Role of the peritoneal cavity in the prevention of postoperative adhesions, pain, and fatigue

Philippe R. Koninckx, M.D., Ph.D.,[a,b] Victor Gomel, M.D., Ph.D.,[c] Anastasia Ussia, M.D.,[b] and Leila Adamyan, M.D., Ph.D.[d,e]

[a] Department of Obstetrics and Gynecology, Catholic University Leuven, University Hospital, Gasthuisberg, Leuven, Belgium; [b] Gruppo Italo Belga, Villa del Rosario and Gemelli Hospitals Università Cattolica, Rome, Italy; [c] Department of Obstetrics and Gynecology, University of British Columbia, Women's Hospital, Vancouver, British Columbia, Canada; [d] Department of Operative Gynecology, Federal State Budget Institution V. I. Kulakov Research Center for Obstetrics, Gynecology, and Perinatology, Ministry of Health of the Russian Federation, Moscow, Russia; and [e] Department of Reproductive Medicine and Surgery, Moscow State University of Medicine and Dentistry, Moscow, Russia, Russian Federation

A surgical trauma results within minutes in exudation, platelets, and fibrin deposition. Within hours, the denuded area is covered by tissue repair cells/macrophages, starting a cascade of events. Epithelial repair starts on day 1 and is terminated by day 3. If repair is delayed by decreased fibrinolysis, local inflammation, or factors in peritoneal fluid, fibroblast growth starting on day 3 and angiogenesis starting on day 5 results in adhesion formation. For adhesion formation, quantitatively more important are factors released into the peritoneal fluid after retraction of the fragile mesothelial cells and acute inflammation of the entire peritoneal cavity. This is caused by mechanical trauma, hypoxia (e.g., CO_2 pneumoperitoneum), reactive oxygen species (ROS; e.g., open surgery), desiccation, or presence of blood, and this is more severe at higher temperatures. The inflammation at trauma sites is delayed by necrotic tissue, resorbable sutures, vascularization damage, and oxidative stress. Prevention of adhesion formation therefore consists of the prevention of acute inflammation in the peritoneal cavity by means of gentle tissue handling, the addition of more than 5% N_2O to the CO_2 pneumoperitoneum, cooling the abdomen to 30°C, prevention of desiccation, a short duration of surgery, and, at the end of surgery, meticulous hemostasis, thorough lavage, application of a barrier to injury sites, and administration of dexamethasone. With this combined therapy, nearly adhesion-free surgery can be performed today. Conditioning alone results in some 85% adhesion prevention, barriers alone in 40%–50%. (Fertil Steril® 2016;■:■–■. ©2016 by American Society for Reproductive Medicine.)

Key Words: Surgery, adhesion prevention, peritoneum, conditioning, endometriosis

Discuss: You can discuss this article with its authors and with other ASRM members at https://www.fertstertdialog.com/posts/11305-role-of-the-peritoneal-cavity-in-the-prevention-of-postoperative-adhesions-pain-and-fatigue

Intraperitoneal adhesions after surgery occur in 80%–90% of women (1). They are a major cause of postoperative pain, infertility (2), small bowel obstruction (3, 4), and surgical reinterventions which cause a huge cost for the society (5–10), as recently confirmed (11–13).

The pathophysiology of adhesion formation has been considered to be a local healing process of opposing surgical lesions (14–17), and prevention was based on barriers. Over the past decade the important role of the entire peritoneal cavity in this process became apparent, and the combined treatment of the peritoneal cavity during surgery together with application of a barrier after surgery resulted in nearly adhesion-free surgery, which provides the additional benefits of less postoperative pain and a faster recovery (18).

This prompted us to review the role of the peritoneal cavity in the pathophysiology and in the prevention of postoperative adhesion formation.

MATERIALS AND METHODS

The United States National Library of Medicine (www.pubmed.com) from 2000 to May 2016 was searched for "postoperative adhesions" OR "peritoneal adhesions" (n = 4,826) together with factors in peritoneal cavity by adding "peritoneal cavity" (n = 257 of which seven relevant), "cooling" (n = 5), "temperature" (n = 39), or "N_2O" (n = 2). Because relevant articles could not be identified the 2,058 articles on adhesions since 2010 were hand searched.

Received June 20, 2016; revised July 30, 2016; accepted August 2, 2016.
P.R.K. is a shareholder of Endosat. A.U. has nothing to disclose. L.A. has nothing to disclose. V.G. has nothing to disclose.
Reprint requests: Philippe R. Koninckx, M.D., Ph.D., Vuilenbos 2, B 3360, Bierbeek, Belgium (E-mail: pkoninckx@gmail.com).

Fertility and Sterility® Vol. ■, No. ■, ■ 2016 0015-0282/$36.00

http://dx.doi.org/10.1016/j.fertnstert.2016.08.012

THE PERITONEAL CAVITY IS AN ORGAN

The peritoneum has a large surface of 1.7 m^2 and is composed of a single layer of mesothelial cells, a basal membrane, and some loose connective tissue resting on the underlying tissues with blood vessels and lymphatics. The mesothelial cells facilitate gliding of bowels by means of microvilli, glycosaminoglycans, and surfactant.

The intact peritoneal cavity is a virtual cavity similar to the inside of mouth and bowels. The peritoneum used to be considered a semipermeable membrane with fast diffusion of fluid and small molecules but limited diffusion of larger molecules. Indeed, the concentrations of smaller blood proteins, such as albumin, LH, and FSH, are 40% lower than in plasma, whereas larger molecules, such as factors V and VIII, are virtually absent, preventing thrombin activation. Locally secreted macromolecules as CA125 and glycodelins accumulate with concentrations much higher than in plasma (19–24). Mesothelial cells also actively regulate the exchange with vessels and extracellular spaces by means of gap junctions and vesicular transport. Surprisingly, the intact mesothelial layer also actively inhibits the diffusion of gases such as CO_2 (25, 26) and N_2O (unpublished observations). In women, the peritoneal fluid also contains transudation from growing ovarian follicles, increasing the volume and the concentrations of sex steroid hormones. The peritoneal cavity thus is a microenvironment with specific concentrations of hormones, cytokines, growth factors, cellular components such as macrophages, natural killer cells, and lymphocytes, and a specific immune system. Peritoneal fluid circulates clockwise, explaining a higher incidence of endometriosis on the left side. The peritoneum also has specific pain receptors (27, 28). The peritoneal cavity therefore has to be considered as a separate active organ and not a passive container (29, 30).

The large flat mesothelial cells react within seconds to minor trauma, such as exposure to air, by retraction resulting in bulging of cells and consequent direct exposure of the basal membrane (31). This retraction is so rapid that in vivo fixation is necessary to study the intact mesothelial layer. This retraction increases over time (25, 26). Identified traumas are mechanical trauma, exposure to a CO_2 pneumoperitoneum (32, 33), desiccation, infection, and chemical irritants. Normal saline solution detaches the mesothelial cells after 30 minutes with a loss of fibrinolytic activity (34). This "toxicity" was confirmed recently in vitro (35–37) and in vivo (38). Within hours transforming growth factor β increases and tissue plasminogen activator decreases. By retraction, the contiguous mesothelial cells are transformed into individual cells which causes passive diffusion through the exposed basal membrane (31, 39–42) and initiates acute inflammation (43). The peritoneal cavity thus becomes part of the body, which is an efficient defense mechanism against infection via recruiting immunoglobulins and macrophages. Similarly the decreased bowel motility helps to keep an infection localized. This retraction and the subsequent passive diffusion also explains the increasing resorption of CO_2 (25, 26) requiring increasing ventilation during laparoscopic surgery.

PATHOPHYSIOLOGY OF ADHESION FORMATION

Repair and Adhesion Formation after Surgical Trauma of the Peritoneum

The repair of a peritoneal injury with damage of the basal membrane and the subendothelial connective tissue is a strictly timed process (Fig. 1). Within minutes, with onset of acute inflammation and activation of the coagulation cascade, platelets attach and coalesce over the lesion. The increased blood flow, dilation of arterioles, increased permeability of the capillaries, and migration of neutrophils and macrophages onto the lesion forms a fibrin mesh. Within hours, the lesion is covered with macrophages and/or "tissue repair cells" which acquire enhanced fibrinolytic activity (34). These cells start to remove cell debris while platelet-derived growth factors activate migration and proliferation of fibroblast/mesothelial cells. Visible mesothelial cell growth starts after 24 hours, followed by fibroblast proliferation on day 3 and angiogenesis on day 5. It is unclear whether these cells are fibroblasts, macrophages, or stem cells (44–47) and whether they originate from the peritoneal fluid, the mesothelium, the submesothelial connective tissue, the vascular endothelium, or blood cells (47–51). Mesothelial cells and the endothelial and hematopoietic cells are derived from a common progenitor cell originating embryologically in the splanchnic mesothelium (52).

Opposing lesions attach with a fibrin mesh. In the absence of bowel movements, nonopposing lesions can attach as well, because the inflammatory process damages the fragile mesothelial cells of opposing organs. The time courses of repair and cell proliferation explain why the speed of fibrinolysis (53) that breaks this fibrin attachment determines whether the healing results in repair (54) or adhesion formation. If fibrinolysis is fast, the mesothelial repair, starting on day 1 from numerous small islands (55), is completed within 3 days, i.e., before the fibroblast and angiogenetic proliferation processes become fully activated. This also explains why repair of small and large areas is equally rapid (56).

If this repair mechanism is not completed by day 3, the proliferating fibroblasts invade the fibrin scaffold, which together with angiogenesis starting on day 5 leads invariably to adhesion formation. Repair can be delayed by local factors such as a decreased fibrinolysis, presence of necrotic tissue, tissue ischemia, and oxidative stress secondary to vascular damage or sutures, and by infection (57). Furthermore, the injured area may be shielded from the blood stream through vascular damage, and from the peritoneal fluid by the fibrin plug. A drug therefore would have difficulty reaching the injured area. This explains why the effect of tissue plasminogen activator, administered intraperitoneally after a minor surgical trauma, varies from poor (58) to 40% effective (59).

Factors in Peritoneal Fluid Enhance Adhesion Formation at Surgical Lesion Sites

The mesothelial cell retraction (31, 39–42) and the acute inflammation (43) in the entire peritoneal cavity release substances into the peritoneal fluid that delay the local