

Introduction: Quality of pelvic surgery and postoperative adhesions

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The health care and the emotional cost of postoperative adhesions that frequently cause chronic pain, infertility, bowel obstruction, and repeat surgery are well known. Our understanding of the pathophysiology of adhesion formation and of its prevention has evolved from good surgical practice based on microsurgical principles, barriers to keep denuded areas separated to the prevention of mesothelial cell damage and of acute inflammation in the entire peritoneal cavity. Oxidative stress, in the surgical lesions and in the peritoneal cavity has an important role in adhesion formation by slowing down repair. This has resulted in virtually adhesion-free surgery, in addition with less CO₂ resorption, less postoperative pain, and a faster recovery. The clinical efficacy had been demonstrated by higher pregnancy rates (PRs) using microsurgical tenets. (Fertil Steril® 2016;106:991–3. ©2016 by American Society for Reproductive Medicine.)

Key Words: Surgery quality, postoperative adhesion formation, microsurgery, oxidative stress

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Surgery causes adhesions in all body cavities lined with a mesothelium. After abdominal or pelvic surgery, adhesions form in >70% of patients irrespective of the surgical access route, open or laparoscopic. Some organs, such as ovaries, are more adhesion prone. Adhesions may cause pain, bowel obstruction, and infertility. During the 10 years that follow the surgery, they necessitate one or more hospital readmissions in more than one third of patients; subsequent surgical interventions are more difficult and associated with more complications. Postoperative adhesions cause a significant economic burden as demonstrated in the surgical and clinical adhesions research (SCAR) studies. In 2005 in the United States 351,777 adhesion-related hospitalizations had an estimated cost of \$2.3 billion, of which 40% were related to prior surgical interventions in the reproductive tract of

women, which comprised more than one third of the total number of patients. There are additional costs associated with outpatient and infertility care and with loss of productivity.

Postoperative adhesion formation is more than a complication of surgery. It is at the crossroads of quality of surgery, of our knowledge of the specific function of the peritoneal cavity, and of the importance of oxidative stress. We are entering a period where surgery without adhesions seems no longer an unrealistic dream. Just imagine the impact of adhesion-free surgery on the patients themselves, on reproduction and cost savings for society.

OXYGEN AND OXIDATIVE STRESS

The major energy source of living animals on this planet is derived from

oxygen combustion. The elegance of this progressive combustion without increase of temperature is obvious, albeit for its near 100% efficacy, 1 kg of fat being sufficient to run more than 100 km. At the beginning of living organisms oxygen concentration in the atmosphere was much less, and during evolution mammals have adapted progressively to deal with the ever-increasing ambient oxygen concentrations, which on earth at present is 20% and results in a partial oxygen pressure of 150 mm Hg. A first adaptation is **the oxygen cascade** in the human body where the partial oxygen pressure decreases progressively from the lungs (104 mm Hg), arteries (95 mm Hg), arterioles and capillaries to some 30 mm of Hg in the peripheral cells. This on earth equals to a concentration of some 4% of oxygen.

A second adaptation consists of mechanisms **to prevent the damaging effects of reactive oxygen species through antioxidants and scavengers, the balance of which is called oxidative stress.** Reactive oxygen species can cause DNA damage and cancer when the DNA repair mechanisms fail. In

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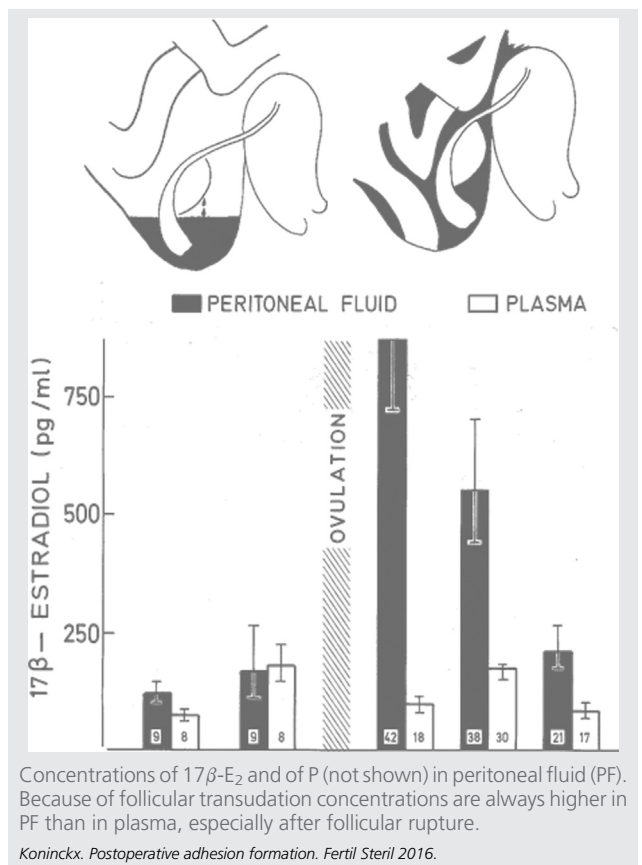
addition we are beginning to appreciate the importance of oxidative stress on cell growth and function in cultures as in IVF.

We are also becoming aware of the important role oxidative stress in the pathophysiology of postoperative adhesion formation through the effect on the tissue trauma on the surgical site as explained by Diamond (1) and also in the entire peritoneal cavity as explained by Koninckx et al. (2). In addition we have to consider the role of oxidative stress in the peritoneal cavity caused by retrograde menstruation and endometriosis as explained by Donnez et al. (3).

THE PERITONEAL CAVITY

The physiology and the pathophysiology of the peritoneal cavity as explained by Mutsaers (4), of the peritoneal fluid (PF) and of the mesothelial cells are still poorly understood. Mesothelial cells regulation actively transport to and from the PF and they react very rapidly to trauma by retraction. This seems an adequate defence mechanism against infection to rapidly mobilize humoral and cellular immunity and to localize an infection by paralytic ileus and abscess formation. Ovulation and oocyte pick-up occur in the peritoneal cavity but we do not understand how the fimbriae finds the oocyte and what is the role of the locally excessive steroid hormone concentrations in PF after ovulation (Fig. 1).

FIGURE 1



Retrograde menstruation seems to occur in most women. Because menstrual blood contains living tissue capable of implantation it would not be surprising that women with abundant retrograde menstruation have more mesothelial cell retraction specifically in the pouch of Douglas, with a higher probability of attachment and implantation of these endometrial fragments. In addition, this is supported by the higher implantation rate of tumor cells in mice after mesothelial cell retraction caused by CO₂ pneumoperitoneum. In addition to the importance for the pathophysiology of endometriosis, this might even be considered an argument to avoid pelvic surgery during or immediately after menstruation.

The exact role and origin of the cellular components in the repair of surgical trauma and the role of stem cells remains unclear. Although not yet clinically useful, the injection of (cultured) mesothelial and/or stem cells, eventually genetically engineered, has proven to be effective in adhesion prevention in animal models.

QUALITY OF SURGERY, POSTOPERATIVE ADHESIONS, AND PERITONEAL CONDITIONING

Diamond (1) reviews the prevention of postoperative adhesions by barriers to keep opposing lesions separated. In addition to the importance of the severity of the local surgical trauma we became aware of the trauma and importance of the entire peritoneal cavity (2).

Quality of surgery remains difficult to define as results, side effects, and complications need to be included in the balance. The experience of the surgeon is a major factor in the complication rates and in the duration of surgery, as evidenced by learning curves in animal models and in the human. In laparoscopic animal models the duration of surgery alone is a major factor in adhesion formation. In the Geneva trial duration of surgery was the only significant variable predicting adhesion formation, thus confirming the importance of the duration of surgery. In addition, duration of surgery predicts the length of postoperative ileus, the duration of hospitalization, and CO₂ resorption during laparoscopic surgery. Carbon dioxide resorption increases linearly with the duration of surgery necessitating increasing ventilation by the anesthetist. Excessive CO₂ resorption and metabolic acidosis can become problematic during very long interventions, for example, a Whipple procedure taking more than 5 hours, especially in obese women, necessitating steep Trendelenburg placement when lung ventilation is impaired.

Our understanding of the peritoneal cavity, of mesothelial cells, and of peritoneal repair has led to the concept of peritoneal conditioning (2), which can be summarized as “keep the mesothelial cells happy.” In laparoscopic surgery, in addition to the prevention of mechanical trauma, the single most effective factor is the addition of 5%–10% of N₂O to the CO₂ pneumoperitoneum. The mechanism of this is not yet understood but oxygen seems involved as it has no additional effect. All other factors that have been experimentally proven at present (cooling, no desiccation, a physiologic rinsing solution, and dexamethasone) are those suggested

by microsurgical tenets, and known to increase fertility rates (5). Because we cannot reproduce perfectly the normal intra-peritoneal conditions, a short duration of surgery remains important. A refined surgeon causes less postoperative adhesions.

Considering the mechanism of the associated acute inflammation of the entire peritoneal cavity it is not surprising that conditioning has a strong antiadhesiogenic effect, that the CO₂ resorption during surgery is much less, that postoperative pain is lower, and that recovery is faster. The concept of peritoneal hypoxia during CO₂ pneumoperitoneum and the beneficial effects of adding more than 5% N₂O and/or 2%–4% of oxygen may also shed new light on the ongoing debates of oncologic surgery and ovarian reserve. The decreased ovarian reserve after laparoscopic ovarian surgery for cystic ovarian endometriosis is generally considered a consequence of pre-existing oocyte damage and of tissue

excision during the intervention and/or of surgical trauma to the ovary. It cannot be excluded that the decreased ovarian reserve is not also a consequence of hypoxia of the thin ovarian wall after excision of the lesion(s) especially when surgery takes longer.

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