

# Effects Hydrocortisone on the Body Weight of the Pregnant Rabbits and their Embryo with Histological Effects Skin, Stomach and Small Intestine of Embryos

Abid AL.Shammary<sup>1</sup>, Rasha Noori Abid AL-Shammary<sup>1</sup>

<sup>1</sup>Dept. Anatomy and biology, College of Medicine. Univ. of Wasit – Iraq

## Abstract

The aim of the study was to investigate the effects hydrocortisone of on the body weight of the pregnant rabbits and their embryo with histological effects pregnant skin ,stomach and intestine of embryos for 45 days. The rabbit were randomly divided into two equal groups (control and one treated groups), and the animals were treated as follow: 1- Control group C. (n = 12) received Distilled water 1ml /kg b.w five times a week intramuscular for 26days. 2-Treatment group. (n=12) treated daily with hydrocortisone 100mg/kg b.w/day/ intramuscular for 26 days. The body weight of the animals detected at the 1<sup>th</sup>,7<sup>h</sup> ,14<sup>th</sup> ,21<sup>th</sup> and 26<sup>th</sup>days of the experimental period. At 26 days animals sacrificed and embryos weighted and skin ,stomach , intestine were removed and taken for histopathological study. The present study showed that treatment with hydrocortisone causes a significant decrease in body weight of embryos and pregnant rabbits .As a conclusion: hydrocortisone cues decrease body weight of embryos and pregnant rabbits

**Keywords:** Rabbits, hydrocortisone, skin , stomach , intestine

## Introduction

Hydrocortisone belongs to a group of medicines called steroids. Their full name is Corticosteroids. These corticosteroids occur naturally in the body, and help to maintain health [1,2]. Hydrocortisone is an effective way to treat various illnesses involving inflammation in the body [3,4]. Indication and clinical use: Primary or secondary adrenocortical insufficiency [5]. Rheumatic disorders: As adjunctive therapy for short-term administration in: psoriatic arthritis, rheumatoid arthritis, including juvenile rheumatoid arthritis, ankylosing spondylitis, acute and subacute bursitis ,acute non specific tenosynovitis, acute gouty arthritis ,post traumaticosteoarthritis, synovitis of osteoarthritis and epicondylitis [6,7].

Collagen Diseases: During an exacerbation or as maintenance therapy in selected cases of systemic lupus erythematosus and acute rheumatic carditis [8].

Dermatologic Diseases: pemphigus, bullous dermatitis, herpetiformis, severe erythema multiforme, exfoliative dermatitis, mycosis fungoides and severe seborrheic dermatitis [9].

Allergic States: Control of severe or incapacitating allergic conditions intractable to adequate trials of conventional treatment: seasonal or perennial allergic rhinitis, bronchial asthma, contact dermatitis, atopic dermatitis, serum sickness and drug hypersensitivity reactions [10].

Ophthalmic Diseases: Severe acute and chronic allergic and inflammatory processes involving the eye and its adnexa such as: allergic conjunctivitis, keratitis, allergic corneal marginal ulcers, herpes zoster ophthalmicus, iritis and iridocyclitis, chorioretinitis, anterior segment inflammation, diffuse posterior uveitis and choroiditis, optic neuritis, sympathetic ophthalmia [11].

Respiratory Diseases: Symptomatic sarcoidosis, Löffler's syndrome not manageable by other means, berylliosis, fulminating or disseminated pulmonary tuberculosis when used concurrently with appropriate antituberculous chemotherapy, aspiration pneumonitis [12].

Hematologic Disorders: Idiopathic thrombocytopenic purpura in adults, secondary

thrombocytopenia in adults, acquired (autoimmune) hemolytic anemia, erythroblastopenia(RBCanemia), congenital (erythroid)hypoplasticanemia [13].

**Neoplastic Diseases:** For palliative management of: leukemias and lymphomas in adults, acute leukemia of childhood [14].

**Edematous States:** To induce a diuresis or remission of proteinuria in the nephrotic syndrome, without uremia, of the idiopathic type or that due to lupus erythematosus [15].

**Gastrointestinal Diseases:** To tide the patient over a critical period of the disease in: ulcerativecolitis, regional enteritis [16].

**CNS:** Acute exacerbations of multiple sclerosis. **Miscellaneous:**Tuberculous meningitis with subarachnoid block or impending block when used concurrently with appropriate anti tuberculous chemotherapy, trichinosis with neurologic or myocardial involvement [17,18]. Hydrocortisone Injection can cause side effects although not everybody gets them. Steroids including hydrocortisone can cause severe mental health problems. These are common in both adults and children. They can affect about five in every100 people taking medicines like hydrocortisone [19,20]. Feeling depressed, including thinking about suicide. Feeling high (mania) or having moods that go up and down. Feeling anxious, having problems sleeping, having difficulty in thinking or being confused and losing your memory. Feeling, seeing or hearing things which do not exist. Having strange and frightening thoughts, changing how you act or having feelings of being alone [21,22].Corticosteroids have been shown to be teratogenic in many species when given in doses equivalent to the human dose. Animal studies in which corticosteroids have been given to pregnant mice, rats, and rabbits have yielded an increased incidence of cleft palate in the offspring [23]. There are no adequate and well-controlled studies in pregnant women. Corticosteroids should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Infants born to mothers who have received corticosteroids during pregnancy should

be carefully observed for signs of hypoadrenalism [24].

The aim of the present study was to investigate the effects of hydrocortisone on the histological section of skin ,stomach and intestine in embryo rabbits

## Materials and Method

Twenty for adult rabbit were obtained from market of Kut .Animals were placed at the animal house, College of science , Wasit University and fed with pellet during experimental periods ,temperature was 25C°. Female was left in a separate cage with one male for the each cage ratio 2:1. Male and female couple were kept together in mating cage for six weeks .

The rabbit were randomly divided into two equal groups (control and one treated groups), and the animals were treated as follow:

1- Control group C. (n = 12) received Distilled water 1 ml /kg b.w five times week intramuscular for 26 days

2- Treatment group. (n=12) treated daily with hydrocortisone 100mg/kg b.w/day/ intramuscular for 26 days [25].The body weight of the pregnant animals detected at the 1<sup>th</sup>,7<sup>th</sup> ,14<sup>th</sup> ,21<sup>th</sup> and 26<sup>th</sup> days of the experimental period by electrical balance . At end of experiment period pregnant rabbit and embryo weighted and sampling skin, stomach ,intestine of embryos preserved in 10% formalin buffer solution until preparation of histopathological section. Tissue was cut at 7-8µm and embedded in paraffin and takes sections of skin, stomach, intestine were stained with hematoxylin -Eiosinstain(H&E)for histopathological study [26].

## Statistical Analysis:

Data were expressed as mean  $\pm$  standard error of mean and were compared by one way ANOVA followed by LSD. P value more than 0.05 was considered as statistically significant [27].

### Result and Discussion

**Table (1): Effect of Hydrocortisone on the body weight of the pregnant rabbit in the different periods**

Groups Time	Control Weight rabbit Kg	Hydrocortisone Weight rabbit Kg
1 day	1.78 + 0.019 a	1.74 + 0.017 a
7 day	2.4 + 0.029 a	1.62 + 0.044 b
14 day	2.8 + 0.097 a	1.54 + 0.056 b
21 day	2.12 + 0.077 a	1.31 + 0.023 b
day 26	2.14 + 0.08 a	1.22 + 0.22 b

The value represent Mean(gram) ±Standard Error-The different small letters show significant effect while the same small letters show insignificant effect between different groups.

Table (1) showed a significant decrease of body weight in hydrocortisone compared with the control along time of the experimental periods. Except one day non significant between hydrocortisone compared with the control. The decrease body weight because hydrocortisone therapy have included gastrointestinal upset, nausea, vomiting, and peptic ulcer disease, pancreatitis, ulcerative esophagitis [28,29]. Or may be due to hydrocortisone that impair carbohydrate, protein and lipid metabolism [30].

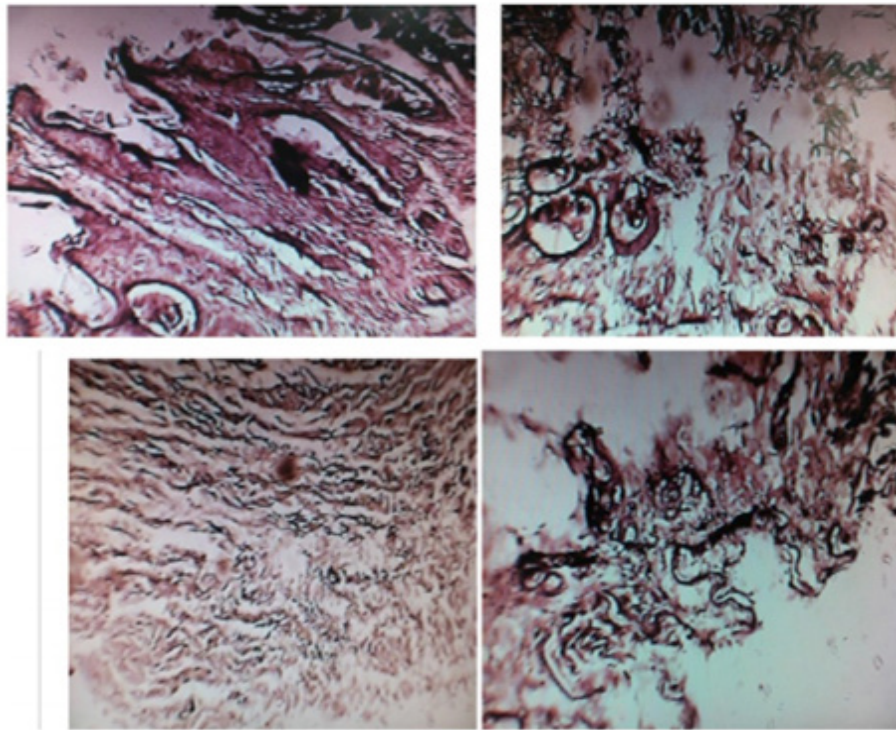
**Table (2): Effect of hydrocortisone on the body weight of the rabbits embryo in 26 day**

Groups Parameters	Control	Hydrocortisone
Body weight (gram)of embryo In 26 day	1.60 + 0.066 a	1.30 + 0.033 b

-The value represent Mean(gram) ±Standard Error

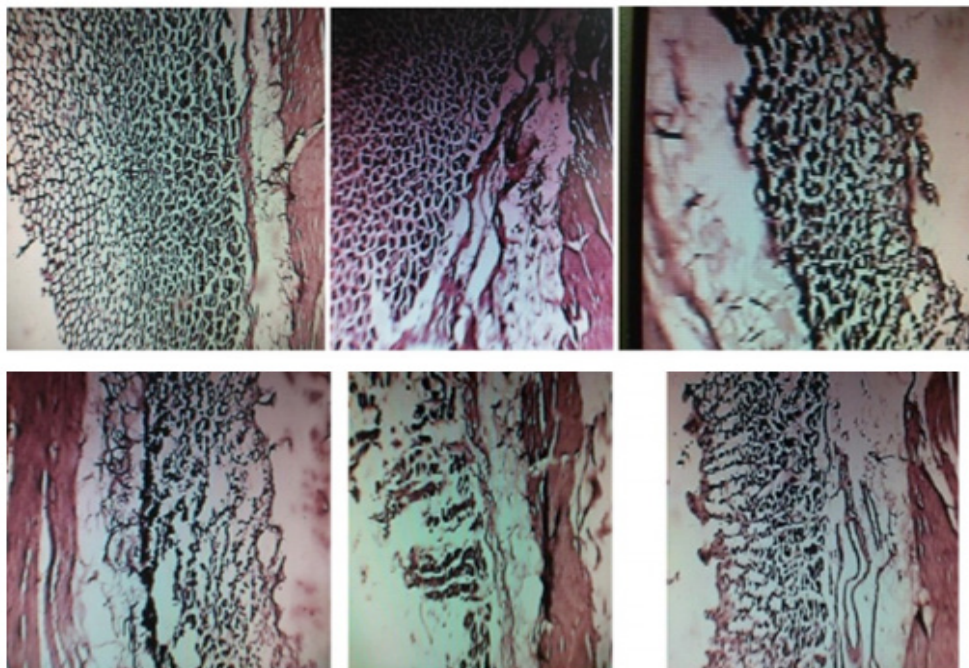
-The different small letters show significant effect while the same small letters show insignificant effect between different groups.

When taken hydrocortisone in high doses and for long period of time can cross the placental parrier causing premature and low birth weight due to inhibition of metabolism and fetal glands [31,32]



**Figure1: histopathological examination of skin embryos (underfox10\*0.25)**

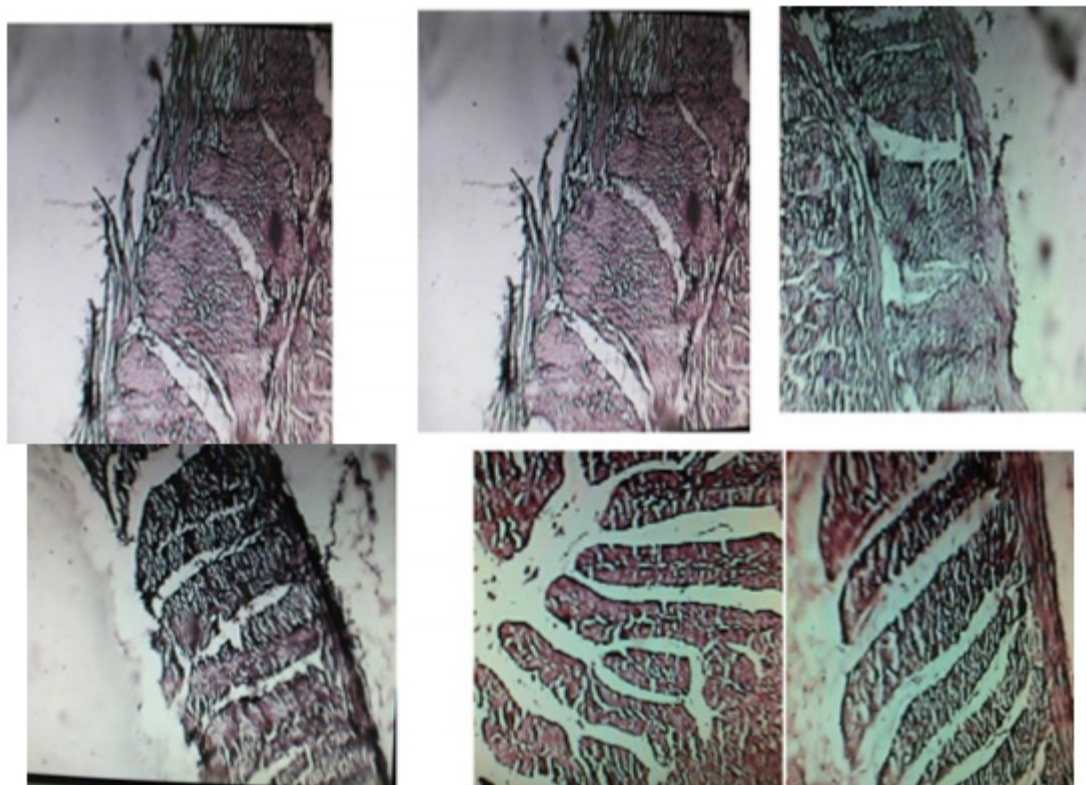
Histopathological examination of skin embryos in (fig. 1-A) control group no change in skin thickness(fig. 1-B) control group show normal dermal cell number and normal dermal collagenous fibres.(fig.1-C) treatment group thinning of the skin .Hydrocortisone inhibition epidermis thickening and keratinization and remove a small amount of the outer layer of the skin which affect by passive diffusion. (fig. 1-D) decrease in dermal cell number and increase of dermal collagenous fibres [33,34]. Hydrocortisone may cause primary irritant reactions which directly damage or kill epidermal cells and dermis [35,36].



**Figure, 2: histopathological examination of stomach embryo (under fox 10\*0.25)**

Histopathological examination of stomach embryo in (fig. 2-A) control group normal in the rate of epithelial cell formation (fig. 2-B) control group no reduction in stomach glandular epithelium (fig. 2-C) control group show normal size blood vessels (fig.2D) treated group reduction in the rate of epithelial cell formation due to hydrocortisone therapy had effect epithelial cell is rapidly turned over ,replaced with irritants leading to a

stomach wall more susceptible to peptic disease(37,38). (fig.2-E)treated group a reduced in stomach glandular epithelium due to a reduced frequency of mitosis in glandular epithelium that incidence of gastric peptic ulcer is actually increased after hydrocortisone therapy [39,40]. (fig. 2-F treated group) hyperplasia blood vessels due to increase in mucosal blood flow secondary effect of hydrocortisone [41].



**Figure, 3: histopathological examination of intestine embryo (under fox 10\*0.25)**

Histopathological examination of intestine embryo rabbits in (fig. 3-A) control group normal epithelial cell height with crypt height (fig. 3-B) control group increased in the number of goblet cells (fig. 3-C) control group increased in the number of the values with normal elongation of villi (fig. 3-D) treated group increased epithelial cell with crypt height and largamente mucosa. hydrocortisone therapy increases cell migration rate, thymidine kinase levels, and RNA and DNA content .The enhanced cell proliferation leads to mucosal hyperplasia and increases in intestinal weight ,crypt height which develops equally throughout the entire small intestine [42] (fig. 3-E)treated group decrease in the number of goblet cells . hydrocortisone inhibited the premature differentiation of goblet cells induced by thyroxine and

lowered mitotic counts, as compared to control [43,44]. (fig. 3-F) treated group decrease in the number of the values with increased elongation of villi. Also higher doses of hydrocortisone had a marked suppressive effect on DNA , the values in the steroid-treated group being about one-half those of the control group .Also hydrocortisone acceleration villus maturation, including the formation of previllous ridges , elongation of villi, vascularization of villi [45].

**Financial Disclosure:** There is no financial disclosure.

**Conflict of Interest:** None to declare.

**Ethical Clearance:** All experimental protocols were approved under the College of Medicine. Univ.

of Wasit – Iraq and all experiments were carried out in accordance with approved guidelines.

### References

1. Abraham, E. and Evans, T. Corticosteroids and septic shock. *Journal of the American Medical Association*;2002, 288(7): 886–887.
2. Annane, D. ; Sebille, V. and Charpentier, C. Effect of treatment with low doses of hydrocortisone and fludrocortisone on mortality in patients with septic shock. *Journal of the American Medical Association*;2002,288(7):2-871.
3. Budesonide . Entocort EC for Crohn’s disease. *Medical Letter on Drugs and Therapeutics*;2002, 44: 6–8.
4. Carson, P. Emergency: Adrenal crisis. *American Journal of Nursing*,2000,100(7): 49–50.
5. Benedictis, F. ;Teper, A.and Green, R.. Effects of 2 inhaled corticosteroids on growth. *Archives of Pediatric and Adolescent Medicine*;2001,155(11): 1248–1254.
6. Yaday, S. and Halday, C. Experimentally induced Stress, Oxidative load and changes in immunity in a tropical rabbits , *perdicula asiatica*: involvement of melatonin and glucocorticoid receptors. *Zoology*;2014, 117 (4): 261- 268.
7. Lee, H.; Barrasa, M.; Li, H. ; Elmes, R.; Peters, L. and Lodish, K. PPAR and glucocorticoid receptor synergize to promote erythroid progenitor self – renewal. *Nature*;2015, 11 (10): 14326-14335.
8. Turpeinen,M. Influence of age and severity of dermatitis on the percutaneous absorption of hydrocortisone in rabbits embryo. *Br J Dermatol*;2000,118:517-522.
9. Mashkilleyson, N. and Bjorksten, F. Percutaneous absorption of hydrocortisone during exacerbation and remission of atopic dermatitis in animals, . *Acta Dermatol Venereol (Stockh)*;2004, .68:331-335.
10. Epstein, N. ;Epstein , L. and Epstein H. Atrophic striae in animals with inguinal intertrigo. *Arch Dermatol*;1999, 87:450-452.
11. Sin, D; Man, J. ; Sharpe, H. ; Gan, W. and Paul Man, S. Pharmacological management to reduce exacerbations in adults human with asthma: A systematic review and meta-analysis. *Journal of the American Medical Association*,2004, 292(3): 367–376.
12. Spencer, M. and Bazarian, J. Are corticosteroids effective intraumatic spinal cord injury? *Annals of Emergency Medicine*,2003, 41(3):410–413.
13. Togger, D. and Brenner, P. Metered dose inhalers. *American Journal of Nursing*;2001, 101(10): 26–32.
14. Axelrod L .Glucocorticoid therapy. *Endocrinology*. Philadelphia. Elsevier Saunders;2006, 5 :2329-2342.
15. Welssmann, G. and Dingle, J. Release of lysosomal protease by ultraviolet irradiation and inhibition by hydrocortisone. *Expl Cell Res*;1991, 25: 207-210.
16. Kerrigan, R. ; Veldhuis, J. ; Leyo, S. ;Iranmanesh ,A. and Rogol,A. Estimation of daily cortisol production and clearancerates in normal pubertal males by deconvolution analysis. *J Clin Endocrinol Metab*;1999, 76: 1505-1510.
17. Esteban ,N. ; Loughlin, T. ;Yergey L. and Zawadzki J. Daily cortisol production rate in man determined by stable isotope dilution/mass spectrometry. *J Clin Endocrinol Metab*;1991, 72: 39-45.
18. Linder ,B. ;Esteban, N. ; Yergey, A. ;Winterer ,J. ;Loriaux ,D. and Cassorla, F. Cortisol production rate in human . *J Pediatr*;1990,117 : 892-896.
19. Shulman, D. ;Palmert ,M. and Kemp S .Lawson Wilkins Drug and Therapeutics Committee. Adrenal insufficiency: still cause of morbidity and death in childhood. *Pediatrics*;2007,119 : 484-494.
20. Lukert ,B. Editorial: glucocorticoid replacement—howmuch is enough? *J Clin Endocrinol Metab*;2006, 91 : 793-794.
21. Merke, D. and Bornstein S. Congenital adrenal hyperplasia.*Lancet* ;2002, 365(9477): 2125-2136.
22. Maguire, A. ; Ambler G. ; Moore. B. and Falletti, M. Prolonged hypocortisolemia in hydrocortisone replacement regimens in adrenocorticotrophic hormone deficiency. *Pediatrics*;2007, 120 : 164-171.
23. Clayton ,P. ;Miller, W. ;Oberfield, S. ;Ritzén, E. ;Sippell,W. and Speiser P. ESPE/ LWPES CAH Working Group. Consensus statement on 21-hydroxylase deficiency from the European Society for Paediatric Endocrinology and the Lawson Wilkins Pediatric Endocrine Society. *Horm Res*;2005, 58 : 188-195.
24. Weise, M. ; Drinkard B. ; Mehlinger L. ; Holzer,S and Eisenhofer,G. Stress dose of hydrocortisone

- is not beneficial with classic congenital adrenalhyperplasia undergoing short-term, high-intensity exercise. *J Clin Endocrinol Metab* ; 2004,89 : 3679-3684.
25. Paton, J. ;Jardine ,E. ; Beaton, S. ; Galloway, P. and Young,D . Adrenal responses to low dose synthetic ACTH(Synacthen) in rabbits receiving high dose inhaledfluticasone. *Arch Dis Animals*;2006 ,91 : 808-813.
  26. Einaudi ,S. ; Bertorello ,N. ; Masera, N. ; Farinasso ,L. ; Barisone, E.and Rizzari, C. Adrenal axis function after high-dose steroid therapy for animals acute lymphoblastic leukemia. *Blood Cancer*;2008, 50 : 537-541.
  27. Torries, J. and Tazuma ,S. Principles and Procedures of Statistics. Abiometrical approach, 2nd edition. McGraw-Hill Book Co. New York, USA.;1998, 33:5-8.
  28. Felner ,E. ;Thompson, M. ;Ratliff, A. and Dickson ,B.Time course of recovery of adrenal function in children treated for leukemia. *J Pediatr*; 2000, 137 : 21-24.
  29. Shah, R. and Kukreja ,S. Immunization in Special Circumstances. Immunization Mumbai .Indian Academy of Pediatric;2007,4.52-58.
  30. Odeniyi, I.; Fasanmade, O.; Ajala, M. and Ohwovoriole, A. Adrenocortical function, Immunodeficiency Virus Infection. *Ghana Medical Journal*;2013,47 (4) : 171-177.
  31. Selim, K.; Dilek, S.; Mustafa, A; Ghaniya, D.; Levent, K. and Seyma, M. adrenal suppression due to maternal corticosteroid use. *J. Clin Res Med Endo* ;2011, (3): 160- 162.
  32. Greenamyre, J. and MacKenzie G. Mitochondrial dysfunction in Parkinson's disease. *Biochemical Society Symposium*; 1999,66: 85-97 .
  33. Radoja,N.; Komine,M.and Bluinenberg, M.Novel mechanism of steroid action in skin through glucocorticoid receptor monomers.A401*Cell Biol*; 2000,20:4328-4339.
  34. Schafer, I. Glucocorticoids for, human skin: Newaspects of the mechanism of action. *Skin PharmacolPhysiol*; 2005,18: 103-114.
  35. Noorizadeh, C.; Elkins, J.; Hanus, J.; Noorizadeh, C and Skelly ,J. In vitro release of hydrocortisone from topicalpreparations and automated procedure. *Pharm Res*; 1991,8:55.
  36. Dinehart, S .and Farmer, E.Guidelines for care for vitiligo.*J Am Acad Dermatol* ; 1996,35:620-626.
  37. Dolcini,H.;Zaidman,I.andGray,S. Hormonal and pharmacologic influences on microcirculationin the rabbits stomach. *Amer. J. Physiol*;1990, 199. 1157-1160.
  38. Desbaillets, L. and Menguy, R. Inhibition of gastric mucus secretion by ACTH. *Amer. J. dig. Dis*;1997,12. 582-588.
  39. Menguy, R. and Masters, Y. Effect of cortisone on mucoprotein secretion by gastric antrum of rabbits . pathogenesis of xteroid ulcer. *Surgery*;1993, 54. 19-27.
  40. Sun, D. The effect of corticotropin on gastric acid, pepsin, and mucus secretion in rabbits with fistulas. *Amer. J. dig. Dis*;1999, 14. 107-112.
  41. Konturek ,S .;Rodecki T.; Brozozowski ,T.; Gryglewski ,R. and Gregory, H. Gastric cytoprotectionby epidermal growth factor; role of endogenous prostaglandins and DNA synthesis. *Gastroenterology*; 1991,81. 438-443.
  42. Jones, R. Intestinalabsorption and gastrointestinal digestion of protein during the normal and cortisone-induced post-closure. *Biochint. Biophys. Acta* ;1992, 274: 4 12.
  43. Rasanen, T. Fluctuations in the mitotic frequency of the glandular stomach and intestine under the influence of ACTH, glucocorticoids, stress, and heparin. *Acta Physiol. Scand* ;1993, 58, 201-210.
  44. Henning, S. and Sims, J. Delineation of the glucocorticoid-sensitive period of intestinal development. *Endocrinology*;1999,104: 1158.
  45. Kato, H.; Saito, M. and Shimazu, T. Attenuated blood corticosterone rhythm with jejunal resection. *LiJe Sci*;1994, 34: 33 1-335.