

Does Estrogen Cause Low Conversion Rates in Laparoscopic Cholecystectomies for Acute and Chronic Cholecystitis in Women?

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ABSTRACT

Laparoscopic cholecystectomy is the preferred treatment for symptomatic cholelithiasis. Severe local inflammation and scar formation are commonly responsible for conversion to open surgery. Fibrosuppressive effects of estrogen on peritoneal inflammatory conditions could provide low, dense fibrosis or scar formation around the gallbladder and make laparoscopic cholecystectomy easier in women and we believe that male sex is a conversion factor in laparoscopic cholecystectomy.

Key Words: Laparoscopic cholecystectomy, Male sex, Conversion.

BACKGROUND

Laparoscopic treatment of symptomatic cholelithiasis is the gold standard in surgery.^{1,2} But one cannot expect laparoscopic cholecystectomy (LC) to be successful in every case. LC has a conversion rate (CR) in both acute and elective (chronic) cholecystitis. In large series, CR is less than 5%, but in acute cholecystitis it is much higher.^{3,4}

Many reasons, such as severe fibrosis, anatomic anomalies, acute cholecystitis, intraoperative complications (bleeding, bile duct, or visceral injuries), age over 65, previous abdominal operations, and instrument failure, can be a cause of conversion from LC to open surgery.^{5,6} In some studies, sex has been mentioned among these reasons.^{7,8} Although symptomatic cholecystitis is considered a different disease in men, it has been explained that women are conscientious about their health problems and try to find a solution before the occurrence of complications, which is not a scientific explanation^{9,10} for the difference of the disease in men and women.

We believe that LC is generally difficult in men and easier in women and is accomplished with a low CR in women, too. We also observed this fact in our LC series of 1610 cases (unpublished) in which CR was 10.15% in men and 3.86% in women. But in acute cholecystitis, CR was 27.50% in men and 13.06% in women.

In many studies, severe local inflammation and scar formation are commonly responsible for conversion from LC to open surgery.^{11,12} Also in our patients, severe fibrosis was the first reason for conversion to the open technique with a ratio of 48.7%.

To the best of our knowledge, no study exists in the literature explaining the relationship between sex hormones, particularly estrogen, and acute or chronic cholecystitis-induced inflammation and fibrosis. But some studies^{13,14} do deal with the effect of estrogen on wound healing and because of the close similarities between acute wound healing and improvement in acute inflammatory diseases, our explanation and comments are based on this biology. We offer here a different point of view of the issue of why LC can succeed with a low CR in women.

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Generally in large series of LC, no data or comments exist on the gender-based conversion from a laparoscopic procedure to the open technique.^{15,16} We think that this is because of the general opinion that no relationship exists between sex and CR; what we believe is that the authors of these studies have not considered sex as a factor in CR.

DATA BASE

Clinical Studies with Male Sex Accepted as a Factor of CR or Risk

In the study of 34,490 LCs in the United States,¹⁰ CR in men was 8.4% and in women it was 4%. At the beginning of this study, CR in men was 9 times higher than that in women. With time, the ratio decreased twofold but never became equivalent between males and females. So, male sex is a conversion factor in LC.

Zisman et al⁷ reported that CR in elective LC in 329 patients (27 females and 62 males) was fivefold greater in males than in females, 21% vs 4.5%, respectively ($P = 0.0001$). Tocchi et al⁸ in 3,047 cholecystectomies accepted that male sex, acute cholecystitis, and cardiopulmonary diseases were related to postoperative complications. In another study of 348 cases of acute cholecystitis,¹⁷ authors reported male sex, advanced cholecystitis, patient delay, and timing of surgery as factors of CR.

Eldan et al³ again reported that male sex, older patients, and large gallbladder stones were associated with higher CR and higher complication rates.

In our study of 1610 cases cholecystectomized laparoscopically, we had 1295 (80.4%) women and 315 (19.6%) men. In 82, we converted from LC to open surgery. The most frequent reason of conversion was severe fibrosis in 40 (47.8%) cases. Of 82 cases of conversion, 50 (60.9%) were women and 32 (29.1%) were men.

Effect of Estrogen on Acute Wound Healing in Clinical and Experimental Studies

Estrogen has different effects on different tissues in the body. It has been shown that topical estrogen increases the level of transforming growth factor Beta 1 (TGF B1) by stimulating dermal fibroblasts and accelerating cutaneous wound healing.¹⁸ Lenhardt et al¹⁹ investigated collagen deposition in subcutaneously located polytetrafluoroethylene implants in males and females older and younger than 45 years undergoing colon resection. They

found that young men and women had the same amount of collagen deposition, and older men deposited less collagen than older women. Calvin et al²⁰ reported that the lack of ovarian hormones delays wound contraction in ovariectomized rats, which is an example of human menopause. Again Ashcroft and coworkers¹³ in a clinical study showed that topical estrogen both in aged women and aged men improved wound healing and increased cutaneous collagen deposition.

Although the above-mentioned studies concern acute wound healing, acute inflammatory conditions from the point of view of pathology are similar to acute wound healing. In both situations, healing follows inflammation, proliferation, and maturation (scar formation) phases.^{21,22}

The Role of Estrogen in the Peritoneal Inflammation

Frazier-Jessen and coworkers¹⁴ showed that estrogen (17 Beta estradiol) inhibits connective tissue deposition in peritoneal inflammation (adhesion formation) by suppressing macrophage activation.

As we have already mentioned in the healing of acute inflammatory conditions that do not resolve, 3 stages of healing exist: inflammation, proliferation, and scar formation as seen in acute wound healing. Macrophages have a major function during inflammation in which they act through growth factors and other mediators on fibroblasts that are the main cells of second phase-induced collagen, fibronectin, proteoglycan, and extracellular matrix.

It is clear that suppression of macrophage activation will inhibit the progress of the acute inflammatory process including local inflammation, proliferation, and scar formation. But because the suppression of macrophages is a pharmacologic effect of estrogen, these phases of healing will be affected in a physiologic pattern or by certain measures. In the end, estrogen will prevent the development of hypertrophied scar formation of peritoneal adhesion. Thus, women will produce less dense tissue in the event of peritoneal inflammation.

It has been shown that pelvic adhesions in reproductive women contain estrogen and progesterone receptors and angiogenesis factors like vascular endothelial and basic fibroblastic growth factors.²³ The manipulation of these receptors will have negative effects on peritoneal adhesion. The availability of these receptors and growth fac-

tors in the other regions of the peritoneum, such as in the upper abdomen and in acute cholecystitis-induced adhesions, is unknown, and if available, their manipulation results in peritoneal inflammation and scar formation is unclear, too.

Yasuda et al²⁴ studied the role of estrogen in dimethylnitrosamine-induced fibrosis in ovariectomized rats. In this study, estradiol has a fibrosuppressive effect on the liver. Based on these data, estrogen inhibits experimental fibrosis that occurs at a rapid rate in males.

In the literature, we were unable to find a satisfactory study dealing with either the effect of testosterone on acute wound healing or on the acute inflammatory process. And we have no experience with this topic either. Most studies that investigated sex hormone effects in these situations concentrate on the role of estrogen. In traumatized and hemorrhagic male rats, testosterone inhibits the immune system.²⁵ We don't know whether testosterone will have the same effect or not in inflammatory situations. If males produce more dense fibrosis and acute cholecystitis that is difficult to remove or dissect, it is expected that testosterone at least should play a role in increasing collagen deposition.

CONCLUSION

Acute cholecystitis per se is a risk factor for CR.^{3,5,17} A combination of acute cholecystitis with male sex makes LC more difficult. Contrary to this, cholecystitis in females generally makes LC easy due to inhibited or soft fibrosis.

Although it has been mentioned¹⁰ that cholelithiasis is a different and more aggressive disease in men than in women, no biological explanation exists in the literature except this report. It has only been reported that men underestimate their disease until it becomes complicated, but women heed medical advice and seek to solve health problems before the occurrence of complications.

What we believe is that symptomatic cholelithiasis is a different and less aggressive disease in women who have 2 to 5 times lower CR than do men. To make this idea more evidence based, we are attempting a new clinical investigation in patients with acute and chronic cholelithiasis to show collagen (hydroxyprolin) deposition in men and women with removed gallbladder walls and in the peripheral adhesions. So, this article is a preliminary report of our ongoing study.

In conclusion, fibrosuppressive effects of estrogen on peritoneal inflammatory conditions could provide low, dense fibrosis or scar formation around the gallbladder and make LC easier in women.

References:

- Schweringer WH, Diehl AK. Changing indications for laparoscopic cholecystectomy. *Surg Clin North Am.* 1996;76:493-504.
- Holbling N, Pilz E, Feil W, Schiessel R. Laparoscopic cholecystectomy-a meta-analysis of 23,700 cases and status of a personal patient sample. *Wien Klin Wochenschr.* 1995;107:158-162.
- Eldar S, Eitan A, Bickel A, et al. The impact of patient delay and physician delay on the outcome of laparoscopic cholecystectomy for acute cholecystitis. *Am J Surg.* 1999;178:303-307.
- Lucidarme D, Corman N, Courtade A, et al. Results of laparoscopic cholecystectomy for acute cholecystitis in elderly patients. *J Surg.* 1997;134:291-295.
- Liu CL, Fan ST, Lai EC, Lo CM, Chu KM. Factors affecting conversion of laparoscopic cholecystectomy to open surgery. *Arch Surg.* 1996;131:98-101.
- Ihasz M, Hung CM, Regoly-Merei J, et al. Complications of laparoscopic cholecystectomy in Hungary: a multicentre study of 13,833 patients. *Eur J Surg.* 1997;163:267-274.
- Zisman A, Gold-Deutch R, Zisman E, et al. Is male gender a risk factor for conversion of laparoscopic into open cholecystectomy? *Surg Endosc.* 1996;10:892-894.
- Tocchi A, Costa G, Leper L, Liotta G, Mazzoni G, Miccini M. Cholelithiasis in men. Observations on a case series of surgically treated 3,047 patients. *G Chir.* 1999;20:474-478.
- Sanabria JR, Gallinger S, Croxford R, Strasberg SM. Risk factors in elective laparoscopic cholecystectomy for conversion to open cholecystectomy. *Am J Surg.* 1994;179:696-704.
- Russel JC, Walsh SJ, Fourquet LR, Mattie A, Lynch J. Symptomatic cholelithiasis: a different disease in men? *Ann Surg.* 1998;227:195-200.
- Shea JA, Healey MJ, Berlin JA, et al. Mortality and complications associated with laparoscopic cholecystectomy. A meta-analysis. *Ann Surg.* 1996;224:609-620.
- Lo CM, Fan ST, Liu CL, Lai ECS, Wong J. Early decision for conversion of laparoscopic to open cholecystectomy for treatment of acute cholecystitis. *Am J Surg.* 1997;173:513-517.
- Ashcroft GS, Dodsworth J, van Boxel E, et al. Estrogen accelerates cutaneous wound healing associated with an increase in TGF-beta 1 levels. *Nat Med.* 1997;3:1209-1215.
- Frazier-Jessen MR, Mott FJ, Witte PL, Kovacs EJ. Estrogen suppression of connective tissue deposition in a murine model of peritoneal adhesion formation. *J Immunol.* 1996;156:3036-3042.

15. Savassi-Rocha PR, Ferreira JT, Diniz MT, Sanches SR. Laparoscopic cholecystectomy in Brazil: analysis of 33,563 cases. *Int Surg.* 1997;82:208-213.
16. Vecchio R, MacFadyen BV, Latteri S. Laparoscopic cholecystectomy: an analysis on 114,005 cases of United States series. *Int Surg.* 1998;83:215-219.
17. Eldar S, Eitan A, Bickel A, et al. The impact of patient delay and physician delay on the outcome of laparoscopic cholecystectomy for acute cholecystitis. *Am J Surg.* 1999;178:303-307.
18. Ashcroft GS, Greenwell-Wild T, Horan MA, Wahl SM, Ferguson MW. Topical estrogen accelerates cutaneous wound healing in aged humans associated with an altered inflammatory response. *Am J Pathol.* 1999;155:1137-1146.
19. Lenhardt R, Hopf HW, Marker E, Akca O, Scheuenstuhl H, Sessler DI. Perioperative collagen deposition in elderly and young men and women. *Arch Surg.* 2000;135:71-74.
20. Calvin M, Dyson M, Rymer J, Young Sr. The effects of ovarian hormone deficiency on wound contraction in a rat model. *Br J Obstet Gynaecol.* 1998;105(2):223-227.
21. Amenta DS, Martinez-Hernandez A, Terlstad RL. Repair and regeneration. In: Damjanov I, Linder J, eds. *Anderson's Pathology* Vol. 1 10th ed. St. Louis: Mosby-Year Book;1996:416-447.
22. Witte MB, Barbul A. General principles of wound healing. *Surg Clin North Am.* 1997;77:509-528.
23. Wiczak HP, Grow DR, Adams LA, O'Shea DL, Reece MT. Pelvic adhesions contain sex steroid receptors and produce angiogenesis growth factors. *Fertil Steril.* 1998;69:511-516.
24. Yasuda M, Shimizu I, Shiba M, Ito S. Suppressive effects of estradiol on dimethylnitrosamine-induced fibrosis of the liver in rats. *Hepatology.* 1999;29:719-727.
25. Angela MK, Ayala A, Monfils BA, Cioffi WG, Bland KI, Chaudry IH. Testosterone and/or low estradiol: normally required but harmful immunologically for males after trauma-hemorrhage. *J Trauma.* 1998;44(1):78-85.