Effect of ovariectomy and female sex hormones administration upon gastric ulceration induced by cold and immobility restraint stress

Dogan Kurt, PhD, Berna G. Saruhan, PhD, Zeki Kanay, PhD, Beran Yokus, PhD, Berna E. Kanay, PhD, Ozkan Unver, PhD, Savas Hatipoglu, PhD.

ABSTRACT

Objective: To investigate the protective effects of estrogen and progesterone administrations on gastric mucosal barrier of rats applied ovariectomy, cold and immobility stress.

Methods: Seventy female Wistar rats, obtained from Medical Science Application and Research Center, Dicle University, Turkey on the year 2004, were divided into 10 separate groups (n=7). Nothing was applied to the animals of Group 1 (control); bilateral ovariectomy was performed on the animals of the Groups 2, 4, 5, 6, 7, 8, 9, and 10. Groups 5 and 6 was applied 5 mg/kg 17beta-estradiol and groups 7 and 8 was applied 10 mg/kg progesterone for 7 days. The animals in the Groups 9 and 10 were applied 2.5 mg/kg 17beta-estradiol and 5 mg/kg progesterone during 7 days. The animals in the groups 3, 4, 6, 8 and 10 were exposed to cold and immobility stress for 4 hours at 4°C.

Results: The levels of mucus and phospholipids were decreased in the rats applied ovariectomy and stress as compared to the control groups (p<0.001). The increase determined the mucus and phospholipids levels in estrogen and progesterone administered rats as compared to stress applied group (p<0.001). While the cold and immobility stress causes important damages in gastric mucosa, estrogen and progesterone administrations has protective effects in ovariectomized rats.

Conclusion: The estrogen and progesterone administration prevents the stress that caused decrease in the levels of mucus and phospholipids, thus females are more resistant to gastric ulcer rather than males due to their sex hormones.

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From the Departments of Physiology (Kurt, Kanay Z), Histology and Embryology (Saruhan), Biochemistry (Yokus), Surgery (Kanay B), Pathology (Unver), Faculty of Veterinary Medicine, and the Department of Anatomy (Hatipoglu), Medical Faculty, University of Dicle, Diyarbakir, Turkey.

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Address correspondence and reprint request to: Dr. Dogan Kurt, Department of Physiology, Faculty of Veterinary Medicine, University of Dicle, Diyarbakir, Turkey. Tel. +90 (412) 2488020 Ext. 8627. Fax. +90 (412) 2488021. E-mail: dogank@dicle.edu.tr

Gastric mucosa is continuously subjected to the action of various irritans, which may lead to the impairment of its integrity and to the development of acute and chronic ulcerations.[1,2] The development of gastric ulcerations is linked to the changes that occur within hormonal cycles, especially those related to the sex hormones secretion. It is accepted that the incidence of gastric peptic ulcers increases among women in menopause.[3,4] Cold and immobility stress causes ulceration in gastric mucosa of rat and many physiological factors such as increase in gastric acid secretion, inhibition of gastric mucosal prostaglandin synthesis, decrease in gastric mucosal blood irrigation and destruction of gastric mucosa, have role in occurrence of these lesions.[5] Experimental studies and clinical observations suggest that gender has an important role in occurrence of ulcerations in gastro-duodenal mucosa.[6,7] It is suggested that experimental ulcer induced by ethanol administration causes more severe gastric erosion in male rats than that of in females.[8] There are results suggest that gonadectomy protects stomach of male rats against mucosal damage caused by ethanol but does not protect in females.[3] Another study suggests that males have more sensitive mucosal barrier than that of females.[9] The concentration of sex hormones physiologically varies in females. It was reported by a study conducted on rats that gastrointestinal lesions decrease significantly following the administration of steroid and cysteamine during pregnancy and lactation period,[10] besides it is known that the incidence of ulcer in pregnant women is low.[7] It is suggested

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that increased progesterone levels in gestation or experimental administration of exogenous progesterone has a protective effect on gastric mucosal barrier and particularly, high progesterone levels during early gestation stages decrease the sensitivity against mucosal damage.[11] Stress caused by mucosal damages were proved in many researches.[12,13] We aimed to investigate the effects of female sex hormones Estrogen (17beta-estradiol) and Progesterone on gastric mucosal barrier of rats' applied ovariectomy, cold and immobility stress.

Methods. The experiments were performed on 70 female Wistar rats obtained from the Medical Science Application and Research Center, Dicle University (DUSAM), Turkey, weighing 180-220 g, and fed with Standard pelleted food (Tavas Inc. Adana, Turkey). The animals were divided into 10 separate groups; each group contained 7 animals.

Group 1 (control group): Nothing was applied to the experimental animals in this group. Group 2, 4, 5, 6, 7, 8, 9, and 10 were applied to bilaterally ovariectomized. After anesthetizing the animals by intramuscular (IM) administration of 40 mg/kg Ketamine (Alfamine® Ege-vet) and 5 mg/kg IM xylazine hydrochloride (Alfazyne® Ege-vet), required asepsis and antisepsis of abdominal region was provided. A parallel incision was made to Linea alba approximately at the length of 10 mm. Peritoneum was opened following the incisions of subcutaneous (sc) connective tissue and muscles one by one. Bilateral ovaries ligature and removed, remained uterus was restored to abdomen. Subsequently peritoneum, muscles and skin were closed by suture. After bilateral ovariectomy, the rats were allowed to recover for 4 weeks before being treated. Group 3 (cold and immobility stress [CIS]): animals in this group were feed and protected for 37 days after CIS was applied to these groups during 4 hours at 4°C in accordance with the method of Basso et al.[14] Group 4 (ovariectomy+stress): CIS was applied to the ovariectomized animals on the 37th day. Group 5 (ovariectomy+estrogen): 5 mg/kg sc estrogen was administered to the animals during 7 days starting from the day 30th following ovariectomy operation. Group 6 (ovariectomy + estrogen + stress): 5 mg/kg sc estrogen was administered to the animals during 7 days starting from the day 30th following ovariectomy operation. Then, the animals were exposed to CIS on the 37th day. Group 7 (ovariectomy + progesterone): 10 mg/kg sc progesterone was administered to the animals during 7 days starting from the day 30th following the ovariectomy operation. Group 8 (ovariectomy+ progesterone + stress): 10 mg/kg sc progesterone was administered to the animals during 7 days starting from the day 30th following the ovariectomy operation. Then, the animals were exposed to CIS on the 37th day. Group 9 (ovariectomy + estrogen + progesterone): 5 mg/kg progesterone and 2.5 mg/kg estrogen was administered sc daily during 7 days starting from the day 30th following the ovariectomy operation. Group 10 (ovariectomy + estrogen + progesterone + stress): 5 mg/kg progesterone and 2.5 mg/kg estrogen was administered sc daily during 7 days starting from the day 30th following the ovariectomy operation. Then, the animals were exposed to CIS on the 37th day.

On the last day of treatment, the animals were scarified under ether anesthesia, the stomachs were opened-cut along the greater curvature and washed with serum physiologic. They were divided into two halves. Mucus quantities were evaluated in one half of the stomachs by UV spectrophotometer according to the method of Corne et al.[15] Phospholipid quantities were evaluated on the other halves of the stomachs by UV spectrophotometer according to the method of Baur et al.[16] The light microscopic examination of all tissue samples had been fixed in 10% neutral formalin and embedded in paraffin. Hematoxylin and eosin stained slides were reviewed. Histopathological examination and microphotographs were taken by Nikon eclipse.

The tissues from stomach were fixed for 2 hours at 4^0C, 2.5 glutaraldehyde solution in 0.1 mol/L phosphate buffer, post-fixed in 1.0% osmium tetroxide in the same buffer at 4^0C for one hour, and then embedded in Araldyte-Cy212. Ultrathin sections were stained with Uranyl acetate and Lead citrate according to double stained method. The results were examined under a Jeol-900 transmission electron microscope. Electron microscopy was performed in Electron Microscopy Unit of The Faculty of Medicine, University of Dicle.

Data from the 7 animals in each group were obtained to calculate the averages and the standard deviations of the findings. The statistical analyses were made by 2 way Analysis of Variance test and Dunnet multiple comparison tests on computer (SPSS).

Results. ***Physiological findings.*** The effects of Estrogen and progesterone on gastric lesions caused by cold and immobility stress and mucus and phospholipid levels of gastric mucosal barrier were shown in **Table 1**. The mucus quantity in cold and immobility stress applied group was 72.23 ± 12.11 µg/kg wet tissue and phospholipid level was 2.19 ± 0.36 µg/kg wet tissue. The mucus quantity in the group, which was not exposed to cold, and immobility stress was 161.4 ± 22.79 µg/kg wet tissue and phospholipid level was 6.35 ± 2.43 µg/kg wet tissue. Cold and immobility stress decreases the mucus and phospholipid levels of gastric mucosal barrier. The statistical significances were $p<0.001$ for mucus level and $p<0.001$ for phospholipid level. Estrogen was determined

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to have protective effects against acute damage caused by cold and immobility stress. The mucus quantity in estrogen administered experimental group was 81.92 ± 13.16 µg/kg wet tissues and phospholipid level was 3.67 ± 0.47 µg/kg wet tissue. The mucus quantity in progesterone administered experimental group was 100.17 ± 18.25 µg/kg wet tissue and phospholipid level was 3.76 ± 0.86 µg/kg wet tissue. Mucus and phospholipid quantities in estrogen and progesterone administered rats were increased as compared to that of stress applied control group. The statistical significances were found $p<0.001$, $p<0.001$ for mucus and $p<0.001$, $p<0.001$ for phospholipids.

Light microscopy findings. In our study, gastric mucosa, cells in the glands in mucosa and gastric pits were normal in control group (**Figure 1**). Gastric pits were observed to deepen after ovariectomy while the cells in the glands were determined using the same structure with the control group. More deepen gastric pits with serrated shape, partial desquamation in surface epithelium and necrotic cells and submucosal edema was observed in those areas in the group with ulcer due to stress exposure after ovariectomy. Inflammatory cell infiltration and vessel congestions in submucosal layer besides degenerative changes in gland cells were observed (**Figure 2**). Surface epithelium was widely undamaged; however there were desquamation in some areas. There were small hemorrhagic points in some of those desquamated areas. Submucosal edema and inflammatory cell infiltration was also observed in this group similar to that of observed in ovariectomy + stress group. There was desquamation in surface epithelial cells and deep ulcers in progesterone administered group. There were hemorrhagic points due to ulcer. Submucosal inflammatory cell infiltration and edema was not different from that of observed in ovariectomy + stress group. The surface epithelium was widely undamaged in the group, which was administrated the estrogen and progesterone together. Submucosal edema and inflammatory cell infiltration was also observed in this group similar to that of observed in ovariectomy + stress group. Parietal cells were observed normal and similar to that of control group.

Electron microscopy findings. In the control group the organelle of parietal cells, transfer tubules and side connection units of gastric glands were observed normal. G cells located in the base of the glands were characterized to have granular endoplasmic reticulum (GER) (**Figure 3**). In electron microscopy of ovariectomy applied group a part of parietal cells in gastric glands were observed normal and similar to that of control group while some parts determined to have degenerative changes, vacuolization of cells and condensation of nuclear chromatin. Granular endoplasmic reticulum dilatations observed in chief cells suggested that those cells were active. No disintegration was observed in side connective complexes of the cells.

The diminished transfer tubules of parietal cells, swollen mitochondria and cristolysis were observed in the group subjected to stress following ovariectomy

Table 1 - The effects of estrogen and progesterone on gastric lesions caused by cold and immobility stress and mucus and phospholipid levels of gastric mucosal barrier.

Group		No. of patients	Phospholipid (mg/g wet tissue)	Mucus (µg/g wet tissue)
Group 1	Control	7	6.35 ± 2.43	161.84 ± 22.79
Group 2	Control + CIS	7	2.19 ± 0.36	72.23 ± 12.11*
Group 3	Ovariectomy	7	3.89 ± 0.32	92.48 ± 01.13
Group 4	Ovariectomy + CIS	7	2.01 ± 0.12†	66.81 ± 11.02†
Group 5	Ovariectomy + Estrogen	7	3.97 ± 0.53	93.13 ± 01.17
Group 6	Ovariectomy + Estrogen + CIS	7	3.67 ± 0.47†	81.92 ± 13.16†
Group 7	Ovariectomy + Progesterone	7	4.09 ± 0.18	142.21 ± 03.28
Group 8	Ovariectomy + Progesterone + CIS	7	3.33 ± 0.40†	90.87 ± 01.98†
Group 9	Ovariectomy + Progesterone + Estrogen	7	3.76 ± 0.86	100.17 ± 02.60
Group 10	Ovariectomy + Progesterone + Estrogen + CIS	7	2.87 ± 0.29†	87.82 ± 02.25†

*Statistical significance was found $p<0.01$ for mucus between control group and control + cold and immobility stress (CIS) group (2 way analysis of variance test). †Statistical significances were found $p<0.001$ for mucus and $p<0.001$ for phospholipids. Mucus and phospholipid levels of bilateral ovariectomy and CIS groups compared to intact control groups were considered as indicative of a significant difference (2 way analysis of variance test).

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Figure 1 - Light microscopic appearance of gastric mucosa from the control group (hematoxylin-eosin x 10). black arrow - gastric pits, G - Gastric glands.

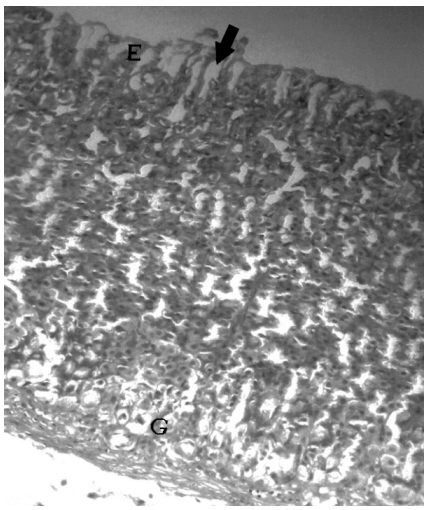

Figure 2 - Light microscopic appearance of gastric mucosa from the bilateral ovariectomy + stress group (black arrow - Gastric pits, E - epithelium, G- gastric glands) (hematoxylin-eosin x 20).

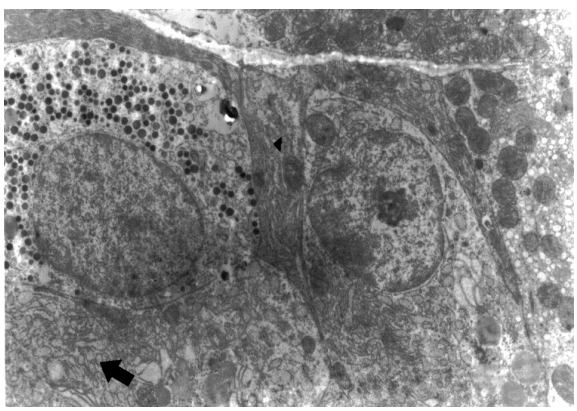

Figure 3 - Electron micrograph of normal ultrastructural observations of rat gastric mucosa sections (black arrow). Uranyl acetate-Lead citrate (x 4400).

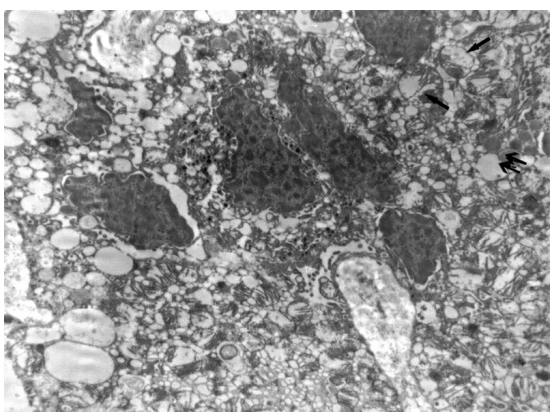

Figure 4 - Electron micrograph of parietal cell from the rat stomach of the ovariectomized + stress group, it has seen that swollen mitochondria (single black arrow), cristolysis and partial intracytoplasmic edema (double-black arrow), large and small granules (*) in G cell. Uranyl acetate-Lead citrate (x 3000).

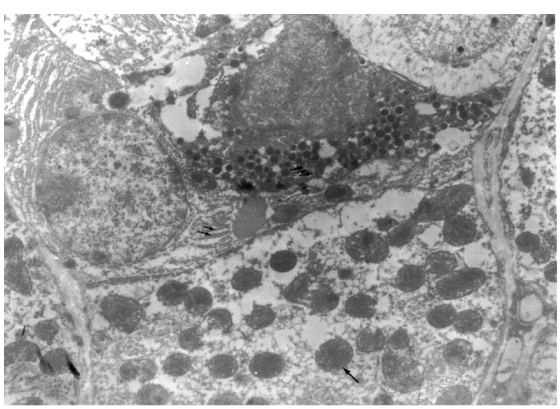

Figure 5 - Electron micrograph of parietal cell from the rat stomach of the ovariectomized + estrogen + progesterone group, it has seen that, intracytoplasmic canalicular dilatation (double-black arrow) and secretion granules in G cell (triple-black arrow). Uranyl acetate-Lead citrate (x 4400).

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operation. Dilatations in GER of chief cells and their inside filled with electron condensed material demonstrated that these cells are active. There were disintegrations in the side connective units of the cells. Partial intracytoplasmic edema and large and small granules were observed in G cells (**Figure 4**). It was observed that the number of eosinophilic cells in Lamina propria was increased while collagen febriles were normal. Side connective units of parietal cells were observed normal, transfer tubules were inactive, and edema in cytoplasm and mitochondria were normal in case of estrogen and progesterone administration following ovariectomy operation. However, dilatation in intracytoplasmic canaliculi of some parietal cells was observed while there were cristolysis in mitochondria of G cells, secretion granules and vacuoles in their cytoplasm. The volumes of chief cells were decreased and their GER cisterns were determined inactive. The connective tissue had the same results with that of control group (**Figure 5**). It was observed that intracytoplasmic cells of parietal cells were dilated and their side connective units and mitochondria were observed normal in case of progesterone administration following ovariectomy operation. The chief cells were electron condensed and particularly with GER dilatations. Some of the G cells were degranulated and some others observed to be granulated but with intracytoplasmic edema.

Discussion. Although the pathogenesis of stress causes ulcer. In recent researches, it was demonstrated that one of the causes are imbalances of many protective and destructive factors.[17,18] Acid, pepsin, bile, reperfusion damage and free oxygen radicals are considered as main destructive factors while main protective factors are listed as sufficient mucosal blood irrigation, mucus-bicarbonate layer, replication ability of epithelial cells and prostaglandins.[19,20] There was a significant increase in incidence of peptic ulcer disease in first half of the 20th century. Many clinicians and researches thought that excess HCl release can be the main reason of that disease. Gastric mucus and natural structure of mucosal epithelium was studied during the last decade.[21] Hollander[22] put forward the barrier theory and suggested that this barrier has self renewable. According to that hypothesis, gastric mucous barrier is consisted of 2 important layers; first layer is called mucous sticky (in charge of defense) and the second layer is called the surface epithelium layer consisted of prismatic and cubic cells.[22] Gastric acid secretion increases and gastric motility and vascularization corrupt due to stress.[9] In our study, ovariectomy caused gastric barrier to become more sensitive against ulceration. The decrease in the levels of mucus and phospholipids, which are important components of gastric barrier was prevented in case of estrogen + cold and immobility stress application. Filippo et al[12] suggested that the protective effect of exogenous estrogen administration on rats applied ovariectomy and stress depends on its doses. Nevertheless we have encountered some contradictory information about the effect of estrogen on mucosal barrier in different researches.[23,24] Steroid sex hormones was well known to have inhibitory effect on mucus production in gastrointestinal system thus there are some suspects that these may have an important role in pathology of peptic ulcer.[17] There were no sufficient number of studies about this issue. The decrease in the levels of mucus and phospholipids, which are important components of gastric mucosal barrier, was prevented significantly in the experimental group administered with exogenous progesterone following cold + immobility stress application. The physiopathology of experimental gastric ulcer formation yet could not be explained sufficiently. However, increase in gastric secretion, gastric mucosal blood irrigation, prostaglandin synthesis, bicarbonate secretion, decrease in mucus production and corruption of gastric mucosal barrier are considered as responsible pathologic mechanisms for gastric lesions caused by stress.[12,25] Machowska et al[13] reported that progesterone accelerates the healing of ulcer by increasing gastric blood irrigation. Li et al,[26] reported that ultra-structures of parietal cells of the normal group as well as stress applied groups for 24, 48 and 72 hours were highly compatible with the results of our study. On the basis of experimental and clinical observations, it is known that ulcers of the gastrointestinal mucosa develop in a sexually-dependent manner. For example, in the fertile age, peptic ulcer disease occurs more frequently among men than in women.[7] Gunal et al[9] determined that Estradiol (10 mg/kg) reduced gastric ulcer index and colonic damage score compared to vehicle treated groups. Standard error of mean and light microscopy demonstrated a significant reduction in the severity of ulcers and colitis by Estradiol treatment. Roland B et al,[27] demonstrated that ovariectomy had no significant effect in altering the extent of gastric pathology. Aguwa et al[28] determined the effects of progesterone 10 mg/kg, estrogen 5 mg/kg and a combination of both at half of the doses in rats. Ulcers were induced in rats by means of various experimental models: drug-induced ulcers (aspirin or indomethacin), stress ulcer and shay rat. The female sex hormones were found to have significant antiulcer activity in almost all models. However, they did not affect the acidity or volume of gastric secretion in shay rat pyloric ligation. As a result, anti-ulcer activity could not be explained by the effects on gastric acidity but by the effects on other factors which may include enhanced mucus activity, or increase in parietal cells activity and maintenance of mucus integrity. Abouzeit

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et al[29] explained that estrogen administration reduces gastric erosions and the mechanism could be through decreasing histamine release from gastric tissue. Peptic ulcer is one of the most common gastrointestinal disorders in clinical practice. Although genesis of ulcers is multifactorial, they are essentially thought to arise due to an imbalance between offensive factors such as acid and pepsin secretion and defensive factors such as mucin secretion, cell shedding, cell proliferation, prostaglandins (PGs), and so forth.[30] Stress appears to play an important role in peptic ulceration and anti-stress drugs have been shown to be effective in stress-induced gastric mucosal damage.[31] There are 5 types of stress ulcers, namely, single bound stress, cold bound stress, socking stress, shock stress and spinal cord injury stress.[32] Our morphological observations on stomach tissue indicate that ovariectomy and stress causes mucosal damaged. Also, the males have parietal cells more than females; therefore they are sensitive to gastric ulcer than females.

Finally, it was concluded that estrogen and progesterone administration prevents the stress caused decrease in the levels of mucus and phospholipids which are important components of gastric mucosal barrier but protective effect of progesterone is stronger, thus these results are in accordance with the researches report that females are more resistant to gastric ulcer rather than males due to their sex hormones.[33] However, the males have parietal cells more than females; therefore they are sensitive to gastric ulcer than females.[34]

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References

1. Yang YX, Lewis JD. Prevention and treatment of stress ulcers in critically ill patients. ***Semin Gastrointest Dis*** 2003; 14: 11-19.
2. Steinberg KP. Stress-related mucosal disease in the critically ill patient risk factors and strategies to prevent stress-related bleeding in the intensive care unit. ***Crit Care Med*** 2002; 30: 362-364.
3. Martin RA. Utility of proton pomp inhibitors in the treatment of gastrointestinal hemorrhage. ***Conn Med*** 2004; 68: 435-438.
4. Van Rensburg CJ, Hartmann M, Thorpe A, Venter L, Theron I, Luhmann R, et al. Intragastric PH during continuous infusion with pantoprazole in patients with bleeding peptic ulcer. ***Am J Gastroenterology*** 2003; 98: 2635-2641.
5. Aase S. Disturbances in the balance between aggressive and protective factors in the gastric and duodenal mucosa. ***Turk J Gastroenterol*** 1985; 24: 17-23.
6. Aston NO, Kalaıchanjxan S, Carr JV. Duodenal ulcer hemorrhage in the puerperium. ***Can J Surg*** 1991; 34: 482-483.
7. Michaletz Onody PA. Peptic ulcer disease in pregnancy. ***Gastroenterol Clin North Am*** 1992; 21: 817-826.
8. Laszlo F, Amanı E, Varga CS, Laszlo FA. Influence of sex hormones on ethanol-induced gastric hemorrhagic erosions in rats. ***Acta Physiol Hung*** 1992; 80: 289-292.
9. Gunal O, Oktar BK, Ozcınar E, Sungur M, Arbak S, Yegen BC. Estradiol Treatment Ameliorates Acetic Acid-Induced Gastric and Colonic Injuries in Rats. ***Inflammation*** 2003; 27: 351-359.
10. Kelly P, Robert A. Inhibition by pregnancy and lactation of steroid-induced ulcers in the rat. ***Gastroenterology*** 1969; 56: 24-29.
11. Montoneri C, Drago F. Effects of Pregnancy in Rats on Cysteamine-Induced Peptic Ulcers: Role of Progesterone. ***Dig Dis Sci*** 1997; 42: 2572-2575.
12. Drago F, Montoneri C, Varga C, Ferenc L. Dual effect of female sex steroids on drug-induced gastroduodenal ulcers in the rat. ***Life Sci*** 1999; 64: 2341-2350.
13. Machowska A, Szlachcic M, Pawlik M, Brozozowski T, Konturek SJ, Pawlik WW. The role of female and male sex hormones in the healing process of preexisting lingual and gastric ulcerations. ***J Physiol Pharmacol*** 2004; 55: 91-104.
14. Basso N, Matteria A, Forlini A, Jaffe BM. Prostaglandin Generation of Rats with Stress Ulcer. ***Surgery*** 1983; 94: 104-108.
15. Corne SJ, Morriessey SM, Woods RJ. A method for quantitative estimation of gastric barrier mucus. ***J Physiol*** 1974; 242: 1169-1179.
16. Baur JD, Ackerman PG. Phospholipids in clinical laboratory methods. St. Louis: CO Mosby Comp; 1974. p. 450-51.
17. Spirt MJ. Stress-related mucosal disease: risk factors and prophylactic therapy. ***Clin Ther*** 2004; 26: 197-213.
18. Duerksen DR. Stress-related mucosal disease in critically ill patients. ***Best Pract Res Clin Gastroenterol*** 2003; 17: 327-344.
19. Andriulli A, Annese V, Caruso N, Pilotto A, Accadia L, Niro AG, et al. Proton pump inhibitors and outcome of endoscopic hemostasis in bleeding peptic ulcers: a series of meta-analyses. ***Am J Gastroenterol*** 2005; 100: 207-219.
20. Daley RJ, Rebuck JA, Welage LS, Rogers FB. Prevention of stress ulceration: current trends in critical care. ***Crit Care Med*** 2004; 32: 2008-2013.
21. Werther JL. The gastric mucosal barrier. ***Mt Sinai J Med*** 2000; 67: 41-53.
22. Hollander F. The two components mucous barrier: Its activity in protecting the gastroduodenal mucosa against peptic ulceration. ***Arch Intern Med*** 1954; 93: 107-120.
23. Fujita H, Takahashi S, Okabe S. Mechanism by which indomethacin delays the healing of acetic acid-induced ulcers in rats. Role of neutrophil anti chemotactic and chemotactic activities. ***J Phy Pharm*** 1998; 49: 71-82.
24. Takeuchi K, Johnson LR. Effect of cell proliferation on healing of gastric and duodenal ulcers in rats. ***Digestion*** 1986; 33: 92-100.
25. Mozsik GY, Javor TA. Biochemical and pharmacological approach to the genesis of ulcer disease I: A model study of ethanol-induced injury to gastric mucosa in rats. ***Dig Dis Sci*** 1988; 33: 92-106.
26. Li YM, Lu GM, Zou XP, Li ZS, Peng GY, Fang DC. Dynamic functional and ultrastructural changes of gastric parietal cells induced by water immersion-restraint stress in rats. ***World J Gastroenterology*** 2006; 12: 3368-3372.
27. Roland B, Grijalva CV. Gastric mucosal damage induced by lateral hypothalamic lesions in female rats: influence of age and ovariectomy. ***Behav Neural Biol*** 1991; 55: 166-178.
28. Aguwa CN. Effects of exogenous administration of female sex hormones on gastric secretion and ulcer formation in the rat. ***Eur J Pharma*** 1984; 3: 79-84.

03Effec-ovar20061227.indd 1026 6/18/07 4:12:58 PM

29. Abouzeit MS, Verimer T, Long JP. Effect of long term estrogen and lithium treatment on resistant induced gastric erosion in intact and OVX rats. ***Pharmazie*** 1982; 37: 593-595.
30. Goel RK, Bhattacharya SK. Gastroduodenal mucosal defense and mucosal protective agents. ***Indian J Exp Biol*** 1991; 29: 701-714.
31. Das D, Banerjee RK. Effect of stress on the antioxidant enzymes and gastric ulceration. ***Mol Cell Biochem*** 1993; 24: 15-125.
32. Bhattacharya A, Ghosal S, Bhattacharya SK. Effect of fish oil on offensive and defensive factors in gastric ulceration in rats. ***Prostaglandins Leukot Essent Fatty Acids*** 2006; 74: 109-116.
33. Johnson LR, Peitsch W, Takeuchı K. Mucosal gastrin receptor. VIII. Sex-related differences in binding. ***Am J Physiol*** 1982; 243: 649-474.
34. Adeniyi KO. Gastric acid secretion and parietal cell mass: effect of sex hormones. ***Gastroenterology*** 1991; 101: 66-69.

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Al-Farra HM, Al-Fahoum SK, Tabbaa MA. Effect of hormone replacement therapy on hemostatic variables in post-menopausal women. ***Saudi Med J*** 2005; 26: 1930-1935.

Saruhan BG, Ozdemir N. Effect of ovariectomy and of estrogen treatment on the adrenal gland and body weight in rats. ***Saudi Med J*** 2005; 26: 1705-1709. Erratum in: Saudi Med J 2006; 27: 131.

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