Fibroids, Endometriosis, PCOS, Autoimmune Diseases and More: Managing Multiple Disorders in One Body

Felice L. Gersh, MD

Medical Director

Integrative Medical Group of Irvine

Affiliate Faculty

Fellowship in Integrative Medicine

University of Arizona School of Medicine

Integrative Medical Group of Irvine

Conditions which can exist in one body

PCOS

Endometriosis (Adenomyosis)

Uterine Fibroids

Cardiovascular Disease

Autoimmune Disorders:

auto-imminue thyroid!!

What links them together?

- **Environmental toxicants**
- **Chronic low level systemic inflammation**
- **Abnormal function of Matrix Metalloproteinases**
- **Hormonal imbalances**
- **Nutritional deficiencies**
- **Circadian rhythm dysfunction**
- **Gut microbiome dysbiosis**

Chronic low levels of inflammation

- PCOS: a foundationally inflammatory condition with documented elevated levels of inflammatory cytokines, such as tumor necrosis factor alpha, and with upregulated macrophages
- Endometriosis: peritoneal inflammation with increased levels of inflammatory cytokines measured in the peritoneal fluid

Chronic low levels of inflammation

- Fibroids: inflammation within the myometrium
- Autoimmunity: a state on elevated inflammation with systemically elevated inflammatory cytokines
- Autoimmune thyroiditis: the thyroid is in a state of inflammation

Matrix metalloproteinases- conventional view

- There are abnormal functioning MMPs in each
- A group of enzymes that, in concert, are responsible for the degradation of most extracellular matrix proteins during organogenesis, growth, and normal tissue turnover
- The expression and activity of MMPs in adult tissues is normally quite low, but increases significantly in various pathological conditions that may lead to unwanted tissue destruction, such as inflammatory diseases, tumor growth, and metastasis

Sorsa T et al. Oral Dis. 2004 Nov;10(6):311-8

Matrix metalloproteinases- expanded view

- MMP web-interconnected in a complex protease web-there are protease and protease inhibitor families
- MMPs regulate cell behavior through finely tuned and tightly controlled proteolytic processing of a large variety of signaling molecules that can also have beneficial effects in disease resolution

Exposure to endocrine disrupting chemicals

- Female fetus is susceptible to environmentally induced reproductive abnormalities
- Gonadal organogenesis is sensitive to synthetic hormones during a critical fetal exposure window
- Reproductive diseases may not appear until decades after exposures
- Many female reproductive disorders co-occur

Gut microbiome – linked to all aspects of health

- Need great diversity of organisms
- Need large numbers of commensals
- Need intact gut barrier integrity
- Need adequate prebiotic foods to maintain a healthy microbiome
- Need many phytonutrients from plant foods
- Need to avoid antibiotics, food additives, chemicals in water, infections, high stress, poor sleep

Gut inflammation and dysbiosis

- Leaky gut-compromised gut barrier integrity
- SIBO-small intestinal bowel overgrowth
- Reduced production of short chain fatty acids
- Reduced production of stomach acid and digestive enzymes
- Malabsorption-malnutrition, poor detoxification
- Irritable bowel syndrome
- Loss of immune tolerance

Bisphenol A (BPA) and gut microbiota

Many studies have demonstrated the metabolic-disrupting effects of BPA on liver and pancreatic function. Now there is data on the possible effects of BPA on the metabolic diversity of the intestinal microbiota

- Dietary intake may influence the gut microbiota composition and functions
- In mice fed BPA, there was a significant reduction of species diversity

Lai KP et al. Environ Pollut. 2016 Aug 20. SO269-7491(16)

High fat diet (HFD) and systemic inflammation

- HFD induced macrophage infiltration and inflammation in the adipose tissue
- HFD increased circulating pro-inflammatory cytokines
- HFD increased both plasma and fecal endotoxin levels and resulted in dysregulation of the gut microbiota
- HFD induced colonic inflammation and increased expression of pro-inflammatory cytokines, induction of Toll-like receptor 4 (TLR4), iNOS, COX-2, and activationof NF Kappa B in the colon

Kim KA et al. PLOS one. 2012;7(10):47713

HFD and systemic inflammation

- HFD reduced expression of tight junction-associated proteins claudin-1 and occludin in the colon
- HFD induces inflammation by increasing endotoxin levels in the intestinal lumen as well as in the plasma by altering the gut microbiota composition and increasing its intestinal permeability through the induction of TLR4, thereby accelerating obesity

Kim KA et al. PLOS one. 2012;7(10):47713

Endometriosis

- Affects 10-15% of all reproductive women
- Characterized by ectopic endometrium
- Major cause of infertility and chronic pelvic pain
- Associated with several chronic diseases: cancer (ovarian, breast, endometrial, melanoma), cardiovascular diseases, autoimmune diseases (SLE, RA, IFD, Celiac, MS, Sjogren's), asthma, allergic manifestations

Nielsen NM et al. Hum Reprod. 2011;26(6):1555-9

Various theories on origins of endometriosis

- Hypothesis: EDC exposures during embryogenesis increases risk, and subsequently as an adult, hormone, immune, and/or EDC irregularities are required for disease onset
- Evidence supporting an environment etiology includes metals/trace elements, dioxins, and other POP's and non-persistent chemicals such as phthalates

Smarr MM et al. Fertil Steril. 2016 Jul 15. Soo15-0282(16)61389-4

Endometriosis

- Primate study links organochlorine exposure to endometriosis
- Endometriosis lesions have increased expression of aromatase, resulting in increased production of estrogen
- Estrogen receptor Beta is up regulated
- Adult exposure to organochlorines has been shown to interfere with both hormonal regulation and immune function and can promote endometriosis

High fat diet-induced gut microbiota

- HFD causes dysregulation of the gut microbiota (dysbiosis), leading to growth of Enterobecteriaceae and the production of endotoxin
- HFD increases both plasma and fecal endotoxin levels
- Endotoxin induces inflammation via the TLR4 signaling pathway at both systemic and intestinal levels

HFD and endometriosis

- Chronic exposure to dietary high-fat intake has been linked to greater systemic inflammation and oxidative stress
- Endometriosis is associated with greater systemic inflammation and oxidative stress
- HFD significantly increased an endometriosis mouse model, with no significant changes in weight, sex hormones, or insulin levels relative to control diet fed mice

Heard ME et al. Endocrinology. 2016 Jul;157(7):2870-82

HFD and endometriosis

- HFD exacerbates endometriosis outcome!
- This occurs in the absence of ovarian dysfunction and insulin resistance in mice

Heard ME et al. Endocrinology. 2016 Jul;157(7):2870-82

HFD and endometriosis

- HFD promotion of “endometriosis lesions” was associated with reductions in stromal estrogen receptor 1 isoform and progesterone receptor expression
- Associated with increased macrophage infiltration, higher stromal proliferation, and enhanced expression of pro-inflammatory and pro-oxidative stress pathway genes

Heard ME et al. Endocrinology. 2016 Jul;157(7):2870-82

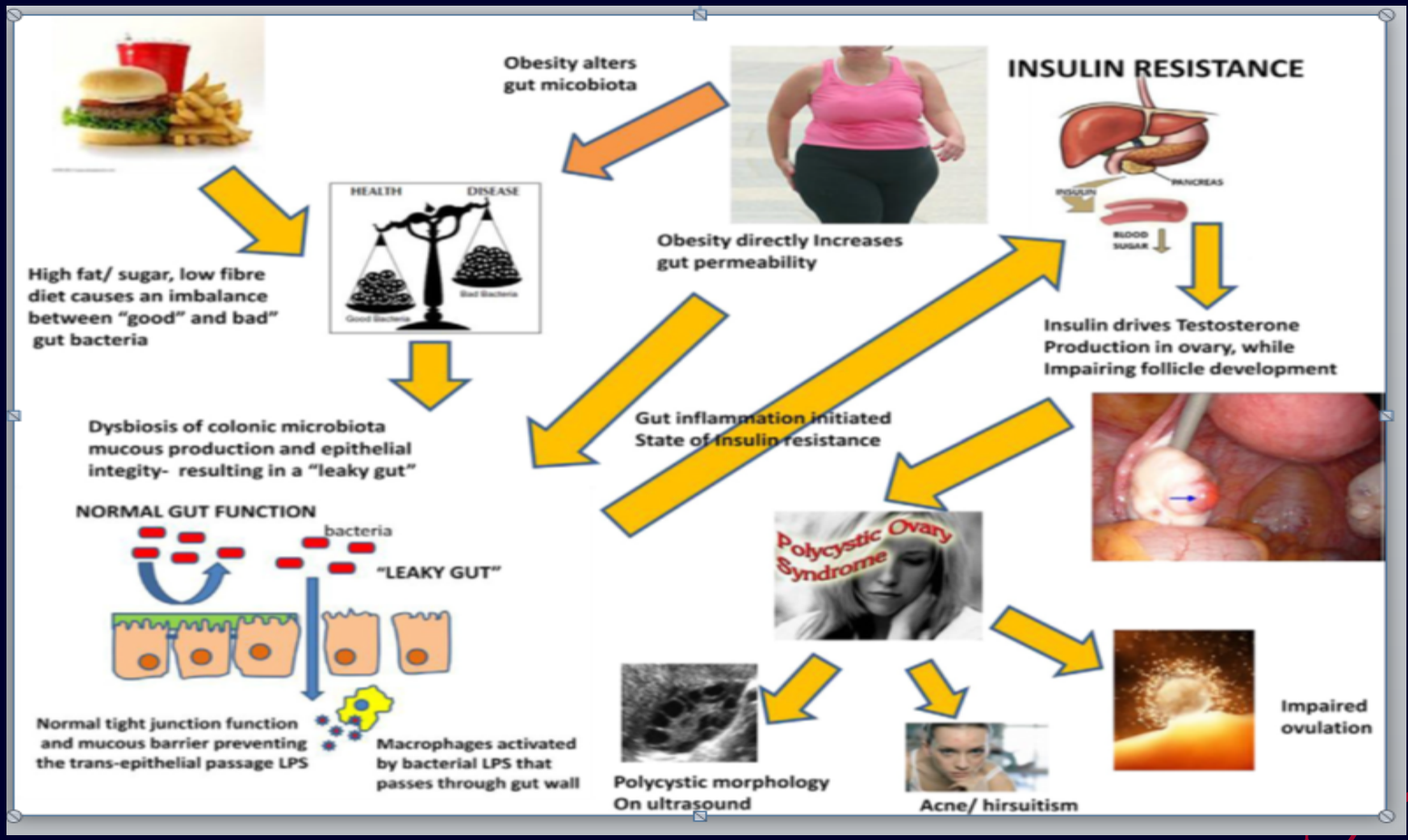
BPA and a high fat diet (HFD) show similar effects on the gut microbiome

- BPA and a high fat/high sugar (HFD) diet favored the growth of Proteobacteria - a microbial marker of dysbiosis
- Growth induction of the family Helicobacteraceae and reduction of Firmicutes and Clostridia populations in mice fed BPA or HFD

Lai KP et al. Environ Pollut. 2016 Aug 20. SO269-7491(16)

Integrative Medical Group of Irvine

Role of HFD and PCOS



Sharing the same body

- Study of 220 premenopausal women, aged 40-50
- Endometriosis found in 40% of women with adenomyosis, 23% with fibroids, 34% with both adenomyosis and fibroids

J Med Assoc Thai. Naphatthalulng et al; 2012 Sep ; 95(9):1136-40

EDC's and leiomymoma cells (fibroids)

- Fibroids develop in the uterine myometrium and are sensitive to ovarian hormones
- Fibroids are target sites for endocrine disruptors
- Organochlorine pesticides act as estrogen receptor agonists in rat uterine myometrial cells

Hodges LC, et al. Toxicol Sci. 2000 Apr; 54(2): 355-64

EDC's and leiomymoma cells (fibroids)

- EDC's have been shown to promote the growth of leiomyoma cells in vitro and in vivo
- Includes: phyotestrogens, organochlorine pesticides, pharmacologic compounds

Walker Cl. Recent Prog Horm Res. 2002;57:277-94

Adenomyosis and leiomyomas

- Women with both adenomyosis and leiomyomas have a number of different clinical features compared with women with only leiomyomas
- Women with substantial pain despite smaller fibroid burden more likely to have concomitant adenomyosis

Hum Reprod. Taran et al. 2010 May;25(5):1177-82

Causative factors for carcinogenesis: fibroids, endometriosis, adenomyosis

- Hormonal factors
- Inflammation
- Familial predisposition
- Genetic alterations
- Growth factors
- Oxidative stress
- Low parity, early menarche, and infertility

Risk for ovarian and endometrial cancers in women with endometriosis

Nearly 10,000 person-years follow up in endometriosis cohort group

36,000 person-years in comparison cohort

- Ovarian cancer-over **4.5X higher risk** in endometriosis cohort group
- Endometrial cancer-over **4X higher risk** in endometriosis cohort group

Int J Gynecol Cancer.2015 Jul;25(6):968-76

Integrative Medical Group of Irvine

Risk for ovarian and endometrial cancers in women with adenomyosis

- Ovarian cancer- **5.5X higher risk** in adenomyosis cohort group
- Endometrial cancer-over **5X higher risk** in adenomyosis cohort group

Int J Gynecol Cancer.2015 Jul;25(6):968-76

Risk for colorectal cancer with coexistent adenomyosis and endometriosis

- Huge increased risk for colorectal cancer in women with both adenomyosis and endometriosis

13 – fold increased risk!!

(It is related to dysbiosis of the gut microbiome)

Int J Gynecol Cancer.2015 Jul;25(6):968-76

Fibroid incidence and PCOS

- The incidence of uterine leiomyoma (fibroid) found to be 65% higher among women with PCOS than women without PCOS

Fertil Steril. 2007 May;87(5): 1108-1115

Study of infertility patients

- Study: 46% (285 pts) had Grades I and II endometriosis, 54% (336 pts) had Grades III and IV
- 21% had fibroids and Grades I and II endometriosis
- 54% had fibroids and Grades III and IV endometriosis
- 77% of the PCOS women (31 women) had Grades I and II endometriosis

Minerva Ginecol. 2016 Jun;68(3): 250-8

Integrative Medical Group of Irvine

Development and stimulation of fibroids

- Commonly thought that uterine fibroids result from hyper-stimulation of myometrium by ovarian hormones
- Cytokines and growth factors are intermediate elements through which the ovarian hormones may exert their growth-stimulatory effects on fibroids
- Amounts of IGF 1 extracted from leiomyomas were distinctly higher in comparison to control myometrium and they increased as a function of tumor growth

Eur J Obstet Gynecol Reprod Biol. 2007 Feb;130(2): 238-44

Factors facilitating fibroid growth

- Many different growth factors play a role in leiomyomas (fibroids)
- Dysregulated mTOR signaling is a component of leiomyoma etiology – an activated mTOR signaling pathway is essential for fibroid growth

Human Reprod Update. 2011 Nov-Dec;17(6):772-90

The autoimmune connection

- It has been proposed that functional autoantibodies could contribute to the development of PCOS – representing hyper-function of follicular recruitment in the ovaries (similar to hyperthyroidism in Graves Disease)
- Higher levels of autoimmune thyroid found in studies of PCOS women
- Over 30% prevalence of thyroid antibodies in women with PCOS
- PCOS women have higher incidence of anti-histone and anti-dsDNA antibodies

Gleicher N et al. Autoimmun Rev. 2007 ;7:42-5

Thyroid and PCOS

- Prevalence of subclinical hypothyroidism in women with PCOS was 17% and 6% in the non-PCOS women.
- One study found incidence of autoimmune thyroid was present in 43% of PCOS women

Gynecol Endocrinol. 2015 Jan;31(1):48-51

Chemical thyroid disruptors can cause autoimmune thyroid disease

- Thyroid disruptors include pharmaceuticals, iodine, phyto-goitrogens and synthetic compounds
- Synthetic compounds include industrial products and pesticides-massively produced and polluting the environment
- Can disrupt at any level of regulation: synthesis, metabolism, transport, cellular level- thyroid hormone signaling, metabolism, or transport

Brucker-Davis F, et al. Presse Med. 2016 Jan;45(1)78-87

Thyroid chemical disruptors

- Industrial chemical contaminants have a variable impact on the hypothalamic-pituitary-thyroid axis
- There is currently a very concerning upsurge in the incidence of thyroid disease
- Thyroid disruptors are ubiquitous, including in our food-interfere with thyroid hormone action, biosynthesis, and metabolism
- Small doses can induce unpredictable, adverse effects

Duntas LH. Endocrine. Feb 2015; 48(1):53-64

Integrative Medical Group of Irvine

Polychlorinated biphenyls and thyroid

- Can centrally inhibit the hypothalamic-pituitary-thyroid axis, or dissociate thyroid receptor and selectively affect thyroid hormone signaling and action
- Can act as agonists or antagonists at the receptor level

Duntas LH. Endocrine. Feb 2015; 48(1):53-64

Endocrine Disruptor Chemicals

- Some environmental contaminants interact with hormones and may exert adverse consequences as a result of their actions as endocrine disrupting chemicals (EDC's)
- Include: pesticides, herbicides, heat stabilizers and chemical catalysts, plastics (BPA, Pthalates), pharmaceuticals (ethinylestradiol, diesthylstilbestrol), dietary components (phytoestrogens).

Frye, E. et al. J Neuroendocrinol. 2012 J: 24(1):144-159

Endocrine Disruptor Chemicals

- Effects across the lifespan
- Most dangerous during the “critical periods” of life when organisms are most sensitive to hormonal disruption: intrauterine, perinatal, juvenile or puberty periods
- Xenoestrogens can alter serum lipid concentrations or metabolism enzymes that are necessary for converting cholesterol to steroid hormones-can alter the production of estrogen and other steroids

Frye, E. et al. J Neuroendocrinol. 2012 J: 24(1):144-159

Endocrine Disruptor Chemicals

- EDC's can have actions via the nuclear or membrane receptor sites
- EDC's can have effects through numerous other substrates: peroxisome proliferator-activated receptor and the retinoid X receptor, signal transduction pathways, calcium influx and/or neurotransmittor receptors
- EDC's can impact reproductively-relevant processes and other functions by mimicking, antagonizing or altering steroidal actions

Frye, E. et al. J Neuroendocrinol. 2012 J: 24(1):144-159

Women with these issues are at risk for many conditions!!

- **Environmental toxicants**
- **Chronic low level systemic inflammation**
- **Abnormal function of Matrix Metalloproteinases**
- **Hormonal imbalances**
- **Nutritional deficiencies**
- **Circadian rhythm dysfunction**
- **Gut microbiome dysbiosis**

Integrative Medical Group of Irvine

Thank You!

Felice L. Gersh, M.D.

fgersh@integrativemgi.com

www.integrativemgi.com

(949) 753-7475

Integrative Medical Group of Irvine