Chinese expert consensus on the prevention of abdominal pelvic adhesions after gynecological tumor surgeries

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Abstract: Adhesion is a postoperative complication that has plagued gynecologists for many years, as 60–90% of gynecological patients develop adhesions after abdominopelvic surgeries. Abdominopelvic adhesions could lead to chronic pelvic pain, infertility, intestinal obstruction, and complicated reoperations. Adhesions might also increase the risk of postoperative chemoradiotherapy failure and endanger patients' lives, especially after surgeries for gynecological malignant tumors. The aim of this consensus was to review the pathogenesis and clinical consequences of adhesions and to summarize various surgical procedures and preventive measures that can reduce the occurrence of adhesions after gynecological tumor surgeries based on a discussion among well-known domestic gynecology specialists.

Keywords: Adhesion; tumor surgery; prevention; expert consensus

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Introduction

Adhesion refers to the connection of separated tissues by fibrous bands under normal circumstances. Adhesions occur in 60% to 90% of patients after abdominopelvic surgeries (1) and are the most common surgical complication. Abdominopelvic adhesions can lead to chronic pelvic pain, infertility, intestinal obstruction, and complicated reoperations (2-4). Adhesions after gynecological tumor surgeries also increase the risk of postoperative chemoradiotherapy failure and endanger patients' lives.

The effect of adhesion on the treatment of gynecological tumors

Adhesions are the most common cause of intestinal obstruction. More than 30% of colonic obstructions and 80% of small bowel obstructions, which have mortality rates of 3–10%, are caused by adhesions. Moreover, 48% of chronic pelvic pain and 20–40% of infertility in females are caused by adhesions (5-10).

Cancer patients usually require retreatment or reoperation [even after adequate treatment, the risk of recurrence of advanced-stage ovarian cancer is as high as 70–90% (11)]. In these patients, adhesions can have an impact on the effects of chemoradiotherapy after surgery and can increase the complexity and risks during surgery, such as prolonged operation time, increased risk of injury, and increased risk of conversion to laparotomy during laparoscopic surgery (12,13). Moreover, 15–20% of patients who undergo radical hysterectomy due to cervical cancer require radiotherapy after surgery (5), while pelvic adhesions caused by previous abdominal surgery are prone to formation of intestinal adhesions and fixation in the radiation area, which will increase the risks associated with radiation therapy. Adhesions affect the uniform distribution of the radiation dose and causes intestinal fistula, intestinal injury and other consequences and will seriously impact the treatment effects. The degree of intestinal damage is directly related to the total radiation dose, number of treatments, and the dose distribution in the surrounding tissue of the target area (14). For patients with ovarian cancer, intraperitoneal chemotherapy can reduce the risk of death by 21.6%. However, extensive adhesion prevents the drug from spreading in the abdominal cavity, which is a relative contraindication of intraperitoneal chemotherapy due to the limited thorough distribution of intraperitoneal chemotherapy drugs because of severe adhesion (15).

Moreover, the cost of treatments for adhesions results in a heavy economic burden on patients and society. In the United States, abdominal adhesions in inpatients cost $2.3 billion in 2005. According to several studies, in the United Kingdom, the cost of hospitalization due to adhesions within 2 years after surgeries was £2.42 million (16,17).

Therefore, preventing postoperative adhesions, improving the quality of patients' lives, and saving medical costs are issues on which every gynecological oncologist must focus.

Formation mechanism and typing of adhesions

Peritoneal adhesion is the pathological result of repair of peritoneal injury. Adhesion formation can be induced by mechanical or thermal injury, dehydration, incomplete hemostasis, radiation, continuous laparoscopic airflow, prolonged exposure to the light source of the laparoscope during surgery, and by the disease itself (e.g., pelvic inflammatory diseases, endometriosis, infection) (12). After peritoneal injury, mesothelial cell islands are formed locally, mesothelial cells divide and proliferate to repair the wound, and mesothelialization is completed, after which fibrin proteins are degraded to form new peritoneum. After proliferation and maturation, proliferating cells interconnect with each other. After 5–7 days, the basal peritoneum is formed, and the peritoneum recovers normally. However, due to local ischemia or infection during wound repair, fibrin will form a bridge on the surface of two opposing exposed tissues. Most fibrin exudates are transient and are degraded within 72 hours, but the activity of the damage-induced peritoneal fibrin lysis system is inhibited (18), and thus, the fibrin bundles cannot be cleared. Fibroblasts enter the fibrin bridge and release collagen within 3–5 days after surgery. By the 7th day, small blood vessels form in the fibrin bridge, which leads to the formation of adhesions (*Figure 1*).

Regarding the grading and classification of adhesions, various international grading standards have been established. Currently, the modified adhesion grading system published by the American Society for Reproductive Medicine (ASRM) (19) is widely used (*Table 1*).

Prevention of adhesions in gynecological tumor surgeries

In view of the prevalence of postoperative adhesions,

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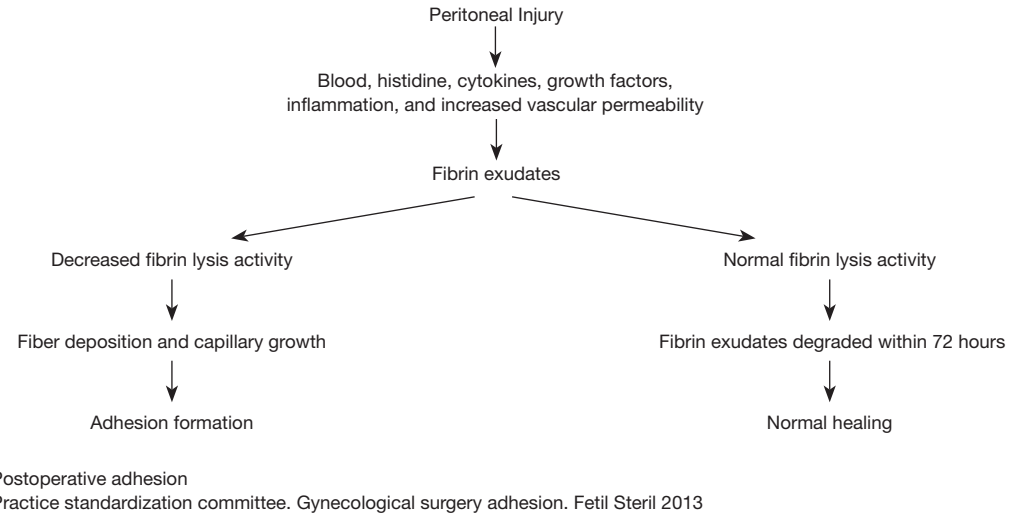

Figure 1 Mechanism of adhesion formation.

Table 1 Modified American Society for Reproductive Medicine (ASRM) adhesion grading standards

The nature and range of adhesions observed during surgery*	Score (points)	Adhesion grading
No adhesion	0	N/A
Membranous, <25%	1	Mild
Membranous, 25–50%	2	Mild
Membranous, ≥51%	3	Moderate
Dense, <25%	4	Moderate
Dense, 25–50%	5	Severe
Dense, ≥51%	6	Severe

*, the range of adhesions observed during surgery. The range of adhesions observed during surgery refers to the surgeon's evaluation of the adhesions at 15 anatomical locations, including the anterior wall of the uterus, the posterior wall of the uterus, the anterior wall of the abdominal cavity, and the anterior wall of the rectal uterine depression (19).

preoperative informed consent and intraoperative prevention of adhesions must be taken seriously by clinicians. At present, sophisticated surgical techniques and the placement of antiadhesion barriers or agents between damaged tissues are the primary measures that are used to prevent adhesions. Sophisticated surgical techniques are the foundation of strategies to reduce adhesions, and these include considering surgical indications, following the principles of minimally invasive surgeries, gently touching the tissues, and avoiding foreign matter, dehydration, and infection. When a risk of postoperative adhesions is present, auxiliary antiadhesion measures should be considered. Based on principles of safety, effectiveness, ease of use, and cost, antiadhesion barriers can be considered (20,21).

Surgical techniques for the prevention of adhesions in tumor surgeries

Cervical cancer is the most common gynecological malignancy in China. Early-stage cases are mainly treated by surgery. The scope of surgery includes extensive hysterectomy + pelvic lymph node dissection + abdominal paraaortic lymph node dissection in some cases. This surgery is a standardized and anatomical operation. The surgical features are as follows: (I) posterior peritoneal lymph nodes require routine dissection, and most of the blood vessels behind the pelvic peritoneum, such as the blood vessels and structures in the common ilium, external ilium, and obturator area of the pelvic cavity,

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the entire pelvic segment of the ureter, and partial para-aorta area, need to be anatomically exposed; (II) extensive hysterectomy requires dissection of the space around the cervix, including the separation of the bladder and rectum. Resection of a wide range of para-uterine and vaginal tissues results in significant tissue damage, as well as in the exposure and changes of the pelvic floor structures after surgery, which increases the chances of postoperative tissue wound bleeding, inflammatory infections, and adhesions.

The primary treatment of endometrial cancer is surgery, which is supplemented by comprehensive treatments of radiotherapy, chemotherapy, and hormones. Extrafascial radical hysterectomy combined with bilateral appendectomy is the most basic surgical method for endometrial cancer. Some patients require pelvic lymph node dissection and abdominal paraaortic lymph node dissection (to the level of the renal blood vessels). Deeply infiltrated endometrial cancer results in a large surgical wound, is associated with a relatively difficult surgical procedure, and is prone to bleeding; this cancer has an incidence of postoperative adhesions as high as 56–100% (22).

Most patients with ovarian cancer are diagnosed at an advanced stage and require open abdominal surgery. Surgical treatments include comprehensive surgery for early-stage patients and tumor cytoreductive surgery for advanced-stage patients. The scope of surgery includes the uterus and appendages, the greater omentum, abdominal paraaortic lymph nodes, bilateral pelvic lymph nodes, tumor-invaded organs, and a large area of tumor-invaded peritoneum. Ovarian cancer surgery results in a large wound surface and a large amount of bleeding and is prone to the formation of adhesions between the intestines and between the abdominal wall and the intestines. After tumor recurrence, tumor cytoreductive surgery is a possibility. Adhesions affect the application and effect of postoperative intraperitoneal chemotherapy, increase the chance of organ damage, cause difficulty in reoperation, and result in a higher probability of postoperative adhesion with a broader range and higher severity (23).

Although surgery is one of the main treatment methods for the three major malignant gynecologic tumors, a large proportion of patients still need chemoradiotherapy after surgery. Patients who undergo malignant tumor surgeries are more prone to adhesions than those who undergo other surgeries. Postoperative radiotherapy or perfusion will increase the chance of adhesions in the surgical area, which will lead to increased adverse complications of radiotherapy or perfusion, as well as an increased probability of organ damage. Therefore, the following characteristics and points should be achieved in gynecological tumor surgeries: (I) use a minimally invasive approach. Minimally invasive refers not only to minimally invasive surgical approaches but also to the avoidance of rough operations during surgery, operations in nonsurgical areas, a large range of electrocoagulation or tearing, and excessive peritoneal loss; (II) minimize the size of the surgical wound, such as by intentionally retaining the peritoneum in the surgical area so that certain areas of the pelvic wall can be peritonealized at the end of the operation; (III) perform sentinel lymph node biopsy in selected appropriate cases to reduce unnecessary peritoneal loss; (IV) avoid bleeding during surgery and strictly perform hemostasis during the surgery; (V) minimize the use of nonabsorbable materials. Rinse the surgical area before the end of the surgery to remove tissue debris and blood clots as much as possible; (VI) pay attention to the principle of sterility and actively prevent infection; (VII) apply antiadhesion products reasonably in areas that are prone to adhesions such as the cervical stump and lymphatic dissection area to further reduce the incidence of adhesions.

Selection of materials and drugs that prevent adhesion

At present, materials that prevent adhesion are divided into two categories: diaphragm materials and gel/liquid materials. The ideal antiadhesion material should be considered comprehensively for its safety, effectiveness, convenience, and economy, such as a lack of foreign body reaction, absorbability, convenient use in laparoscopic and laparotomic surgeries, and effective prevention of new and regenerative adhesions (12). Five types of widely used antiadhesion materials are shown (*Table 2*).

Diaphragm materials

Antiadhesion diaphragm materials are antiadhesion barriers that are easy to use and are currently the most widely studied. According to the surgical location and scope, this material is placed at the location of the wound, stump, and lymphatic dissection area during tumor surgery, where it plays a role in physical insulation and reduces the occurrence of adhesions.

(I) Oxidized regenerated cellulose (ORC) antiadhesion membrane: this is an absorbable antiadhesion barrier composed of ORC (tree pulp extract). After standing for 8 hours, ORC forms a continuous and dense hydrophilic gel on the surface of the tissue and covers the damaged surface. It remains

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Table 2 Materials that prevent adhesion

Components	Source and process	Safety	Effectiveness
Membrane-type antiadhesion materials			
Oxidized regenerated cellulose (ORC)	Extracted from natural plant fibers, oxidative regeneration process	Fully absorbed in 28 days without any adverse reactions	Remains intact during the peritoneal recovery period, 29 years of clinical research, good adherence, the first antiadhesion material approved by the US FDA
Sodium hyaluronate-carboxymethyl cellulose	Chemically synthesized membrane-like absorbable material	Fully absorbed in 28 days without any adverse reactions	Remains intact during the peritoneal recovery period, FDA-approved
DL-polylactic acid (PLA)	Chemically synthesized DL-polylactic acid (DL-PLA), produced by extended pressure processing	The complete degradation cycle ranges from 8–12 weeks, no serious adverse reactions are found, individual patients may develop mild discomfort or local soreness	Good insulation and adhesiveness
Gel/liquid-type antiadhesion materials			
Sodium hyaluronate gel (HA)	Cockscomb extract or bacterial fermentation, uronic acid and hexosamine condensation, animal extraction	Nontoxic, immunogenic, animal-derived products that may cause adverse reactions in individual patients	Unstable degradation time ranging from 72 hours to 2 weeks, strong fluidity, ordinary adhesiveness
Carboxymethyl chitin (Chitosan)	Crustacean shell extract, glucosamine 14-2-acetamido-a-deoxy-B-, water as solvent, animal extraction	Nontoxic, individual patients may have allergic reactions	Unstable degradation time ranging from 1–4 weeks, repairing effect, strong fluidity, ordinary adhesiveness

intact during the peritoneal recovery cycle (5–7 days) and physically insulates the tissue surface to prevent adhesion formation. After 28 days, ORC is hydrolyzed into carbon dioxide and water, which is completely absorbed by the human body. ORC is convenient to use and operate without the requirement of sutures.

ORC antiadhesion membrane is currently the most widely studied product, as this material has the highest number of clinical literature reports in China and other countries. In randomized controlled clinical trials, this product has been demonstrated to reduce adhesion formation because it reduces the incidence and extent of new and recurrent adhesions after laparoscopic and laparotomic surgeries by 50% to 60% (24). A multicenter randomized study showed that ORC antiadhesion membrane (Interceed) could significantly reduce the occurrence and severity of ovarian adhesions after surgery, and the involved area of ovarian surface adhesions was significantly reduced (25). In 2014, the European Society of Human Reproduction and Embryology (ESHRE) guidelines recommended that surgeons apply ORC to prevent adhesion formation after laparoscopic endometriosis surgery (26).

A health economics study evaluated the cost of ORC antiadhesion membrane (Interceed) in the prevention of abdominopelvic adhesions after gynecological and obstetric surgeries. The results showed that the application of this product could significantly reduce the postoperative adhesion rate after ovarian cancer surgeries, reduce the incidence of adhesion complications, and reduce the probability of reoperation, thereby saving patients 2,320 Yuan in medical costs during the 3-year observation period (27).

(II) Sodium hyaluronate-carboxymethyl cellulose antiadhesion membrane: this is a bioabsorbable antiadhesion membrane composed of hyaluronic acid and carboxymethyl cellulose. The material adheres to the wet surface of tissues and turns

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into a near-mature gel 24 hours after placement to physically insulate the tissue surface. It is completely absorbed by the human body within 28 days. This material should not be folded, and therefore, caution is required during its use.

A randomized controlled clinical study showed that, compared with the control group, the incidence of chronic abdominal pain (more than 3 months) was significantly reduced in surgical patients with a chemically modified sodium hyaluronate-carboxymethyl cellulose antiadhesion membrane placed in the abdominopelvic cavity. However, no significant difference was observed between the two groups in the incidence of postoperative small bowel obstruction and postoperative quality of life (28).

(III) DL-polylactic acid (DL-PLA) antiadhesion membrane: this is a kind of absorbable diaphragm material made of polylactic acid fiber. After placement in the human body, it maintains its membrane shape to separate the surgical wound surface from adjacent organs and tissues. The degradation process is divided into hydrolysis and enzymatic metabolism. A randomized controlled clinical study showed that adhesions of the abdominal cavity in patients with polylactic acid antiadhesion membrane placed in the abdominopelvic cavity were significantly milder than those of the control patients who did not receive application of the antiadhesion membrane (29). When using it, attention should be paid to the unsatisfactory antiadhesion effect caused by changes in the membrane covering position due to intestinal peristalsis and other reasons, in which case absorbable sutures can be used for proper fixation.

Gel/liquid materials

Gel/liquid materials are a type of easy-to-use, degradable, and absorbable antiadhesion material placed on the surface of tissues to reduce the occurrence of adhesions. Such materials are quickly absorbed, while the degradation time is unstable, and the effectiveness of antiadhesion is controversial (12). The gel/liquid materials are substances that flow easily, and thus, the effect of the patient's position change on the efficacy should be noted.

(I) Hyaluronic acid (HA) gel: this is a type of high molecular weight mucopolysaccharide prepared from natural materials. HA gel is both degraded and absorbed. HA gel covers the plasma membrane surface of tissues, physically insulates the wound surface, reduces the formation of adhesions, and avoids the exacerbation of existing adhesions (30). HA gel has a short degradation time due to its unstable molecular structure, but whether HA gel can remain intact and lead to effective insulation during the peritoneal recovery period requires further investigation. Due to different preparation processes, a variety of different HA-based preparations have been developed. HA gel is easy to manipulate and requires a catheter to apply the liquid to the wound surface during laparoscopic or hysteroscopic surgeries.

(II) Carboxymethyl chitin (chitosan): this material is derived from shrimp shell extract and is naturally degraded and absorbed by the human body. It has the biological characteristics of selectively promoting the growth of epithelial cells and endothelial cells and inhibiting the growth of fibroblasts; therefore, chitosan promotes tissue physiological repair, inhibits scar formation, reduces tissue adhesion, and prevents new adhesion formation (31). Chitosan is easy to manipulate, but a catheter is required to apply the liquid to the wound surface during laparoscopic or hysteroscopic surgeries.

Summary

Abdominopelvic cavity adhesions after gynecological tumor surgeries are extremely common. Adhesions can cause postoperative complications that affect the implementation and effect of chemoradiotherapy after malignant tumor surgeries, and therefore, adhesions must be taken seriously by gynecological oncologists. Before gynecological tumor surgeries, clinicians should fully inform patients about the risk of postoperative adhesion, the impact on subsequent treatments, and preventive measures. Prevention of adhesion is extremely important. Sophisticated tumor surgical techniques are the most important factor in adhesion prevention. The combined application of antiadhesion materials on the basis of sophisticated surgical operations is conducive to the further reduction in the incidence of adhesion. The ideal antiadhesion material should possess the characteristics of safety, effectiveness, convenience, and economy. Appropriate antiadhesion material is selected

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according to the requirements of the surgery, which can comprehensively and effectively prevent the formation of adhesions, decrease medical costs, reduce surgical risks, and improve the quality of life of tumor patients.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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