

A Web Of Evidence: The Pill & Gut Health

Dr. Devaki Lindsey Berkson

Estrogen Receptor

- Estrogen receptors (ERs) are expressed throughout the digestive tract.
- Estrogen receptor Alpha Er1.
- Estrogen receptor Beta Er2.
- Their expression is lost during colorectal carcinogenesis.
- With ER knock out mice, deficiencies of these receptors cause a significant increase in intestinal abnormalities, and tumor growth, number and size.
- Estrogen receptors play a critical role in restitution of epithelium after injury.

Carcinogenesis vol.30 no.9 pp.1581–1590, 2009. Disruption of estrogen receptor signaling enhances intestinal neoplasia in ApcMin/1 mice

Gastroenterology 2011 Jan. Role of Estrogen Receptor in the Regulation of intestinal Restitution After Mucosal Injury

ER alpha

- ER α is present mainly in mammary gland, uterus, ovary (thecal cells), bone, lungs, male reproductive organs (testes and epididymis), prostate (stroma), liver, adipose tissue
- And, throughout intestinal wall.

ER beta

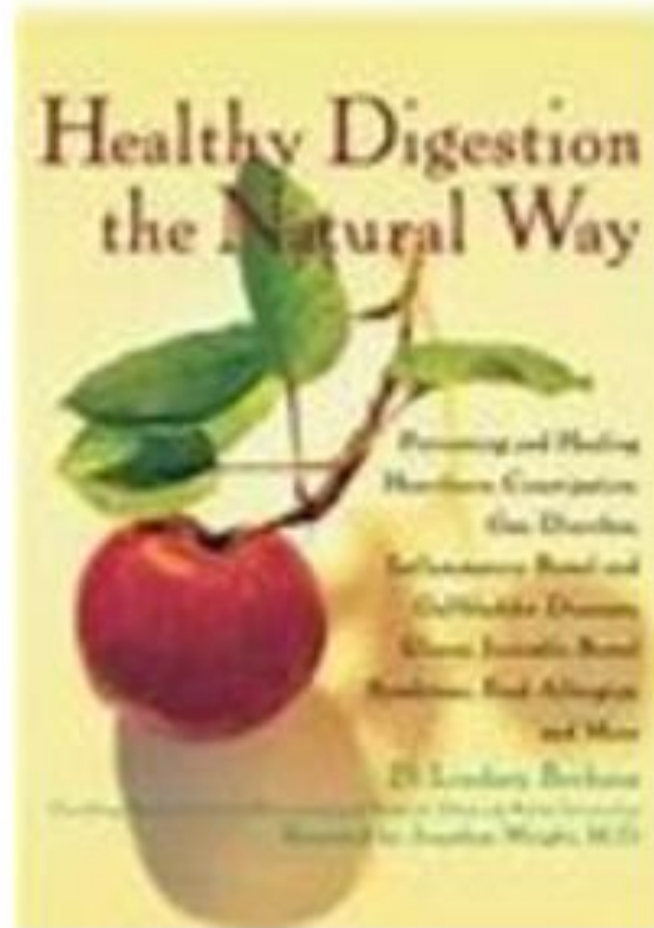
- ER β is found mainly in the prostate (epithelium), bladder, ovary (granulosa cells), lungs, adipose tissue, immune system, and throughout intestinal wall.
- Both subtypes are markedly expressed in the enteric nervous system.

[Steroids. 2014 Nov 15; 0: 13–29.](#) **Estrogen Receptors Alpha (ER α) and Beta (ER β): Subtype-Selective Ligands and Clinical Potential**

[Cancer Lett. 2016 Mar 1; 372\(1\): 48–56.](#) **Estrogen Receptor Beta as Target for Colorectal Cancer Prevention.**

[J Endocrinol. 2001 Oct;171\(1\):65-73.](#) **Immunolocalization of estrogen receptor alpha and beta in gastric epithelium and enteric neurons.**

Because of this book my practice was robustly full of gut disorders especially IBD



Over the years observed...

- Young women with IBD.
- Many who had surgery or were recommended surgery.
- Observed a theme.
- Having initiated oral birth control pills within a year of onset of disease.
- When hormones were added to their protocol, rapid improvement in bowel habits, disease on scoping, ability to get off meds and overall health.

Testimonial

inflammatory bowel disease



- I wanted to let you know that I went to see my colorectal doctor today for my annual checkup and he was blown away at how great things look in my j-pouch. Yes, he scopes my pouch every year. He has been my doctor for 16 years and has seen my ups and downs so for him to be blown away by this is pretty exciting. He told me to keep doing what I am doing and gave me a hug. He also told me that last year he was thinking that I would need a permanent ileostomy and now it doesn't even look like I have colitis.
- I also had my annual wellness check with Dell a few months back and every year they set goals for me to improve my health status but this year they were speechless and said I don't need to set any goals because whatever I am doing is working. This is the first year this has ever happened as well.
- WOW and THANK YOU is all I can say! I have lost 25 pounds and feel great only bummer thing is that I needed to back on the anti depressants but I feel more like myself now and I guess that is fine for now.
- Thanks again for all your wisdom and knowledge,



- Female, 27 years old
- Ulcerative Colitis, inflammatory arthritis, 50 polyps+ and moderate dysplasia
- Started one year after on BCP and antibiotics for acne
- Recommended colectomy the next week
- Uceris
- Cortifoam
- Lialda (mesalazine)
- Prednisone
- Flagyl

Started to review peer review literature of female hormones, oral birth control pills & IBD

- 1st mention 1978
- 4 cases of ulcerative colitis.
- The patients were all young women who had been on oral contraceptives (OCs) for at least 1 year.
- **All cases regressed spontaneously without treatment when going off OCs.**
- Their appears to be an association between OCs and gastrointestinal effects which needs to be explored.

[Gastroenterol Clin Biol.](#) 1978 Apr;2(4):442-3.

[Spontaneously regressive ulcerative colitis: the result of contraceptive agents?].

1987

- A statistically significant association between the use of oral contraceptives and extra-hepatic bile duct cancer was observed among women under 60 years of age.
- Patients reported significantly higher frequencies of history of **ulcerative colitis** and/or diseases of the gallbladder.

[Cancer](#). 1987 Jun 15;59(12):2112-6. **Extrahepatic bile duct cancer and smoking, beverage consumption, past medical history, and oral-contraceptive use**

1990

- Ample body of research suggesting a link between OCs and chronic inflammatory bowel disease, especially Crohn's disease.
- The finding of reduced bioavailability of estrogen and progesterone in women who have undergone jejunostomy demonstrates that **OCs are mainly absorbed in the small bowel and have a resultant damaging effect.**
- Reconsider recommending Ocs to patients with chronic inflammatory disease, non-colonic diarrhea, ileostomy, and jejunostomy.

[Am J Obstet Gynecol.](#) 1990 Dec;163(6 Pt 2):2204-7. **Gastrointestinal disease and oral contraception.**

1992

- 239 patients with Crohn's disease followed in South African hospitals.
- A non-significant trend existed for combined oral contraceptive use
- And increased numbers of inflammatory attacks and ileo-colitis.

[J Clin Gastroenterol.](#) 1992 Jul;15(1):12-6.

Factors influencing first relapse in patients with Crohn's disease.

1993

- Investigated the association between different risk indicators and inflammatory bowel disease in a case-control study based on the population of Stockholm County during 1980-1984. Information on physical activity, oral contraceptives, some previous diseases and childhood characteristics was collected using a postal questionnaire for 152 cases of Crohn's disease, 145 cases of ulcerative colitis, and 305 controls.
- The relative risk of Crohn's disease was inversely related to regular physical activity.
- Having psoriasis prior to the inflammatory bowel disease was associated with an increased relative risk of Crohn's disease.
- **Use of oral contraceptives was associated with a statistically significant increased risk for both Crohn's disease and ulcerative colitis.**

[Int J Epidemiol.](#) 1993 Apr;22(2):268-72. **Risk indicators for inflammatory bowel disease.**

1994

- Higher ulcerative colitis risk tended to occur among users of high estrogen dose oral contraceptives,
- **Crohn's disease risk was increased regardless of estrogen potency.**

[Am J Epidemiol.](#) 1994 Aug 1;140(3):268-78.

Increased risk of inflammatory bowel disease associated with oral contraceptive use.

[Epidemiology.](#) 1992 Jul;3(4):374-8.**Oral contraceptive use and the risk of inflammatory bowel disease.**

1995

- Meta-analysis: The GI Research Group of the University of Calgary in Alberta, Canada used data from seven case control studies (719 cases of inflammatory bowel disease and 3198 controls) and two cohort studies (32,673 users of oral contraceptives [OCs] and 30,379 nonusers).
- A positive (though modest) association between OC use and **both CD and UC**, even when smoking is controlled.

[Gut.](#) 1995 Nov;37(5):668-73. **Meta-analysis of the role of oral contraceptive agents in inflammatory bowel disease.**

1998

- 819 cases of IBD (594 ulcerative colitis: UC; 225 Crohn's disease: CD) originating from populations resident in 10 Italian areas, and age-sex matched paired control
- **Females who reported use of oral contraceptives for” at least one month” before onset of symptoms had a higher risk of CD.**
- No significant risk was observed for UC.

[Int J Epidemiol.](#) 1998 Jun;27(3):397-404.

Risk of inflammatory bowel disease attributable to smoking, oral contraception and breastfeeding in Italy: a nationwide case-control study. Cooperative Investigators of the Italian Group for the Study of the Colon and the Rectum (GISC).

2013 Nurse's Study

- Oral contraceptives associated with increased risk of Crohn's disease and ulcerative colitis.
- A prospective cohort study was carried out of 117,375 US women enrolled since 1976 in the Nurses Health Study I (NHS I) and 115,077 women enrolled since 1989 in the Nurses' Health Study II (NHS II) with no prior history of UC or CD.
- Women provided information every 2 years.
- Among 232,452 women with over 5,030,196 person-years of follow-up, 315 cases of CD and 392 cases of UC were recorded through 2007 in NHS II and 2008 in NHS I.
- **In these 2 large prospective cohorts of US women, oral contraceptive use was associated with risk of CD. The association between oral contraceptive use and UC was limited to women with a history of smoking.**
- Smoking affects estrogen receptors, linked to infertility, reduced androgens and abnormal metabolism of downstream catechol estrogens and risk of hormone dependent cancers.

[Gut.](#) 2013 Aug;62(8):1153-9. **Oral contraceptives, reproductive factors and risk of inflammatory bowel disease.** Division of Gastroenterology, Massachusetts General Hospital and Harvard Medical School,

[Fertil Contracept Sex.](#) 1989 Feb;17(2):133-8. **[Cigarette smoking: male and female infertility].**

[J Ark Med Soc.](#) 1986 May;82(12):597-604. **The effect of cigarette smoking on female reproduction.**

[J Steroid Biochem.](#) 1983 Jun;18(6):759-63. **Effects of chronic smoking on testosterone metabolism in dogs.**

2016

- The use of oral contraceptives is associated with the development of IBD.
- Oral contraceptives and IBD are independently associated with an increased risk for thromboembolism.
- Depot medroxyprogesterone acetate injection should be avoided in patients with or at risk for osteopenia.
- Intrauterine devices and implants are the most effective form of contraception and should be a first-line recommendation.

[Gastroenterol Hepatol \(N Y\)](#). 2016 Feb;12(2):101-9. **Fertility and Contraception in Women With Inflammatory Bowel Disease.**

2017

- An analysis of **20 studies found a 30% increased risk for the development of IBD in patients exposed to OCP compared with patients not exposed to OCP.**
- A 24% higher risk for developing Crohn's Disease and a 30% higher risk for developing ulcerative colitis.
- The use of OCP is associated with an increased risk for development of Crohn's disease and ulcerative colitis in the genetically susceptible host.

[Eur J Gastroenterol Hepatol.](#) 2017 Sep;29(9):1064-1070.
Exposure to oral contraceptives increases the risk for development of inflammatory bowel disease: a meta-analysis of case-controlled and cohort studies.

Progression?

- Use of exogenous hormones in the form of oral contraceptives has been linked **consistently** to risk of Crohn's disease. But how do Ocs contribute to the progression of CD?
- A prospective study of female patients with CD (age, 16-51 y), identified from the inpatient and outpatient care components of the Swedish National Patient Register from January 2002 through December 2013.
- Identified 482 incident cases of surgery among 4036 patients with CD with a median follow-up period of 58 months.
- **The risk of surgery increased with longer duration of use and higher prescribed daily dose.**
- **Significant increased risk to over 3 years of use or with combined use.**
- **For every 83 patients with CD receiving the combination type of oral contraceptives for at least 1 year, 1 extra surgery was required.**
- The rate of steroid prescriptions did not appear to increase with past or current use of OCs, compared with patients who have not taken OCs.
- In a nationwide analysis of patients in Sweden, long-term use of OCs, particularly the combination type, was associated with an increased risk of surgery among women with established CD.

[Gastroenterology](#). 2016 Jun;150(7):1561-1567.e1. **Association Between Long-term Oral Contraceptive Use and Risk of Crohn's Disease Complications in a Nationwide Study.**

Initiation but not progression?

- 1Division of Gastroenterology, Massachusetts General Hospital and Harvard Medical School, Boston, Massachusetts, USA.2Clinical and Translational Epidemiology Unit, Massachusetts General Hospital and Harvard Medical School, Boston, Massachusetts, USA.3Clinical Epidemiology Unit, Department of Medicine Solna, Karolinska Institutet, Stockholm, Sweden.4Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Solna, Sweden.5Department of Pediatrics, Orebro University Hospital, Orebro, Sweden.6Division of Epidemiology and Public Health, School of Medicine, University of Nottingham, Nottingham, UK.7Division of Digestive and Liver Diseases, Columbia College of Physicians and Surgeons, New York, New York, USA.8Channing Division of Network Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts, USA.9Sachs' Children's Hospital, Department of Pediatric Gastroenterology, Stockholm, Sweden.
- **Oral contraceptive use has been consistently linked to increased risk of inflammatory bowel disease.**
- Over 31,421 person-years of follow up.
- In a large nationwide registry of UC patients, we found no association between OC use and UC progression.

[Am J Gastroenterol.](#) 2016 Nov;111(11):1614-1620. **Oral Contraceptive Use and Risk of Ulcerative Colitis Progression: A Nationwide Study.**

Androgens

- Studies consistently demonstrate an association between oral contraceptive use and risk of CD and menopausal hormone therapy and risk of UC.
- A number of hypotheses:
 1. **Oral estrogens modify intestinal permeability**, a critical step in the pathophysiology of inflammatory bowel disease.
 2. **Exogenous hormones lower endogenous levels of hormones** (estrogens and androgens) which may increase development of Th1- and Th2-mediated inflammatory diseases.
 3. **The gut microbiome may be adversely effected with resultant “lower levels endogenous levels of androgens”**, which are also known to be altered with exogenous hormone use and increase risk of autoimmune diseases.

[Drug Saf.](#) 2016 Mar;39(3):193-7. **Risk of Inflammatory Bowel Disease with Oral Contraceptives and Menopausal Hormone Therapy: Current Evidence and Future Directions.**

Copper/Zinc

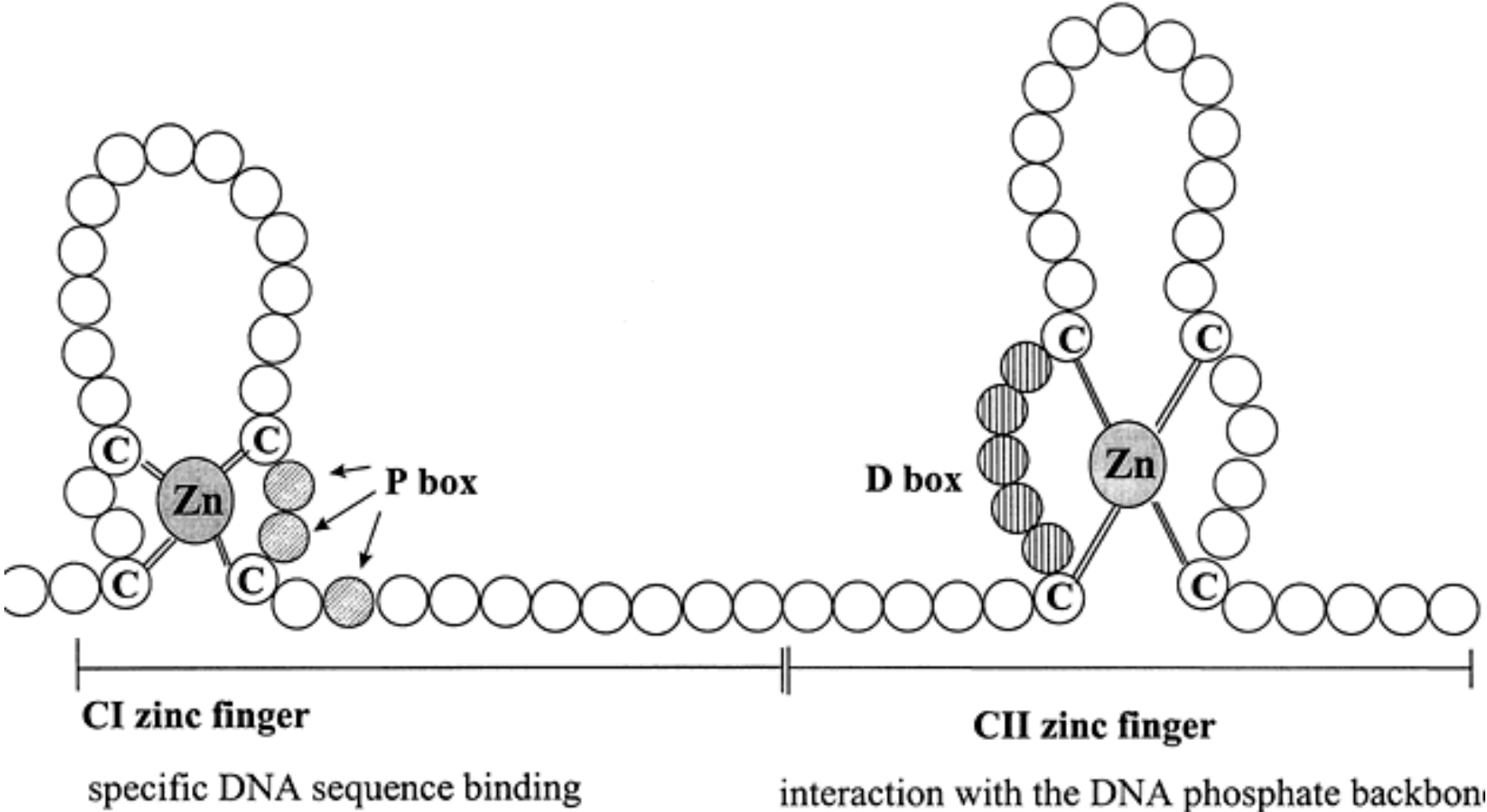
- Epidemiologic studies show an increased mortality from cardiovascular diseases in people with higher serum copper levels.
- **Higher serum copper concentrations in women using oral contraceptives is well known**, with uncertainty about the influence of newer progestin compounds in oral contraceptives on serum copper concentration. This issue is of particular interest in the light of recent findings of an increased risk of venous thromboembolism in users of oral contraceptives containing newer progestins like desogestrel compared to users of other oral contraceptives.
- Nonpregnant and nonlactating women aged 18-44 y (n = 610).
- **While elevated serum copper concentration was found in users of all types of oral contraceptives, elevation was more pronounced among women taking oral contraceptives with antiandrogen effective progestins.**
- **High serum copper concentration--a well-known effect of oral contraceptive, use--has been linked to increased mortality from cardiovascular disease and,**
- **May be part of vulnerability to IBD.**

[Eur J Clin Nutr.](#) 1998 Oct;52(10):711-5. **Effect of oral contraceptive progestins on serum copper concentration.**

[Toxicol Sci.](#) 2017 Apr 1;156(2):469-479. **Combined Effects of Gestational Phthalate Exposure and Zinc Deficiency on Steroid Metabolism and Growth.**

International Union of Biochemistry and Molecular Biology Volume 38, Number 2, March/April 2012, Pages 107–113
Copper Excess, zinc deficiency, and cognitive loss in Alzheimer's disease

Sex Steroid Binding Requires Zinc Fingers



Estriol and T anti-inflammatory

- It's been known for decades that females are more susceptible than men to inflammatory autoimmune diseases, including multiple sclerosis, rheumatoid arthritis, and psoriasis.
- In many female patients with these diseases have clinical improvements or remission during pregnancy with a temporary "rebound" exacerbation postpartum.
- These clinical observations indicate an effect of sex hormones on disease and suggest the potential use of the male hormone testosterone and the pregnancy hormone estriol, respectively, for the treatment of inflammation as part of MS (or other inflammatory conditions).
- **Both testosterone and estriol have been found to induce anti-inflammatory as well as neuro-protective effects.**
- Findings from two recent pilot studies of transdermal testosterone in male MS patients and oral estriol in female MS patients are encouraging.

[Prog Brain Res.](#) 2009;175:239-51. **Estrogen and testosterone therapies in multiple sclerosis.**

Ethinyl estradiol

- Ethinyl estradiol competes with endogenous estrogens.
- The competitive adsorption of bisphenol A (BPA) and 17 α -ethinylestradiol (EE2) with different endocrine disrupting compounds (EDCs), such as estrone (E1), β -estradiol (E2), and estriol (E3) was investigated in the water-sediment system.

[Mar Drugs](#). 2014 Mar 7;12(3):1349-60. **Single and competitive adsorption of 17 α -ethinylestradiol and bisphenol A with estrone, β -estradiol, and estriol onto sediment.**

EEs as EDCs

- EDCs are compounds that disrupt wildlife's reproductive system by imitating and blocking the activity of natural hormones.
- The synthetic EDCs 17 α -ethinylestradiol (EE2) and bisphenol A are frequently found in wastewater, marine water, and sediments.
- EE2 is generally used in contraceptive pills.
- Because of the long half-life, the toxicity of EE2 in fish was determined to be 10–50 times greater than estrone (E1) and β -estradiol (E2).

[Mar Drugs](#). 2014 Mar; 12(3): 1349–1360. Published online 2014 Mar 7. **Single and Competitive Adsorption of 17 α -Ethinylestradiol and Bisphenol A with Estrone, β -Estradiol, and Estriol onto Sediment**

National Toxicology Program. Abstract for TR-548 - Ethinyl Estradiol (CASRN 57-63-6) July 2010. Toxicology and Carcinogenesis Study of Ethinyl Estradiol (CAS No. 57-63-6) in Sprague-Dawley Rats (Feed Study)

ER beta – tight junctions

- Estradiol modulates paracellular permeability and tight junction function in endothelia, reproductive tissues and intestinal tissues.
- Estrogen receptors are expressed in intestinal epithelial cells, and oestradiol regulates epithelium formation.
- Examined the effects of oestrous cycle stage, oestradiol benzoate (EB), and progesterone (P) on colonic paracellular permeability in the female rat, and whether EB affects expression of the TJ proteins in the rat colon and the human colon cell line Caco-2.
- **Oestradiol increased occludin mRNA and protein in the colon, but not zona occludens. EB enhanced occludin and junctional adhesion molecule (JAM)-A.**
- This effect is blocked by estrogen receptor antagonists.
- Estrogen reinforces intestinal epithelial barrier through ER beta-mediated up-regulation of the transmembrane proteins occludin and JAM-A determining paracellular spaces.
- These findings highlight the importance of the ER beta pathway in the control of colonic paracellular transport and mucosal homeostasis.
- Emphasize role of estriol and other natural ER beta agonists in IBD.

[J Physiol.](#) 2009 Jul 1;587(Pt 13):3317-28.. **Oestradiol decreases colonic permeability through oestrogen receptor beta-mediated up-regulation of occludin and junctional adhesion molecule-A in epithelial cells.**

Permeability

- Gut epithelial cells contain functional Ers.
- The EB-mediated decrease in epithelial permeability is mimicked by Er β research agonist DPN.
- Although both ERs were expressed in the colon, Er β predominates in normal colonic mucosa.
- Because impaired paracellular permeability is a trigger for inflammatory bowel disorders and chronic inflammation in humans,
- The Er β pathway may represent a novel target to prevent or limit the epithelial barrier defect in these diseases.

The presence of functional estrogen receptors in intestine epithelial cells. *Endocrinology*. 1993.132, 426–430.

Expression of estrogen receptor (ER) subtypes and Er β isoforms in colon cancer. *Cancer Res* 61, 632–640.

Birth Control Pills Block ER beta

- Oral contraceptives are widely used; however, these drugs occasionally cause liver injury.
- Female Wistar rats were given intraperitoneally a combination of estradiol (35 ng/kg of 17 alpha-Ethynylestradiol) and progesterone (2 microg/kg of Norethindrone), each dose being similar to that contained in oral contraceptives (EP treatment).
- After 24 hr, a sublethal dose of lipopolysaccharide (LPS; 5 mg/kg) was injected via the tail vein.
- Liver histology in rats given EP treatment intraperitoneally followed by an injection of LPS 24 hr later revealed pronounced liver damage with massive necrosis.
- Was blocked completely by antibiotics.
- **These results indicate that birth control pills block estriol action of the gut, increases portal increase of gut-derived endotoxin, increasing gut permeability and liver injury and vice versa.**

[Alcohol Clin Exp Res.](#) 2002 Aug;26(8 Suppl):70S-74S. **Oral contraceptives worsen endotoxin-induced liver injury in rats.**

Estrogen Receptor beta

- Colorectal carcinoma is an important cause of death in inflammatory bowel diseases.
- Females show a lower incidence to hormonal factors so this study evaluated a role of estrogen receptors in carcinoma-associated colitis.
- 48 patients affected by long-lasting pancolitis were retrospectively investigated. Samples were divided into four groups: UC, low-grade dysplasia/high-grade dysplasia (UC-HGD), and CAC. Normal colon samples were used as controls.
- ER-beta expression revealed an impressive reduction in CAC .
- **ER-beta fall could be considered as a biomarker of UC-dysplasia progression.**
- It occurs in HGD and overt neoplasia; in LGD shows a normal expression.

[Scand J Gastroenterol.](#) 2015 Aug;50(8):1002-10. **The sharp decline of beta estrogen receptors expression in long-lasting ulcerative-associated carcinoma**

Estriol

- Estriol binds preferentially to estrogen receptor beta.

Physiological Reviews Published 1 July 2007 Vol. 87 no. 3, 905-931. **Estrogen Receptors: How Do They Signal and What Are Their Targets**

Literature Review

[Altern Med Rev.](#) 1998 Apr;3(2):101-13. **Estriol: safety and efficacy.**

[Menopause.](#) 2017 Apr 3. **Estriol: emerging clinical benefits.**

[Climacteric.](#) 2017 Aug;20(4):321-330. **The efficacy and safety of estriol to treat vulvovaginal atrophy in postmenopausal women: a systematic literature review.**

Physiological Reviews. **81** (4): 1535–65. Mechanisms of estrogen action.

Pharmacological Reviews. **58** (4): 773–81. International Union of Pharmacology. LXIV. Estrogen receptors".

Estriol

- Selectively binds ER beta.

PostGrad Med. 2009;121(1):1-13. The bioidentical hormone debate: are bioidentical hormones (estradiol, estriol, and progesterone) safer or more efficacious than commonly used synthetic versions in hormone replacement therapy?

Estriol

- Review: Out of 393 articles 72 articles on estriol.
- Estriol has an immunoregulatory role by reducing pro-inflammatory cytokines.
- Important new therapeutic option for chronic autoimmune, inflammatory and neurodegenerative illnesses.
- It's a relatively weak estrogen so even potential for treatment in men.

[Menopause](#). 2017 Apr 3. **Estriol: emerging clinical benefits.**

Department of Internal Medicine 2School of Medicine
3Section of Endocrinology, Texas Tech University Health
Science Center

Estriol

- Estriol is the main estrogen in pregnancy but has received less attention outside gestation.
- Pregnancy has an immunosuppressive effect on many autoimmune diseases such as multiple sclerosis, psoriasis, thyroiditis, uveitis, and rheumatoid arthritis.
- Emerging evidence that estriol has potential immuno-modulatory benefits for many disease states including autoimmune, inflammatory, and neurodegenerative conditions.
- Estriol appears to offer a potentially cost-effective approach to a variety of conditions such as menopausal symptoms, osteoporosis, cancer, hyperlipidemia, vascular disease, and multiple sclerosis.

[Menopause](#). 2017 Apr 3. **Estriol: emerging clinical benefits.**

Department of Internal Medicine 2School of Medicine 3Section of Endocrinology, Texas Tech University Health Science Center

Estriol

- Estriol is neuro-protective and anti-inflammatory.
- A growing number of studies using the MS animal model experimental autoimmune encephalomyelitis (EAE) support a therapeutic effect of **estriol and testosterone**.
- **Both testosterone and estriol have been found to induce anti-inflammatory as well as neuroprotective effects.**
- Findings from two recent pilot studies of transdermal testosterone in male MS patients and oral estriol in female MS patients are encouraging.

[Prog Brain Res.](#) 2009;175:239-51. **Estrogen and testosterone therapies in multiple sclerosis.** Department of Neurology, Geffen School of Medicine, University of California Los Angeles

Testosterone Metabolite

- 3-Beta Diol.
- Estrogen receptor beta agonist.

Reproductive Biology and Endocrinology .

20064:51. Effects of 3-beta-diol, an androgen metabolite with intrinsic estrogen-like effects, in modulating the aquaporin-9 expression in the rat efferent ductules

ER receptor beta as ligand candidate or anti-inflammatory action

- Protective effects of pregnancy during MS have led to clinical trials of estriol, the pregnancy estrogen, in MS.
 - Since estriol binds to estrogen receptor beta, ER beta ligands could represent the "next generation estriol" treatment.
 - ER beta ligand treatment was protective in EAE in both sexes and across genetic backgrounds.
 - Neuroprotection was shown in spinal cord, sparing myelin and axons, and in brain, sparing neurons and synapses. Longitudinal in vivo MRIs showed decreased brain atrophy in cerebral cortex gray matter and cerebellum during EAE.
 - ER beta ligands as new anti-inflammatory and neuroprotective tools.
- [J Neuroimmunol.](#) 2017 Mar 15;304:63-71 **Bedside to bench to bedside research: Estrogen receptor beta ligand as a candidate neuroprotective treatment for multiple sclerosis.**

Gender differences in autoimmune diseases

- Higher incidence in females vs. males
- Systemic lupus erythematosus, rheumatoid arthritis, Graves disease and multiple sclerosis.
- Though males have more autoimmune nephropathies.
- Differences linked to sex hormones.

Age and sex associations of 40 autoimmune diseases. *Am. J. Med.* 1994;96:457–462

Welcome to the Microgenderome

- Division of Gastroenterology, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School and Harvard Digestive Diseases Center, Boston, MA 02115, USA.

[Science](#). 2013 Mar 1;339(6123):1044-5. doi: 10.1126/science.1236226. [Flak MB](#), [Neves JF](#), [Blumberg RS](#).

Testosterone & Gut Immunity

- The composition of the commensal microbiota of male and female animals diverged at the time of puberty; maleness and femaleness exerted specific influences on the composition of the microbiota.
- REMOVE MICROBIOTA IN FEMALES – MORE T
- REMOVE MICROBIOTA IN MALES – LESS T.
- Bi-directionality between T levels and microbiota.
- Commensal microbiota may “record” the state of maleness, which is then “played back” to the host in a self-reinforcing program of masculinizing action.
- May be part of basis of protection of males against autoimmunity (& 3-Beta Diol)
- Gut – T communications part of immunity
- Our results favor a “two-signal model” of gender bias, in which hormones and microbes together trigger protective pathways and communicate with each other.

[Immunity](#). 2013 Aug 22;39(2):400-12.

[Science](#). 2013 Mar 1;339(6123):1044-5. .

ER beta improves microbiome diversity

- Estrogen receptor beta directly affects the composition of intestinal bacteria.
- To investigate the effects of both receptors and diet on intestinal microorganisms, female mice were fed either a fiber-rich diet containing plant-derived estrogenic compounds called isoflavones (complex diet) vs. an isoflavone-free diet that was rich in highly refined sugars for two weeks, (a simple diet).
- The composition of the fecal bacteria was analyzed during both feedings.
- Distinct patterns for Lactobacillales were exclusive to and highly abundant among mice fed a complex diet containing isoflavones.
- They linked **ER betas signaling to healthier and more diverse microbime.**

[Appl Environ Microbiol.](#) 2013 Sep;79(18):5763-73. **Diet complexity and estrogen receptor β status affect the composition of the murine intestinal microbiota.**

ER beta & the gut

- A large body of evidence from preclinical studies indicates that expression of the **estrogen receptor beta (ER β /ESR2) demonstrates an inverse relationship with the presence of colorectal polyps** and stage of tumors, and can mediate a protective response.
- Natural compounds, including phytoestrogens, or synthetic ER β selective agonists, activate or upregulate ER β in the colon, and promote apoptosis in preclinical models and in clinical experience.
- ER beta signaling has been associated with a reduction in polyp formation and, in rodent models of CRC, and to lower incidence of colon adenocarcinoma.
- Er β represents a novel clinical approach for management of colorectal adenomatous polyps and prevention of colorectal carcinoma in high risk patients.

[Cancer Lett. 2016 Mar 1; 372\(1\): 48–56.](#) **Estrogen Receptor Beta as Target for Colorectal Cancer Prevention**

Estrogens Colorectal Cancer

- The Women's Health Initiative showed that pre-menopausal women are 40% less likely to suffer from CRC compared to age-matched men.
- Older women, in comparison, have a worse overall survival prognosis than similarly aged men, because of the loss of estrogen associated with menopause.
- In IBD patients followed for more than 10 years, the overall risk for CRC was 60% higher among men than women.
- Suggesting that female sex hormones, specifically estrogen, form the basis for this protective effect in women.

ER beta Soy

- Study assessing the safety and effect of the supplementation of a patented blend of dietary phytoestrogens and insoluble fibers on estrogen receptor (ER)- β and biological parameters in sporadic colonic adenomas.
- A randomized, double-blind placebo-controlled trial.
- Patients scheduled to undergo surveillance colonoscopy for previous sporadic colonic adenomas were identified, and 60 eligible patients were randomized to placebo or active dietary intervention (ADI) twice a day, for 60 d before surveillance colonoscopy.
- ADI was a mixture of 175 mg milk thistle extract, 20 mg secoisolariciresinol and 750 mg oat fiber extract.
- ER- β and ER- α expression, apoptosis and proliferation (Ki-67) were assessed in colon samples.
- ADI administration showed a significant increases in ER- β /ER- α proteins in ADI vs. placebo group with significant control of proliferation.

[World J Gastroenterol.](#) 2013 Jul 21;19(27):4325-33. **Phytoestrogens/insoluble fibers and colonic estrogen receptor β : randomized, double-blind, placebo-controlled study.**

ER beta in the gut

- A large body of evidence from preclinical studies indicates that expression of the estrogen receptor beta (ER β /ESR2) demonstrates an inverse relationship with the presence of colorectal polyps and stage of tumors, and can mediate a protective response.
- Natural compounds, including phytoestrogens, or synthetic ER β selective agonists, can activate or upregulate ER β in the colon and promote apoptosis in preclinical models and in clinical experience.
- Increased ERB signaling linked to a reduction in polyp formation and, in rodent models of CRC, has been shown to lower incidence of colon adenocarcinoma.
- ER beta:
 - Repairs broken DNA fragments
 - Represses oncogenes
 - Tightens gut permeability by up-regulating adhesion proteins

[Cancer Lett. 2016 Mar 1; 372\(1\): 48–56.](#) **Estrogen Receptor Beta as Target for Colorectal Cancer Prevention.** [Cecilia Williams](#), [Alfredo DiLeo](#), [Yaron Niv](#), and [Jan-Åke Gustafsson](#)¹ Center for Nuclear Receptors and Cell Signaling, Department of Biology and Biochemistry, University of Houston

ER beta agonists

- The administration of dietary phytoestrogens, with a higher affinity for ER β than for ER α .
- Are potential sources for management of adenomatous polyps and protection of the gut.

Estrogen receptor beta acts as a dominant regulator of estrogen signaling. *Oncogene*. 2000;19:4970–4978.

Oestrogen and the colon: potential mechanisms for cancer prevention. *The Lancet Oncology*. 2008;9:385–391

Milk Thistle

- The major active constituent of milk thistle seeds extract silymarin, silibinin, binds selectively to Er β .
- Rats fed silibinin showed reduced aberrant crypt foci formation when exposed to toxic compounds.

Evidences for antiosteoporotic and selective estrogen receptor modulator activity of silymarin compared with ethinylestradiol in ovariectomized rats. *Phytomedicine*. 2010;17:116–125.

Inhibition of azoxymethane-induced colonic aberrant crypt foci formation by silibinin in male Fisher 344 rats. *Cancer Prev Res (Phila)* 2008;1:376–384

Milk thistle

- Mice fed silibinin also had reduced formation of polyps.

Pharm Res. 2009;26:2558–2567. Silibinin suppresses spontaneous tumorigenesis in APC min/+ mouse model by modulating beta-catenin pathway

Cancer Res. 2010;70:2368–2378. Chemoprevention of intestinal tumorigenesis in APCmin/+ mice by silibinin.

Milk Thistle + Flaxseeds (lignins)

- Mice fed silymarin, lignin, or both, significantly reduces total number of polyps, the total number of polyps in the distal small intestine.
- Silymarin in combination with lignin achieved the greatest reductions of polyps and also increased apoptosis in adenomatous tissue to levels similar to those found in nonadenomatous tissue.
- Lignin may enhance the activity of silymarin by delaying its absorption from its preferred uptake in the duodenum to the more distal ileal segments.

Dietary-induced ERbeta upregulation counteracts intestinal neoplasia development in intact male ApcMin/+ mice. *Carcinogenesis*. 2010;31:269–274

Polyps

- A randomized, double-blind, placebo-controlled clinical study.
- Sixty subjects received dietary supplementation or placebo for 60 days.
- After 60 days, 63% of subjects given the combination mixture had ER β protein levels above the median.
- Increased ER β expression showed a trend to correlate with markers of apoptosis but not for the placebo group.

Phytoestrogens/insoluble fibers and colonic estrogen receptor β : randomized, double-blind, placebo-controlled study. *World J Gastroenterol.* 2013;19:4325–4333.

Milk Thistle + Flax

- A case in which the same mixture achieved reduction in size and number of small intestinal polyps in a patient affected by Lynch syndrome.

Intestinal microbiota: The explosive mixture at the origin of inflammatory bowel disease? World journal of gastrointestinal pathophysiology. 2014;5:550–559

Milk Thistle

- Silibinin suppressed tumor growth without safety concerns,
- Decreased the proliferation index and strongly inhibited tumor angiogenesis.
- Silibinin may have potential as an antimetastatic agent for patients with existing cancer or as prevention, boosts ER beta, boosts epithelial tightness and protection.

Cancer Metastasis Rev. 2010;29:447–463. Antimetastatic efficacy of silibinin: molecular mechanisms and therapeutic potential against cancer.

Ethinyl Estradiol (EE) as EDC

[Reprod Biol Endocrinol](#). 2014 May 15;12:40.

Use of antagonists and morpholinos in loss-of-function analyses: estrogen receptor ESR2a mediates the effects of 17alpha-ethinylestradiol on primordial germ cell distribution in zebrafish.

ER beta vs. EE

- **Estrogen receptor-beta was significantly decreased by EE.**
- ER alpha is increased.
- The decreased transcription of male-predominant genes supports a demasculinization of testes by EE2
- Net effect, less T signaling, less ER beta signaling, increased ER alpha but protective ratios disrupted.
- Sets the scene for gut unwellness.

[Comp Biochem Physiol C Toxicol Pharmacol.](#) 2014 Aug;164:35-42. **Short-term treatment of adult male zebrafish (*Danio Rerio*) with 17 α -ethinyl estradiol affects the transcription of genes involved in development and male sex differentiation.**

Progestins

- **MPA reduces estrogen and progesterone receptors.**

Effects of tamoxifen, medroxyprogesterone acetate, and their combination on human endometrial estrogen and progestin receptor concentrations, 17 beta-hydroxysteroid dehydrogenase activity, and serum hormone concentrations. American Journal of Obstetrics and Gynecology. 1982 Jun 15; 143(4):382-8.

ER beta Research???

- ER β has a predominantly anti-proliferative, pro-apoptotic and tumor-suppressive role but controversial.
- Our results have **demonstrated marked variation in the ability of commonly used commercially available ER β antibodies to accurately detect Er β .**

[Mol Cell Endocrinol](#). 2017 Jan 15; 440: 138–150.

Comprehensive assessment of estrogen receptor beta antibodies in cancer cell line models and tissue reveals critical limitations in reagent specificity

Candidiasis

- Candidiasis, the infection caused by *Candida albicans*, is one of the most common infections of the oral cavity in humans.
- Several previous studies have demonstrated an increased frequency of vaginal candidiasis with oral birth control.
- This analytic, case-control study included 40 non-pregnant women divided into two groups: 20 who used oral contraceptive pills and 20 who did not. The frequency of positive cultures and the number of *Candida* colonies were compared between the two groups.
- The number of *C. albicans* and *C. krusei* was significantly higher for the case group compared to the control group.
- The results of the present study demonstrate that oral contraceptives containing estradiol can lead to *Candida* colonization in the oral cavity.

[Iran Red Crescent Med J.](#) 2016 Aug 17;18(10):e38909. **Frequency of Candidiasis and Colonization of *Candida albicans* in Relation to Oral Contraceptive Pills.**

Berkson's IBD protocol

- Agonists of ER beta – estriol, milk thistle & flaxseed (Berkson's seed only muffins)
- Get off birth control pills
- Test and support androgens if necessary
- Identify and avoid food intolerances & treat seasonal allergies: off gluten and dairy
- Promote butyrate production (replacement vs. resistant starch)
- Use of DHEA
- Coconutculture.com
- Melatonin
- Curcumin
- High dose Fish oil (omega-3)
- Swab oral mucosa, treat candidiasis with nyastatin +/- xylitol
- Sometimes oxytocin nasal spray
- Multi-mineral with zinc: balance zinc to copper
- Need a trial to replicate.
- Swab mouth/nasal cavity

[Nutrients](#). 2017 Jul 14;9(7). pii: E756. **Effects of Consuming Xylitol on Gut Microbiota and Lipid Metabolism in Mice.**

Identify & Avoid Food Intolerances

- Food antibodies in serum of 80 patients with active UC were determined by standard enzyme-linked immuno sorbent assay (ELISA).
- 83.8% of patients (67/80) were found to be seropositive for food intolerance.
- Active UC patients have high seropositive in food intolerance, particularly in female and young patients (China).

[Asia Pac J Clin Nutr.](#) 2016;25(3):529-33. **Food intolerance prevalence in active ulcerative colitis in southwest China.**

Allergies

- Chronic **ulcerative colitis** due to pollen allergy with six case reports.
- **ROWE AH**, Acta Med Scand. 1955 Aug 30;152(2):139-51..
- Chronic **ulcerative colitis** and regional enteritis; their **allergic** aspects.
- **ROWE**. Ann Allergy. 1954 Jul-Aug;12(4):387-402. Chronic **ulcerative colitis**, an **allergic** disease.
- **ROWE**. Ann Allergy. 1949 Nov-Dec;7(6):727-51

Recommended colectomy, stat.

Melissa



- 27 years old
- Ulcerative Colitis, inflammatory arthritis, 50 polyps+ and moderate dysplasia
- Started one year after on BCP and antibiotics for acne
- recommended colectomy the next week
- Uceris
- Cortifoam
- Lialda (mesalazine)
- Prednisone
- Flagyl

Recurrent Diverticulitis

- 63 yr. old female
- 20 bouts recurrent severe diverticulitis
- Over 6 months
- Past 19th episode, treated with high dose antibiotics by Austin Regional Gastroenterology
- With present 20th severe acute episode, recommended endoscopic removal of affected bowel
- Instead:
- 3 mg of estriol
- 3 mg of T
- And Berkson protocol
- Rapid relief within 2 days
- No more recurrences over 6 years now

Helpful Links

Email:

admin@drlindseyberkson.com

Substack- Agile Thinking:

<https://drlindseyberkson.substack.com/>

Mentoring:

<https://drlindseyberkson.com/mentoring/>

Membership:

www.drlindseyberkson.com/membership

General Website:

www.drlindseyberkson.com