscopic hysterectomy is much more frequently used than the abdominal approach, as providing a quicker postsurgical recovery and a reduction in hospital stay [1, 4]. Indeed, laparoscopy can be used with diagnostic and/or curative intent and may involve simple and complex gynaecological interventions up to oncologic surgeries [5-7]. Nevertheless, also the laparoscopic approach presents potential complications, obviously increasing in frequency along with the complexity of the surgery and including vascular and gastrointestinal injuries and lesions of the urinary system [6, 8].
Anyway, whatever the surgical approach, despite the use of advanced procedures and the surgeon's expertise, in some cases traditional surgical maneuverers to prevent or treat perioperative complications may not be successful.
Overall, haemorrhage and haematoma formation are the complication with the highest incidence in gynaecological and obstetric surgery, while lymphocele, occurring if a large amount of lymphatic tissue has been resected, is more frequently observed in women undergone radical hysterectomy and lymph node dissection for the treatment of cervical and endometrial carcinoma [1].
In such circumstances, topical haemostatic agents and surgical sealants may offer an additional tool to the surgeon's armamentarium.

HAEMORRHAGE IN GYNAECOLOGICAL AND OBSTETRIC SURGERY

Excessive bleeding during surgery, and consequent need for blood transfusions, are among the most frequent major adverse events across all surgeries [9]. Indeed, haemorrhage and development of haematoma are still the most common complications in gynaecological and obstetric surgery in spite of surgical procedures like compression, sutures, clips and electrocoagulation [1, 10].
Acute postoperative haemorrhage is the most frequent cause of reoperation in non-oncological gynaecological surgery and myomectomy for large fibroid uterus, most in obese patients, is the surgical operations with the highest risk for haemorrhage [1, 10]. In obstetrics occasionally haemorrhage may arise after abdominal or vaginal delivery as an uncontrollable uterine, vaginal, or pelvic haemorrhage [11]. Furthermore, postpartum haemorrhage may be potentially fatal and haemorrhage during caesarean section is the leading cause of morbidity [12].
In oncological surgery, a perioperative blood loss of more than 1liter complicates 15-40% of radical oncological operations, resulting in transfusion rates of 30-60%, while uncontrollable and possibly life-threatening bleeding may occur during lymphadenectomy and debulking for advanced ovarian cancer [10, 11].
It is worthy to consider that in women with pelvic cancers, the prognosis may be worsened in case of low perioperative haemoglobin level and blood transfusions [10].
In general, the perioperative bleeding in turn may lead to additional complications, like infection and abscess formation, thus also contributing to prolong the surgical and hospitalization times and to increase the need for transfusion, with a negative impact on therapy costs [10].
In the last decades, the use of a minimally invasive laparoscopic surgeries has significantly increased

compared to open procedures, but inability to maintain haemostasis can potentially lead to longer operating times and possible conversion to laparotomy, thus nullifying the benefits deriving from the laparoscopic approach [13].

Risk factors for perioperative haemorrhage

Risk factors for perioperative haemorrhage in gynaecological surgery include both those generally linked to any surgery and those more strictly depending on specific surgical procedures.
In general, patients may be at increased risk of bleeding for advanced age, decreased preoperative red blood cell volume (small body size and/or preoperative anaemia), medications affecting haemostasis, including complementary medicines, medical conditions causing haemostatic defect such hereditary bleeding disorders and acquired medical conditions like chronic kidney or liver disease, and high-risk procedures [14]. Furthermore, risk factors in any kind of surgery are previous surgery and extended and multiorgan resections, while gender, body mass index, and comorbidities including arterial hypertension, diabetes mellitus and renal dysfunction are independent risk factors for bleeding and transfusion [14, 15].
A recent large retrospective cohort study in patients undergoing caesarean myomectomy for intramural leiomyoma, showed that the large size and lower segmental position of the leiomyoma are significantly risk factors for intraoperative haemorrhage during caesarean myomectomy [16]. This finding is of much interest, as uterine leiomyoma is most frequently observed in about 10 to 20% of fertile women, is associated to several complications and its occurrence during pregnancy has been increasing, as the prevalence of uterine leiomyoma is age related and the average age of pregnant women has increased over time. Clearly, the occurrence of leiomyoma in less young women, sensibly increases difficulties and risks associated with the obstetric manoeuvres [16].
In obstetric surgery, severe postpartum haemorrhage is the principal cause of maternal deaths and severe maternal diseases, with an incidence from 3 to 8% and accounts for 27.1% of maternal deaths worldwide [17]. The risk factors for postpartum haemorrhages vary in literature [17]. A recent large and long-lasting retrospective case-control study identified the following risk factors for severe post-partum haemorrhage: maternal age < 18 years, previous caesarean section, history of post-partum haemorrhage, conception through in vitro fertilization, predelivery anaemia, stillbirth, prolonged labour, placenta praevia, placental abruption, placenta accrete spectrum, and macrosomia [17]. Risk factors for haemorrhage in gynaecological surgery are listed in **Table 1**.

Traditional management of haemorrhage in gynaecological and obstetric surgery

Prevention of perioperative haemorrhage includes some actions to implement prior to surgery, including treatment of preoperative anaemia, withdrawal of drugs involving an increased risk for haemorrhage, like nonsteroidal anti-inflammatory drugs, anticoagulant drugs, antiplatelet agents and some herbal supplements [15].
Preoperative anaemia is a frequent condition, affecting up to 40% of patients undergoing major surgery and is an independent risk factor for blood transfusion, morbidity, and mortality. Anaemia should be treated accordingly to its cause and a careful evaluation of blood coagulation status prior to surgery should be performed [15]. Management of intraoperative bleeding involves several factors, including surgical approach, as well as medical measures and surgical manoeuvres [8].

Table 1. *Risk factors for perioperative haemorrhage in gynaecological and obstetric surgery [1, 10, 14-17].*

Surgical setting	Risk factor	Reference
Any surgery	Advanced age Small body size Preoperative anaemia Medication affecting haemostasis Medical conditions causing haemostatic defect High risk procedure Extended and multiorgan resections Gender Hypertension Diabetes mellitus Renal dysfunction	[14, 15]
Myomectomy	Large fibroid uterus	[1, 10]
Caesarean myomectomy	Large sized and lower segmental position leiomyoma	[16]
Delivery, vaginal and abdominal	Maternal age < 18 years Previous cesarian section History of postpartum haemorrhage Conception through in vitro fertilization Pre-delivery anaemia Stillbirth Prolonged labour Placenta praevia Placental abruption Placenta accrete spectrum Macrosomia	[17]

Medical measures include maintenance of patient core temperature, use of antifibrinolytic agents (*e.g.*, tranexamic acid) and blood transfusion [15].
Surgical manoeuvres to achieve haemostasis may consist in manual pressure, suture ligation, electro-cautery, ultrasonic coagulation, laser ablation, staples and clips, all accompanied by meticulous surgical technique [9, 11, 15]. When these measures fail, application of a topical haemostatic agent can help to control bleeding [11].
In obstetrics, traditional techniques for controlling postpartum haemorrhage are uterotonic agents, vessel ligation, packing, balloon tamponade, over sewing the placental bed, compression sutures, or uterine artery embolization. In case of failure, topic haemostats can be applied [12].

LYMPHOCELE/SEROMA

An abnormal collection of fluids in tissues may represent a complication of surgical procedures.
The term "seroma" should refer to a sac collection of free liquid, while the term "lymphocele" should indicate a lymph sac collection. Collection of serous fluid is due to extravasation caused by inflammatory response to a surgical trauma and/or foreign material and following also minimally invasive operations, while lymphocele may occur after interventions with significant tissue destruction and lots of dead space, like occurring in oncologic surgery. Despite this distinction, the published papers generally group the two phaenomena under the same term (lymphocele) or pool the data concerning both.
Postoperative seroma formation represents a frequent complication following breast surgery, reconstructive surgery, and abdominoplasty and very few cases are reported after caesarean section [19]. If not diagnosed or properly treated, over time seroma can acquire a fibrous pseudo capsule and turn into a chronic condition, potentially triggering infections [19].
Lymphoceles are an early postoperative complication affecting 7 to 40% of patients undergone inguinal–femoral lymphadenectomy and its incidence has not decreased despite advances in surgical technique [18]. Lymphocele is often asymptomatic, but can result in infection, oedema, pain, and deep venous thrombosis [18, 20].
Postoperative pelvic lymphocele is considered quite a common but underreported event among women operated for gynaecological malignancies, with an incidence ranging between 23% and 63%. As often asymptomatic, it may resolve spontaneously without intervention and can only be detected by imaging technique [20]. Conversely, symptomatic lymphocele occurs less frequently, but represents a serious postoperative complication, often requiring medical or surgical intervention and possibly negatively impacting the oncological treatment, since delay in the start of adjuvant chemotherapy or radiotherapy may be required [20, 21].

Risk factors for lymphocele

The use of subcutaneous heparin, the presence of drains and early drain removal are regarded as risk factors for lymphocele formation. Indeed, prophylactic anticoagulation with low molecular weight heparin has been shown to be associated with the development of inguinal lymphocele after vulvectomy, probably because of delay in clotting of lymphatic fluid [18]. In contrast, a recent large multicenter, randomized, clinical trial involving women with pelvic lymphadenectomy, showed no independent risk factors for the development of a symptomatic lymphocele [20].
Ovarian cancer was found to be a significant risk factor for the formation of any lymphoceles and for the formation of symptomatic lymphocele, while conflicting data are available on potential effect of the type of lymphadenectomy (pelvic *vs* pelvic and para-aortic lymphadenectomy) on lymphocele development. A recent large prospective study showed that the combination of pelvic and paraaortic lymphadenectomy is a significant risk factor for lymphocele development, but not for formation of symptomatic lymphoceles [22]. With regards to the choice of surgical approach, the largest report published on this issue and involving patients operated for endometrial cancer, found a significantly lower incidence of lymphocele in patients following laparoscopic approach than in those treated with laparotomy. Similarly, a recent prospective study of patients undergoing exclusive pelvic or combined pelvic and para-aortic lymphadenectomy for gynaecological cancer, showed laparotomy to be a risk factor for the occurrence of any lymphoceles as well as symptomatic lymphoceles [22].
Preoperative or postoperative radiotherapy as well as adjuvant or neoadjuvant chemotherapy are considered risk factors for lymphocele formation, but data on the radiotherapy role in the lymphocele formation are inconsistent, presenting contrasting results from different studies [22].

In a recent large prospective study on lymphadenectomy in ovarian cancer, a higher number of lymph nodes obtained (> 27), or more than 14 lymph nodes excised in endometrial carcinoma and radical hysterectomy in cervical cancer have been found to be independent risk factors for the development of symptomatic lymphoceles [22, 23]. Risk factors for lymphocele/seroma in gynaecological surgery are listed in **Table 2**.

Traditional management of lymphocele/seroma

The management strategies for treatment or prevention of seroma/lymphocele consist in non-operative management, percutaneous drainage, or surgical drainage [19].
Currently, the most frequently utilized intraoperative methods for reducing the occurrence of early seroma are the use of closed suction drains with volume-controlled drain (the most used and useful method according to a recent systematic review), ultrasonic dissection (with lower rates of seroma than cautery and sharp dissection), use of fibrine, and use of clip or ligation of vessels (with lower rate of seroma compared to cautery). In addition, it should be taken into consideration the immobilization of the surgical site for a few days postoperatively. It has also been suggested to use a Negative Pressure Wound Therapy System KCI-V.A.C.Ulta™, in order to induce collapse of the seroma cavity and promote adherence of the cavity surface, that can be rendered gluey by using the sclerosant [19].
Concurrently, no consensus seems reached about the most effective method for preventing lymphocele formation [24].
Retroperitoneal drainage has been traditionally recommended as a method to prevent lymphocyst formation and associated postoperative morbidities, but recent studies have shown that there is no advantage to the routine use of this method following radical hysterectomy and pelvic lymphadenectomy. In fact, it was hypothesised that the drain itself, acting as a foreign body, could negatively affect the reparative and absorptive functions of the peritoneum, thus even contributing to the formation of lymphocystis [25].
The application of fibrin-collagen coated patches in the area of lymphadenectomy has been proposed to prevent the formation of lymphocele after lymphadenectomy, similarly to what already experienced in cardiovascular, hepatic, pulmonary and kidney surgeries for haemostatic purposes. Nevertheless, results from studies conducted to evaluate the efficacy of this agents in prevention of lymphocele after lymph node dissection for cancer, are controversial [26, 27].

Table 2. *Risk factors for lymphocele/seroma in gynaecological surgery [18, 22].*

Surgical setting	Risk factors	Reference
Gynaecologic malignancies	Postoperative radiotherapy Neoadjuvant chemotherapy Adjuvant chemotherapy Ovarian cancer is risk factor for any and for symptomatic lymphocele Exclusive pelvic lymphadenectomy or Combination of pelvic and para-aortic lymphadenectomy are risk factor for symptomatic or asymptomatic lymphocele	[22]
Excisional procedures, lymphatic reconstruction, tissue transfer	Subcutaneous heparin Presence of drains Early drain removal	[18]
Ovarian cancer	> 27 lymphnodes removed is an independent risk factor for symptomatic lymphocele	[22]
Cervical cancer	Radical hysterectomy with positive lymphnodes is independent risk factor for symptomatic lymphocele	[22]
Vulvectomy	Prophylactic low molecular weight heparin	[18]
Groin dissection	Obesity Number of lymphnodes removed Extent of surgery Postoperative infection Radiation therapy to the groin Postoperative deep venous thrombosis	[18]
Endometrial cancer	Laparotomy results in higher incidence of lymphocele than laparoscopy	[22]

TOPICAL HAEMOSTATIC AGENTS AND SURGICAL SEALANTS

Since the early 1990s, topical haemostatic agents of various origin and liquid fibrin sealants, have been inserted in the surgical equipment, as additional means to achieve satisfactory control of haemostasis during surgery, thus improving surgical outcomes, preventing early postoperative complications and reducing operation and hospitalization times [11].
These products have a longstanding history, as already in 1909 fibrin was suggested as a haemostatic agent and in 1915 was introduced in neurosur-

gery. Oxidized glucose was developed in 1942 and oxidized regenerated cellulose from wood pulp in 1960, while gelatin foam was introduced in 1945 and microfibrillar collagen from purified bovine corium in 1970 [28].

Currently, a large variety of topical haemostatics and sealants are available, and the gynaecologist must know the specific characteristics of each one to assure optimal results [28]. Furthermore, it is of importance understanding the regulatory framework, as strongly impacting both on the choice and legitimate use of topical haemostatics and sealants [29]. The principal regulatory distinction among all these agents, is based on whether they are identified as drugs or as medical devices, thus following a different evaluation path, regulators/registrations (authorization, definition of the price and possible reimbursement) and pharmacovigilance procedures [30].

According to the Regulation (Eu) 2017/745 of The European Parliament and of The Council of 5 April 2017, a medical product identified as "device", must not contain, or consist of "human blood, blood products, plasma or blood cells of human origin or not incorporate, when placed on the market or put into service, such blood products, plasma or cells". Similarly, a device must not consist of "transplants, tissues or cells of animal origin, or their derivatives, or products containing or consisting of them, unless the product is manufactured utilising tissues or cells of animal origin, or their derivatives, which are non-viable or are rendered non-viable" [31].

Topical haemostatics classified as medical devices, thereby do not contain human hemoderivatives and consist in sterile products which may be of vegetal (polysaccharides, cellulose derivatives), animal (collagen and gelatine) or mineral origin (zeolite: only surgically removable). These haemostatics exert their action by facilitating the platelets aggregation on the surface to treat and therefore preparing the substrate for the coagulative cascade. In this way, these agents achieve their final result both chemically and mechanically. Because of the requirement of platelets for the mechanism of action, this type of haemostats should not be used in thrombocytopenic patients [32].

Conversely, local haemostats identified as drugs, include topical agents that contain human blood products and, in some cases also animal derivatives, and acting both by influencing the coagulative cascade, showing therefore a metabolic action of haemostasis, and by exerting a mechanical action as haemostatic adhesive. These products are also indicated as adhesive haemostats [30, 32].

The local haemostats identified as drugs, also include tranexamic acid, inhibitor of fibrinolysis, and adrenaline, vasoconstrictor, historically also used as topic agents [30, 32].

Surgical sealants are sterile medical devices of synthetic or semi-synthetic origin, which have exclusive adhesive properties. They mechanically join the edges of a wound and therefore present an indirect action on haemostasis [29, 32]. They can help to prevent blood and lymphatic leakage from tissues [15].

In spite of their classification, the different types of agents have clinical indications that, sometimes, overlap: some facilitate haemostasis, while others, in addition to haemostasis, favour sealing and provide support to suture.

In summary, depending on the composition, the mechanism of action and the regulatory/registration aspects, topical agents can be divided into 3 macro-categories: haemostats classified as medical devices (not containing human blood derivatives), haemostats classified as drugs (adhesive haemostats, containing human blood derivatives) and surgical sealants classified as medical devices (pure adhesives or sealants) (**Table 3**) [29, 30, 32-34].

Currently, producers of haemostats and surgical sealants, with a view to the application of the European Regulation on medical devices (Regulation 2017/745), are re-evaluating their products regulatory profile, commercialization, or market launch. Products marketed in Italy on December 3rd, 2021, are reported in **Table 4**.

It is of importance to point out that the effective and successful use of haemostats and surgical sealants considerably relies on their physical and chemical characteristics, that should fit the differences in function and morphology among body tissues, thus determining their indication of use and site of application [35].

From a practical point of view, of particular interest are the powder-based haemostats, like products made of microporous polysaccharide spheres, or oxidised regenerated cellulose, or combinations of collagen, thrombin and chondroitin sulphate. Indeed, the powder formulations, differently from the other haemostatic preparations, may be effective in broad surface areas, sticking appropriately everywhere even on irregular surfaces without leaving gross residue [15].

Table 3. *Classification and main features of topical haemostatic agents and surgical sealants [12, 28-30, 33-35, 40, 41, 43].*

Family	Regulatory class	Active substances	Origin	Mode of action	Possible side effects
HAEMOSTATS Not containing human haemoderivatives		Regenerated oxygenated cellulose	Vegetal	Mechanical activation of the clotting cascade and vasoconstriction from low pH	Foreign body reaction, Infection, Adhesions
Not indicated for patients with coagulative disorders	*Medical device*	Porcine or bovine gelatine	Animal origin	Mechanical activation of the clotting cascade.	Increased incidence of infection at the surgical site Granuloma and fibrosis formation Potential disruption of the clot when the sponge is removed
		Microfibrillar collagen	Animal origin	Mechanical activation of the clotting cascade and platelet aggregation.	Local oedema Granuloma formation, infection
		Microporous Polysaccharide Spheres	Vegetal origin	Absorption of water leading to platelets concentration and accelerated clot formation	No specific surgical adverse reactions reported Potential alteration of glucose loads in diabetic patient if used excessively
ADHESIVE HAEMOSTATS Containing human haemoderivatives	*Drug*	Fibrinogen + thrombin	Human origin	Action on the coagulative cascade, independently from platelets concentration, leading to the fibrin clot formation. Indicated for patients with coagulative disorders.	Poor mechanical strength and adhesion in wet environment Transmission of blood-borne diseases, especially viral transmission from formulations prepared using pooled blood. Allergic reactions. Thromboembolism
		Fibrinogen + thrombin	Human-animal origin		
		Collagen + thrombin	Human-animal origin		
PURE ADHESIVES OR SEALANTS	*Medical device*	Cyanoacrylate	Synthetic	Quick polymerization of liquid monomers in the presence of water or blood, with formation of covalent bonds between the cyanoacrylate and functional groups in the tissue proteins.	Possible toxicity if in contact with not cutaneous tissues. Potential delay of wound healing. Reporting of pancreatic tumors development.
		Bovine albumin and glutaraldehyde	Semi-synthetic	Reaction between glutaraldehyde and the lysine residues in albumin, leading to development of a reticulation	Cytotoxicity Tissue compression Myonecrosis and nerve injury, Adhesive embolism Limitation of blood vessel growth, Pseudoaneurysm formation, Wound complications. Infections and allergic reactions
		PEG	Synthetic	Covalent bonds with tissues, generating a sealing action and a mechanical haemostatic effect	Possibly increase of pressure on the surrounding tissues when applied in closed cavities, due to high swelling ratio
		Recombinant human albumin + PEG	Synthetic human		No specific adverse events reported

HAEMOSTATS: MEDICAL DEVICES

Haemostatics agents classified as medical devices, include the oxidized regenerated cellulose, microfibrillar collagen, gelatins, microporous polysaccharide spheres.

This family of haemostats has shown to be useful during surgery, when a single source of bleeding cannot be identified, or in case of failure or contraindication of electrocautery [36]. These agents are largely used in gynaecological surgery, even if most of published data come from other surgical specialties [36].

Table 4. *Topical haemostatic agents and surgical sealants in the Italian market [12, 29, 31, 43].*

Family	Regulatory class	Active substances	Trade name	Formulation
HAEMOSTATS Not containing human haemoderivatives		Regenerated oxygenated cellulose	Surgicel Tabotamp Equicel Gelitacel	Powder
Not indicated for patients with coagulative disorders	*Medical device*	Animal gelatine	Cutanplast (porcine) Equispon (porcine) Floseal (bovine) Gelita tampone (porcine) Gelitaspon (suine) Spongostan (porcine) Surgiflo (porcine)	Powder Foam Sponge
		Microfibrillar collagen	Avitene Lyostypt Helitene, Helistat	Powder Sheet Sponge
		Microporous Polysaccharide Spheres	Arista AH	Powder
ADHESIVE HAEMOSTATS Containing human haemoderivatives	*Drug*	Fibrinogen + thrombin.	Tissucol Beriplast P Quixil	Liquid Frozen liquid Powder reconstituted with sterile saline
		Collagen + thrombin.	TachoSil Vitagel	Sponge Patch
PURE ADHESIVES OR SEALANTS	*Medical device*	Cyanoacrylate .	Glubran 2 Omnex Histoacryl Internal	Liquid
		Bovine albumin and glutaraldehyde	BioGlue	Liquid
		PEG	Coseal Duraseal Pleuraseal Vascuseal	Liquid
		Recombinant human albumin + PEG	ProGel	Liquid

They are best used for minimal bleeding, are available in a variety of formulations and are easy to prepare. The mechanism of action makes these agents suitable to heparinized patients, while their efficacy is reduced in thrombocytopenic patients. These haemostatics generally swell once applied; therefore, it is advisable not to use them in restricted spaces, especially near bony or neural structures, and remove the surplus agent once haemostasis is achieved [37].

Oxidized regenerated cellulose

Oxidized regenerated cellulose (ORC) is a powder haemostat, made of cellulose dissolved and woven into a dry gauze sheet, then oxidized [15, 36]. The final product can be applied directly to the tissue where it favours haemostasis both by creating a skeleton for platelets aggregation and by decreasing tissue pH, with consequent activation of the coagulation cascade and vasoconstriction in small blood vessels. ORC presents some bactericidal activity, probably due to its capacity to decrease tissues pH, and has also shown to prevent the development of peritoneal adhesions [36]. The antibacterial activity is carried out against a wide range of gram-positive and negative microorganisms, including methicillin-resistant *Staphylococcus aureus*, *Beta streptococcus*, *Bacteroides fragilis*, *Clostridium perfringens*, *Streptococcus faecalis*, methicillin-resistant *Staphylococcus epidermidis*, vancomycin-resistant *Enterococcus*, penicillin-resistant *Streptococcus pneumoniae*, strains of *S. aureus* and *Pseudomonas aeruginosa* [28].
Usually, ORC absorption occurs in about 14 days, although greater lengths of time have been reported. It is relatively easy to use. In fact, it can

be folded or rolled and therefore it can be easily passed through small laparoscopic trocars. ORC has been largely used in gynaecologic surgery as a surgical barrier to prevent postoperative adhesions [28]. One prospective study found the use of ORC to be effective for control of tubal haemorrhage in a small group of women undergoing laparoscopic sterilization. Indeed, its best application seems to be in areas of the uterine or the fallopian tube bleeding [36]. Thanks to their antibacterial activity, ORCs may be particularly helpful in developing countries to prevent postoperative infections [38].

Microfibrillar collagen

Microfibrillar collagen is an absorbable acid salt obtained from bovine collage. It is available as powder or sponge sheet. Microfibrillar collagen provides a physical matrix for coagulum development, where platelets are attracted and activated, is applied directly to the tissue, does not produce excessive swelling, and is absorbed in approximately 3 months [15, 28, 36]. In addition, it is recognized that chondroitin sulphate exerts a regulatory effect of on cellular activities, wound closure and wound contraction [15]. Few data are available on the use of microfibrillar collagen in gynaecologic surgery, but it seems to be at least equivalent to conventional haemostatic measures on cervical procedures such as cold knife conization and loop electrode excisional procedure. Thus, microfibrillar collagen may be of support to other surgical measures to achieve haemostasis in uterine bleeding surfaces [36].

Gelatins

Gelatin matrices derive from animal collagen dried into a powder or foam form. The product is applied directly to the bleeding tissue, where it absorbs blood and consequently swells and increases in weight. After application, pressure should be exerted for several minutes, in order to achieve optimal haemostasis. Gelatin matrices, due to their neutral pH, do not directly activate the clotting cascade and are completely absorbed by approximately 4 to 6 weeks after placement. Gelatin products may be formed into any shape and, when moistened, can be passed easily through laparoscopic trocars. Based on data from vascular and urologic surgery literature, in gynaecology these products may be useful in case of slow oozing from deserosalized surfaces [36].

Microporous polysaccharide spheres

Microporous polysaccharide spheres are a product consisting in a polysaccharide powder made from potato starch. The powder should be applied generously on a dry surgical field, with mild pressure after application [36]. This agent absorbs water, thus concentrating platelets and proteins that generate a gel matrix on the surface of the powder particles resulting in accelerated clotting. This product is absorbed quite quickly, within 48 hours, thus reducing the risk to originate foreign body reaction, infection or transmission of alloantigens, a considerable risk when using products derived from animal or human tissue [15, 36].
In absence of specific data from gynaecological surgery, this agent is expected to be useful principally in situations of slow bleeding from surgical surfaces [36].

ADHESIVE HAEMOSTATS: DRUGS

Thrombin based agents

These agents provide thrombin that rapidly converts the patient's fibrinogen into a fibrin clot [37]. Thrombin may be of bovine, human, or recombinant origin. Products thrombin based, are packaged as a solution and can be applied via a spray or syringe. Thrombin can also be used in combination with other absorbable delivery methods such as a gelatin foam or matrix or as a biological adhesive, made of collagen associated with fibrinogen and thrombin [36, 39]. This combination provides a mechanical tamponade to the bleeding through the gelatine swelling, while the thrombin component converts the patient fibrinogen at the surgical site into fibrin, activating the clotting cascade [37].
The publications on use of these agents in gynaecological surgery suggest that thrombin and thrombin combination agents can be successfully applied in situations of extensive venous and capillary oozing from a dissected or deserolized area, as often occurs in surgery for endometriosis, retroperitoneal mass resections, and ovarian cancer cytoreduction [36].

Fibrin based agents

Fibrin based agents are composed of a thrombin and a concentrated fibrinogen component that must be mixed before application [36]. These agents, next to

the haemostatic action present also a sealing action and therefore supply suture support [30]. For these reasons, these agents are also named "fibrin sealants or fibrin glue". Deriving from pooled donor human plasma, fibrin glues can theoretically transmit viral infections. Differently from topical thrombin haemostats, these products form a fibrin clot by its own fibrinogen and not by the circulating one, thus being suitable also for patients with coagulative disorders. The available data suggest that the use of fibrin glues in gynaecologic surgery may be useful in situations of diffuse venous and capillary oozing from a dissected or deserolized area, in case of bleeding in areas not tractable with cautery such as in the obturator space, or as an adjunct to staple closure in patients undergoing colostomy reversal [36].

PURE ADHESIVES/SEALANTS: MEDICAL DEVICES

Surgical sealants have a synthetic or semisynthetic origin, prevent liquid, gas or solid leakage, and are used on dry tissue surfaces creating a barrier to blood flow [40].
Differently from fibrin sealants, these agents do not intervene actively in the coagulation process, have exclusive properties adhesive and therefore mechanically bond the wound margins after their polymerization in the presence of water, exerting consequently only an indirect haemostatic action [29].
Surgical sealants include various types of synthetic and semi-synthetic materials such as cyanoacrylates, polyurethanes, PEG-based dendrimers, and PEG. These agents are characterized by strong adhesive properties and mechanical strength and, according to their compositions, structures, and physical properties may be differently addressed to specific surgical situations [41].

Cyanoacrylates

Synthetic adhesives based on cyanoacrylate consist in liquid monomers that can polymerize rapidly in the presence of weak bases such as water or blood, through an anionic process, thus forming an elastic pellicle that joints the edges of the wound [41]. These agents, whilst presenting highly favourable adhesive effects, depending on molecular weight of polymers may produce toxic residuals inducing local inflammatory reactions with consequent impairment of wound healing or generate less toxic but more persistent products, therefore potentially leading to medical complications [35]. The generation of formaldehyde and cyanoacetate following the polymerization process, is considered the source of cyanoacrylates' tissue toxicity and additional components have been brought to their formulation to minimize the risk of complications [35, 42]. The use of these agents has been proposed for general surgery in surgical anastomosis as an alternative to microsurgery, mainly in centres or situations where facilities are unavailable [35].

PEG-Based adhesives and sealants

Polyethylene glycol (PEG) is a neutral, hydrophilic, biocompatible polymer, that doesn't cause a serious immune response and that therefore is widely employed in the biomedical field [35, 43]. PEGs are prepared by polymerization of ethylene oxide and are commercially available over a wide range of molecular forms. PEG adhesive sealants are equipped with reactive parts to establish covalent bonds with biological tissues, as PEG per se is not able to play such interactions; the derived hydrogels can be efficiently used to enhance wound closure and suture, supporting haemostasis in the injured site [35].
In addition to their sealing action, PEG-based adhesives remain flexible, allowing a physiological dilation without stiffening and therefore reducing mechanical stress, but with some limits, for long-term wound strengthening, as they are rapidly degraded [35].

CLINICAL STUDIES ON USE OF HAEMOSTATIC AGENTS AND SEALANTS IN GYNAECOLOGICAL AND OBSTETRIC SURGERY

Most of publications on the use of topical haemostatic agents and sealants in surgery, report experiences and clinical trials conducted in general surgery or anyway in surgical fields different from gynaecology or obstetrics.
For this reason, currently gynaecological surgeons often choose the haemostat, or the sealant based on situations illustrated in the available literature, rather than according to a specific gynaecological/obstetric condition, because studies evaluating these agents are limited in the gynaecologic literature [36]. Therefore, large meta-analysis and reviews have been recently undertaken, to provide gynaecologists with as much information as possible about the use of these agents in their setting.

Haemorrhage control

A Cochrane review on haemostatic agents/fibrin sealants has shown the efficacy of these agents in reducing postoperative blood loss and perioperative transfusions in minimally invasive surgeries among specialties different from gynaecology or obstetrics, such as general surgery, cardiothoracic, urology, and orthopaedics [44].

A prospective study on application of oxide regenerated cellulose (ORC) was performed in 28 women undergoing laparoscopic sterilization on request [38]. ORC was placed in the prongs of the laparoscope and taken to the tubal haemorrhage site. Haemostasis was achieved in 26 (92.8%) women, with 93.7% of success in the right fallopian tube and 91.7% in the left. The 2 failures were due to non-adherence of the ORC agent in situation of active arterial bleeding with large broad ligament hematoma in both fallopian tubes [38].

A recent systematic review conducted to clarify the role of haemostatic agents in minimally invasive surgery for specific benign gynaecologic conditions, showed that the use of topical haemostatics can reduce operative time, blood loss, and ameliorate damage to ovarian function [13]. The analysis included all studies evaluating the intraoperative use of haemostatic agents in women undergoing minimally invasive gynaecologic procedures for benign conditions, without date restrictions. The haemostats evaluated included oxidized regenerated cellulose, microfibrillar collagen, microporous polysaccharide, gelatins, topical thrombin, topical thrombin plus gelatin, and fibrin sealant. Parameters analysed were the impact of haemostatic agents on haemostasis, need for peri-operative transfusion, impact on ovarian reserve, and other postoperative complications. Limit of this analysis was the inclusion of studies sometimes presenting different outcomes and involving different types of gynaecologic procedures: myomectomy, surgery for ectopic pregnancy, ovarian cystectomy, and uterine perforation. Furthermore, data from follow-up longer than 3 months, are lacking [13].

In particular, studies conducted on different fibrin sealants, but referring to a different approach to myomectomy, confirm that the use of haemostats over the suture line at the time of myomectomy can improve haemostasis parameters [13]. Indeed, a case control study and a prospective randomized trial conducted to evaluate the use of fibrin sealants respectively during laparoscopic myomectomy for a single fibroid and during open myomectomy *versus* traditional methods of bipolar energy and suture, showed a favourable haemostasis profile and decreased overall operative time with the use of fibrin sealants. Nevertheless, the latter study, even if showing a significant reduction in estimated blood loss and postoperative haemoglobin decrease, did not find any significant effects from the use of the fibrin sealant on the operating time [13].

A recent European position paper has reviewed and steered the use of haemostatic powders in surgical practice. The surgeons involved in this operation, both in the steering committee and locally, were from different surgical specialties, as working in breast surgery, gynaecological and obstetric surgery, general and emergency surgery, thoracic surgery, and urological surgery in Europe [15]. With regard to the gynaecological and obstetric settings, the document states that haemostatic powders should be used in closed cavities during gynaecological oncologic procedures, that these agents should be applied to reduce the risk of bleeding after ovarian cystectomy and to achieve haemostasis in laparoscopic surgery (*i.e.*, for endometriosis) and myomectomy. In addition, there was very high agreement that polysaccharide powder haemostats do not cause adhesions and that this is mainly important in gynaecological surgery, where pelvic adhesions may compromise future fertility [15].

Lymphocele treatment and prevention

The impact of surgical sealants on prevention and treatment of lymphocele following gynaecological surgery, has been investigated in interventional and observational clinical studies, sometimes with contrasting results.

According to a recent general literature review, fibrin sealant patches do not seem to reduce lymph collection, the need for puncture or the infection risk after lymphadenectomy and therefore should not routinely be used for prevention of lymphoceles after inguinofemoral lymph node dissection for vulvar cancer [45].

Similar results were obtained from a double-blind randomized-controlled trial, showing that the application of an equine collagen, human thrombin, and fibrinogen adhesive haemostatic agent, does not seem to improve postoperative lymphorrhagia nor to reduce the incidence of postoperative complications in patients undergoing bilateral inguinofemoral lymphadenectomy for vulvar cancer.

Inguinofemoral areas of each patient were randomized intraoperatively to the study treatment or not treatment, and consequently one of the two inguinofemoral areas was randomly assigned to application of the adhesive agent while the contralateral had a standard closure without fibrin sealant patch [26].
Conversely, results from a retrospective case-control study, indicate that the application of fibrin sealants after pelvic and/or para-aortic lymphadenectomy may reduce lymphatic drainage in gynaecologic malignancy. The study involved 27 patients in the fibrin sealant group and 18 in the control group [24].
Positive results have been obtained also from a case–control analysis, that showed that use of a fibrin sealant application reduced the incidence of postoperative complications, including lymphocystis formation, wound breakdown and/or infection, and chronic lymphedema. The study involved 8 patients who received the fibrin sealant and 16 controls (standard technique) treated for vulvar cancer or recurrent ovarian/breast cancer [21].
Accordingly, a meta-analysis supports the safety of the use of fibrin sealant patches in women undergoing pelvic and/or para-aortic dissection due to gynaecologic cancer, but its benefit remains uncertain. Despite the fact that fibrin sealant patches were proven effective in reducing the duration and volume of the lymph drainage, they were not associated with difference in the incidence of lymphocele [27].

OBSTETRICS

In obstetrics, topical haemostatic agents are most often used to control postpartum haemorrhage in the setting of postpartum hysterectomy, commonly practiced for abnormal placentation and uterine atony.
Topical haemostats should be applied in case of failure of traditional techniques for controlling postpartum haemorrhage, with particular advantages in cases of placenta praevia with lower segment and implantation site bleeding, condition generally presenting intense bleeding over large surfaces. In patients presenting haemorrhage and with factor and fibrinogen deficiencies, fibrin sealants and agents that have both mechanical and biological properties, are preferred [12].
Fibrin sealants have also been used as an adjunct to control haemostasis at the placental implantation site [12]. A retrospective study on a series of 15 patients with placenta praevia, delivered by caesarean section and all complicated by persistent bleeding from the lower uterine segment, showed that haemostasis was controlled with the topical application of a fibrin sealant patch. Interestingly, the operations were carried out by 15 different surgeons [12, 46].
Anyway, topical haemostatic agents have also been used to control haemostasis from vaginal and vulvar lacerations following traumatic vaginal deliveries [12].
A retrospective analysis of consecutive cases undergoing fetoscopy directed laser surgery for in pregnancies affected by twin–twin transfusion syndrome, showed that the use of an absorbable gelatin sponge as a chorioamnion "plug" placed at the conclusion of the intervention, did not reduce the rate of preterm premature rupture of membranes (PPROM) [47]. PPROM was defined as rupture of membranes before 34 weeks' gestation and a comparison was performed between the PPROM group and a no-PPROM group to determine risk factors and outcomes [47].
More recently, a systematic review was performed to assess and compare the effects of different sealing techniques following PPROM *versus* standard care (including no sealant), on maternal and neonatal outcomes. Randomised and quasi-randomised controlled studies were included, while cluster-randomised trials and trials with a cross-over design were not eligible for inclusion in the review, thus two studies only (involving 141 women, with data from 124 women) were selected, but both were considered at high risk of bias. In addition, meta-analysis was not possible because the two studies involved different interventions [48]. Consequently, due to the heterogeneity of the studies and the lack of sufficient data, it was not possible to evaluate effectiveness and safety of the sealing procedures for PPROM, and the review essentially revealed the scarcity of randomised clinical trials in this area.

CONCLUSIONS

A broad number of topical haemostatic agents and surgical sealants are available nowadays. These products have been classified according to their composition, mechanism of action and regulatory pathway, although some degree of overlap may occur.
Currently, most of publications on these agents relate to surgical specialties different from gynaecology and obstetrics, even if these products are widely

used in these settings. For that reason, meta-analyses and reviews have been undertaken, with the intent to provide gynaecologists with as much information as possible about the use of topical haemostats and sealants in their surgical practice. Perhaps due to the scarcity of proper randomized clinical trials focused on gynaecological and obstetric surgery, the results of these studies may be conflicting. Moreover, for future studies, it will be useful to distinguish the two populations (gynaecological and obstetrics) in consideration of the different coagulation status and the different haemostasis sites.

Nevertheless, some basic advice for use of topical haemostats and sealants in gynaecological and obstetric surgery may be gathered from the available literature.

Primarily, there is no product that is suitable for all situations and all patients. The right choice in gynaecological and obstetric surgery depends on many factors, such as the products physiochemical characteristics, the morphology and physiology of the surgical site as well as the surgical context and issues, and the patient's conditions, including possible underlying diseases.

It follows from this, that the ideal topical haemostatic agent, besides presenting a quick haemostatic effect, should be safe, handy, and suitable to patient clinical disorders.

Topical haemostatics classified as medical devices and therefore not containing human blood products as active ingredients, are not active on the coagulative process and just provide a surface for blood to clot; therefore, they should not be administered in patients with factor and fibrinogen deficiencies. Conversely, in such patients, adhesive haemostatic agents, containing fibrin and therefore also called fibrin sealants, are preferred, as they have both mechanical and biological properties. In fact, these products, identified as drugs from a regulatory position because containing human derivatives, actively interfere with the coagulative cascade.

Finally, the current evidence definitely supports the use of haemostatic powders, that may be particularly helpful for treatment of bleeding from broad and raw surface areas, where powder is easily spread and effective in achieving haemostasis before field closure, with positive expectations in case of closed cavities during gynaecological oncological procedures, ovarian cystectomy and laparoscopic surgery for endometriosis and myomectomy. In addition, there is agreement that haemostatic powders, beside enhancing recovery and reducing the length of hospital stay, are easy to learn, not subject to waste and not confounding subsequent imaging leading to diagnostic difficulties. The powder formulation of microporous polysaccharide spheres showed the strongest evidence- based agreement in the recent European consensus on use of the haemostatic powders in surgery.

Anyway, it is advisable that specific and appropriate prospective clinical trials on topical haemostatics and surgical sealants are carried out in the future, focused on gynaecological and obstetric surgery, to allow specialists of these clinical areas to obtain the maximum benefits from the use of these agents in their practice.

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REFERENCES

1. Paspulati RM, Dalal TA. Imaging of complications following gynecologic surgery. Radiographics. 2010;30(3):625-42. doi: 10.1148/rg.303095129.
2. Bahadur A, Mundhra R, Kashibhatla J, Chawla L, Ajmani M, Sharma S, et al. Intraoperative and Postoperative Complications in Gynaecological Surgery: A Retrospective Analysis. Cureus. 2021;13(5):e14885. doi: 10.7759/cureus.14885.
3. Desai RS, Kumar KS. Urological injuries during obstetric and gynaecological procedures: a retrospective analysis over a period of eleven years. Int J Reprod Contracept Obstet Gynecol. 2016;5(6):1916-20. doi: 10.18203/2320-1770.ijrcog20161690.
4. Hindman NM, Kang S, Parikh MS. Common postoperative findings unique to laparoscopic surgery. Radiographics. 2014;34(1):119-38. doi: 10.1148/rg.341125181.
5. Chen X, Zhao N, Ye P, Chen J, Nan X, Zhao H, et al. Comparison of laparoscopic and open radical hysterectomy in cervical cancer patients with tumor size ≤2 cm. Int J Gynecol Cancer. 2020;30(5):564-71. doi: 10.1136/ijgc-2019-000994.
6. Fuentes MN, Rodríguez-Oliver A, Naveiro Rilo JC, Paredes AG, Aguilar Romero MT, Parra JF. Complications of laparoscopic gynecologic surgery. JSLS. 2014;18(3):e2014.00058. doi: 10.4293/JSLS.2014.00058.
7. Daniilidis A, Hatzis P, Pratilas G, Dinas K, Loufopoulos A. Laparoscopy in Gynecology - How Why When. In: Advanced Gynecologic Endoscopy. InTech. 2011.
8. Pabuccu EG. Laparoscopic Complications of Gynecologic Procedures. Obstet Gynecol Int J. 2016;4(1):7-10. doi: 10.15406/ogij.2016.04.00092
9. Harris JA, Uppal S, Kamdar N, Swenson CW, Campbell D, Morgan DM. A retrospective cohort study of hemostatic agent use during hysterectomy and risk of post-operative complications. Int J Gynaecol Obstet. 2017;136(2):232-7. doi: 10.1002/ijgo.12037.
10. Watrowski R, Jäger C, Forster J. Improvement of Perioperative Outcomes in Major Gynecological and Gynecologic-Oncological Surgery with Hemostatic Gelatin-Thrombin Matrix. In Vivo. 2017;31(2):251-8. doi: 10.21873/invivo.11053.
11. Santulli P, Marcellin L, Touboul C, Ballester M, Darai E, Rouzier R. Experience with TachoSil in obstetric and gynecologic surgery. Int J Gynaecol Obstet. 2011;113(2):112-5. doi: 10.1016/j.ijgo.2010.11.019.
12. Patriarco M, Shenoy S, Taylor N. Biologic Hemostatic Agents in Obstetrics and Gynecology. In: Contemporary Applications of Biologic Hemostatic Agents across Surgical Specialties - Volume 2 (Working Title). IntechOpen. 2021.
13. Ito TE, Martin AL, Henderson EF, Gaskins JT, Vaughn VM, Biscette SM, et al. Systematic Review of Topical Hemostatic Agent Use in Minimally Invasive Gynecologic Surgery. JSLS. 2018;22(4):e2018.00070. doi: 10.4293/JSLS.2018.00070.
14. National Blood Authority Australia. Preoperative bleeding risk assessment tool - Guidance for Australian Health Providers. 2015.
15. Eden C, Buonomo OC, Busch J, Gilabert-Estelles J, Medrano R, Nosotti M, et al. An international multidisciplinary peer-driven consensus on the optimal use of hemostatic powders in surgical practice. Updates Surg. 2021;73(4):1267-73. doi: 10.1007/s13304-021-01136-x.
16. Kwon JY, Byun JH, Shin I, Hong S, Kim R, Park IY. Risk factors for intraoperative hemorrhage during cesarean myomectomy. Taiwan J Obstet Gynecol. 2021;60(1):41-4. doi: 10.1016/j.tjog.2020.11.007.
17. Liu CN, Yu FB, Xu YZ, Li JS, Guan ZH, Sun MN, et al. Prevalence and risk factors of severe postpartum hemorrhage: a retrospective cohort study. BMC Pregnancy Childbirth. 2021 26;21(1):332. doi: 10.1186/s12884-021-03818-1.
18. Wills A, Obermair A. A review of complications associated with the surgical treatment of vulvar cancer. Gynecol Oncol. 2013;131(2):467-79. doi: 10.1016/j.ygyno.2013.07.082.
19. Damiani GR, Lombardi C, Pulerà E, Loizzi V, Villa M, Schonauer LM, et al. Management of abdominal wall recurrent subfascial seroma after pelvic surgery. Acta Biomed. 2020;91(4):e2020092. doi: 10.23750/abm.v91i4.9024.
20. Grimm C, Polterauer S, Helmy-Bader S, Zikan M, Cibula D, Heitz F, et al. A collagen-fibrin patch for the prevention of symptomatic lymphoceles after pelvic lymphadenectomy in women with gynecologic malignancies: A randomized clinical trial. Gynecol Oncol. 2018;149(1):140-5. doi: 10.1016/j.ygyno.2018.01.012.
21. Buda A, Ghelardi A, Fruscio R, Guelfi F, La Manna M, Dell'Orto F, et al. The contribution of a collagen-fibrin patch (Tachosil) to prevent the postoperative lymphatic complications after groin lymphadenectomy: a double institution observational study. Eur J Obstet Gynecol Reprod Biol. 2016;197:156-8. doi: 10.1016/j.ejogrb.2015.12.005.

22. Zikan M, Fischerova D, Pinkavova I, Slama J, Weinberger V, Dusek L, et al. A prospective study examining the incidence of asymptomatic and symptomatic lymphoceles following lymphadenectomy in patients with gynecological cancer. Gynecol Oncol. 2015;137(2):291-8. doi: 10.1016/j.ygyno.2015.02.016.
23. Franchi M, Ghezzi F, Riva C, Miglierina M, Buttarelli M, Bolis P. Postoperative complications after pelvic lymphadenectomy for the surgical staging of endometrial cancer. J Surg Oncol. 2001;78(4):232-7; discussion 237-40. doi: 10.1002/jso.1158.
24. Kim HC, Choi C, Kim WY. Effectiveness of Fibrin Sealant Patch in Reducing Drain Volume after Pelvic Lymph Node Dissection in Women with Gynecologic Malignancy. Biomed Res Int. 2017;2017:3086857. doi: 10.1155/2017/3086857.
25. Charoenkwan K, Kietpeerakool C. Retroperitoneal drainage versus no drainage after pelvic lymphadenectomy for the prevention of lymphocyst formation in women with gynaecological malignancies. Cochrane Database Syst Rev. 2017;6(6):CD007387. doi: 10.1002/14651858.CD007387.pub4.
26. Baggio S, Laganà AS, Garzon S, Scollo M, Raffaelli R, Tateo S, et al. Efficacy of a collagen-fibrin sealant patch (TachoSil®) as adjuvant treatment in the inguinofemoral lymphadenectomy for vulvar cancer: a double-blind randomized-controlled trial. Arch Gynecol Obstet. 2019;299(5):1467-74. doi: 10.1007/s00404-019-05113-z.
27. Prodromidou A, Iavazzo C, Fotiou A, Psomiadou V, Drakou M, Vorgias G, et al. The application of fibrin sealant for the prevention of lymphocele after lymphadenectomy in patients with gynecological malignancies: A systematic review and meta-analysis of randomized controlled trials. Gynecol Oncol. 2019;153(1):201-8. doi: 10.1016/j.ygyno.2019.01.011.
28. Duenas-Garcia OF, Goldberg JM. Topical hemostatic agents in gynecologic surgery. Obstet Gynecol Surv. 2008;63(6):389-94; quiz 405. doi: 10.1097/OGX.0b013e31816ff805.
29. Peverini D, Ciuti S, Fabrizio R di, Spaziante L, Spinelli D. Emostatici locali e sigillanti a uso chirurgico: clinica e appropriatezza d'uso. Bollettino SIFO. 2008;54(4). doi: 10.1704/403.4749.
30. Bettoni D. Farmaci e dispositivi medici: è possibile un confronto? Il caso degli emostatici e dei sigillanti in chirurgia. Clinico Economics Italian Articles on Outcomes Research. 2015;10:61-72.
31. Regulation [Eu] 2017/ 745 of the European Parliament and of the council - of 5 April 2017 - on medical devices, amending Directive 2001/ 83/ EC, Regulation [EC] No 178/ 2002 and Regulation [EC] No 1223/ 2009 and repealing Council Directives 90/ 385/ EEC and 93/ 42/ EEC.
32. Peghetti A, Carati D. Emostatici locali e sigillanti chirurgici. Dalle evidenze della letteratura alla pratica quotidiana. Delibera Giunta Regionale n. 1523/2008. 2014 Sep. Report No.: Delibera Giunta Regionale n. 1523/2008.
33. Bruckner BA, Blau LN, Rodriguez L, Suarez EE, Ngo UQ, Reardon MJ, et al. Microporous polysaccharide hemosphere absorbable hemostat use in cardiothoracic surgical procedures. J Cardiothorac Surg. 2014;9:134. doi: 10.1186/s13019-014-0134-4.
34. Tschan CA, Nie M, Schwandt E, Oertel J. Safety and efficacy of microporous polysaccharide hemospheres in neurosurgery. Neurosurgery. 2011;69(1 Suppl Operative):ons49-63. doi: 10.1227/NEU.0b013e3182155a52.
35. Scognamiglio F, Travan A, Rustighi I, Tarchi P, Palmisano S, Marsich E, et al. Adhesive and sealant interfaces for general surgery applications. J Biomed Mater Res B Appl Biomater. 2016;104(3):626-39. doi: 10.1002/jbm.b.33409.
36. Wysham WZ, Roque DR, Soper JT. Use of topical hemostatic agents in gynecologic surgery. Obstet Gynecol Surv. 2014;69(9):557-63. doi: 10.1097/OGX.0000000000000106.
37. Stachowicz AM, Whiteside JL. Topical Hemostatic Agents in Gynecologic Surgery for Benign Indications. Obstet Gynecol. 2020;135(2):463-8. doi: 10.1097/AOG.0000000000003670.
38. Sharma JB, Malhotra M. Topical oxidized cellulose for tubal hemorrhage hemostasis during laparoscopic sterilization. Int J Gynaecol Obstet. 2003;82(2):221-2. doi: 10.1016/s0020-7292(03)00138-3.
39. Oliveira FM de, Carvalho MVH de, Marchi E, Pinto CAL. Collagen, fibrinogen and thrombin biological addesive is effective in treating experimental liver injuries. Revista do Colégio Brasileiro de Cirurgiões. 2016;43(4):254-61. doi: 10.1590/0100-69912016004004.
40. Gruppo di lavoro Regionale permanente sui Dispositivi Medici [GR-DM] istituito con D n. 7468 del 17. 05 2018. Evidenze sull'appropriatezza di impiego e indicazioni sulla variabilita' dei consumi degli emostatici e sigillanti. 2020.
41. Annabi N, Tamayol A, Shin SR, Ghaemmaghami AM, Peppas NA, Khademhosseini A. Surgical Materials: Current Challenges and Nano-enabled Solutions. Nano Today. 2014;9(5):574-89. doi: 10.1016/j.nantod.2014.09.006.

42. Lins RD, Gomes RC, Santos KS, Silva PV, Silva RT, Ramos IA. Use of cyanoacrylate in the coaptation of edges of surgical wounds. An Bras Dermatol. 2012;87(6):871-6. doi: 10.1590/s0365-05962012000600008.
43. Ge L, Chen S. Recent Advances in Tissue Adhesives for Clinical Medicine. Polymers (Basel). 2020;12(4):939. doi: 10.3390/polym12040939.
44. Carless PA, Henry DA, Anthony DM. Fibrin sealant use for minimising peri-operative allogeneic blood transfusion. Cochrane Database Syst Rev. 2003;2003(2):CD004171. doi: 10.1002/14651858.CD004171.
45. Saner FA, Schötzau A, Mackay G, Heinzelmann-Schwarz V, Montavon Sartorius C. Fibrin-thrombin sealant does not reduce lymphocele formation in patients with inguinofemoral lymphadenectomy for vulvar cancer. Cancer Manag Res. 2019;11:3575-82. doi: 10.2147/CMAR.S197143.
46. Fuglsang K, Petersen LK. New local hemostatic treatment for postpartum hemorrhage caused by placenta previa at cesarean section. Acta Obstet Gynecol Scand. 2010;89(10):1346-9.
47. Papanna R, Molina S, Moise KY, Moise KJ Jr, Johnson A. Chorioamnion plugging and the risk of preterm premature rupture of membranes after laser surgery in twin-twin transfusion syndrome. Ultrasound Obstet Gynecol. 2010;35(3):337-43. doi: 10.1002/uog.7476.
48. Crowley AE, Grivell RM, Dodd JM. Sealing procedures for preterm prelabour rupture of membranes. Cochrane Database Syst Rev. 2016;7(7):CD010218. doi: 10.1002/14651858.CD010218.pub2.