Uterine Fibroids, Endometriosis, Adenomyosis and PCOS: Common Themes - Etiologies and Therapies

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Linked together
in the functional medicine web

- Inflammation
- Detoxification
- Blood sugar metabolism
- Immune function
- Nutrition
- Gut function

Commonalities

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

**PCOS**: chronic systemic inflammation with elevated levels of inflammatory cytokines and upregulated macrophages

**Endometriosis**: localized pelvic inflammation with increased levels of inflammatory cytokines measured in peritoneal fluid

**Uterine Fibroids**: inflammatory induced upregulation of aromatase

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**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

Endometriosis (EMS)
Endometriosis: associated with various medical issues

Affects 10-15% (some say 20%!) of all reproductive women, and up to half of all infertile women
Major cause of infertility and chronic pelvic pain, dysmenorrhea, dyspareunia, pelvic masses
Associated with cancers: ovarian, breast, endometrial, melanoma


Endometriosis: associated with various medical issues

Headaches
Arthralgias and Myalgia, Fibromyalgia, Chronic Fatigue Syndrome
Vaginal Candidiasis
Cardiovascular diseases
Autoimmune diseases: SLE, RA, IFD, Celiac, MS, Sjogren’s Syndrome, Hashimoto’s thyroiditis
Asthma, Allergies, and Eczema
Painful bladder syndrome/Interstitial cystitis
Panic Syndrome

Various theories on origins of endometriosis

**Hypothesis:** Endocrine disruptor exposures during embryogenesis increases risk, and subsequently as an adult, hormone, immune, and/or EDC irregularities are required for disease onset. Evidence supporting an environmental etiology includes higher levels of metals/trace elements, dioxins, and other POP’s and non-persistent chemicals such as phthalates.


Endometriosis, E2 Receptor and aromatase

Endometriosis lesions have increased expression of aromatase, resulting in increased production of estrogen.

Estrogen receptor Beta is up regulated.

Endometriosis

Abnormal levels of immune cells - macrophages, dendritic, natural killer cells in peritoneal cavity
The peritoneal immune cells are dysfunctional
Pro-inflammatory changes – impact on angiogenesis, apoptosis, extracellular matrix remodeling, hormonal production, fertility


Endometriosis

Extra-uterine growth of endometrial tissue
Viable endometrial cells enter peritoneum via retrograde menstruation, implantation, establishment of ectopic growths
Growths become extensively innervated and vascularized and contain mast cells
Other theories: Stem cells, genetic risk, Polymorphisms of MMP-1, Vitamin D

Burney et al. Fert and Steril, 2012;98(3):511-19
Endometriosis (EMS) and the immune system

Maybe an autoimmune disease
Stress can exacerbate symptoms
Peritoneal fluid has higher levels of some cytokines than those without EMS
Mast cells (MCs) likely central to lesion development and progression
Degranulated MCs in EMS lesion and activated MCs implicated in the associated fibrosis

Konno et al. Human Cell. 2003;16(3):144-49

Introducing the first immune cell: the mast cells

Existed over 500 million years ago
Original prototype neuro-immuno-endocrine cell
Master regulator of inflammatory interactions
(most diseases involve neuro-inflammation that worsens with stress)
A “first responder”

Theoharides. Exp Dermatol. 2017
Mast cells and estrogen receptors

Mast cells express estrogen receptors, especially ER alpha
Mast cells found in close approximation to neural elements in EMS, supports concept of active neuroinflammation and pain in EMS
Involves neuroinflammation with mast cell involvement, fibrosis, loss of function
Estrogen dependent chronic inflammatory disorder

Hart, David. 2015. Intern J of Inflam. 2012;452095

Mast cells
“Universal alarm cells”

Starts the inflammatory cascade: activation of immune cells, release of TNF alpha – only cell that stores ready-made THF alpha that can be released in seconds
Can be triggered by infection, allergens, environmental factors: pollution, emotional stress
Mast cell activation linked to cancers, CVD, connective tissue disorders, inflammation (incl brain-linked to depression and anxiety and other mental health issues), RA, Lupus, IBS, skin disease, allergy, asthma
Mast cells (MCs)

MCs link autoimmune conditions with allergies, connective tissue disorders and autonomic dysfunction, conditions that cause chronic pelvic pain in women

Stress is the number 1 trigger for mast cell activation: illness, toxicities from heavy metals, chemicals, surgery, reactions to medications, trauma (emotional and physical), lifestyle choices, environmental factors

Urb et al. PLOS Pathog. 2012;8(4)
Mast cells: play an important role in the pathogenesis of endometriosis

Combination of a local inflammatory process plus altered function of immune-related cells in the peritoneal environment: mast cells, eosinophils, plasma cells, macrophages

Endometriotic lesions shown to have invasion by mast cells, and mast cell degranulation

Increased amounts of TNF alpha and nerve growth factor

Involved in chronic pain and neuropathic pain

A disrupted immune system: endometriosis and mast cells

Numbers of mast cells and activated mast cells are increased in endometriotic lesions
Use of mast cell stabilizers and inhibitors may be a new avenue of therapy for endometriosis and associated pain


Mast cells increase blood vessel growth and permeability

Release of vasoactive mediators increases vascular permeability and local blood flow and acts on smooth muscle
Induces angiogenesis

Innate immune response:
Enhances epithelial cell mucous production
Production of chemotactic factors-enhance recruitment of multiple inflammatory cells, including eosinophils, NK cells, neutrophils(IL8 and TNF alpha)

Qiao et al. Blood. 2006;107:610-18
Mast cell induced pain

Release mediators: histamine, leukotrienes, tryptase, TNF alpha, PGs, serotonin, IL-1, IL-8,
Recruitment of leukocytes that release algesic mediators by histamine released by MCs
In deep-infiltration endometriosis, MCs increased in deposits and located in close proximity to nerves – direct impact on neurons
Cross talk with MCs and neurons

Alvarez et al. Neuroscience. 2014;258:111-120

Nerve-Mast cell-myofibroblast axis

Nerve-Mast Cell-Myofibroblast Axis is an interactive relationship
Neuroinflammation a potential key element of dysregulated responses to injury
Nerves important in normal healing
Abnormal neural activation could result in fibrotic outcomes
Mast cell stabilizers may have efficacy in conditions with known neuroinflammatory component and mast cell involvement

Hart, David. 2015. Intern J of Inflam. 2012;452095
Activated mast cells and fibrosis

Hart, David. 2015. Intern J of Inflam. 2012;452095

Mast cells and endometriosis

Figure 1. Mast cells as key players in the pathology of endometriosis. Kirchhoff D et al. [31] are acknowledged for kindly providing.
Endometriosis and peritoneal inflammation

Impaired immune function: associated with changes in cellular and humoral immunity
Peritoneal fluid contains high numbers of immune cells
Immune cells – macrophages – promote the disease by secreting growth factors and cytokines that stimulate proliferation of ectopic endometrium and inhibit their scavenger functions
Local inflammation and upregulated aromatase involved in endometriosis

Bulun et al. Sme Repr Med 2004;22(1):45

Endometriosis and Matrix Metalloproteinases

Peritoneal fluid contains activated macrophages and other immune cells that secrete various local products: growth factors, cytokines – exert a paracrine action on endometriotic cells
Matrix metalloproteinases (MMPs)-groups of enzymes that mediate physiologic tissue turnover (endometrial breakdown) –and also play important role in development of invasive and destructive diseases

Sharpe-Timms et al. Ann NY Acad Sci.2002;955:147-56
Endometriosis: conventional approach

NSAIDs
Oral Contraceptives
GnRH agonists
Immune modulators (blockers of TNF alpha suggested)
Surgery

*These approaches are often not as effective as desired*

Resveratrol to treat endometriosis

A phytoalexin polyphenol, with anti-angiogenic, anti-oxidant, anti-inflammatory properties
In rat model of endometriosis, resveratrol showed potential to reduce implants, likely to antioxidant effects
Rat study, resveratrol a potential novel therapeutic agent through inhibiting angiogenesis and inflammation
Reduced in rats: immunoreactivity to MMP2, MMP9, VEGF, plasma and peritoneal levels IL-6&8, TNF alpha

Quercetin to treat endometriosis

May work through stabilizing mast cells
May work by decreasing expression of estrogen and progesterone receptors in endometrium
Rat study-inhibits growth ectopic endometrial tissue

Cao et al. Evid Based Complement Alternat Med. 2014;781684

Epiallocatechin-3-gallate (EGCG) and endometriosis

A polyphenol with anti-carcinogenic and anti-oxidant properties
Found in green tea
In mouse study-significantly reduced quantity of implants
Inhibits development, growth, and angiogenesis in mouse model of endometriosis
Suppresses vascular endothelial growth factor receptor 2 expression

Xu et al. Fertil Steril. 2011;96(4);1021-8
Endometriosis – lack of nutrients?

Antioxidants Vitamin C and E may be involved in clearing free radicals and reactive oxygen species – implicated in growth and adhesion of endometrial cells in peritoneal cavity

B vitamins (esp. B6) enhance metabolism of estrogen into inactive form and support conversion of linoleic acid to gamma linolenic acid – essential component of production of anti-inflammatory prostaglandins, which may inhibit growth of endometrial tissue

Consumption of Omega 3 – 22% decrease in endometriosis


Nutrition and endometriosis

Omega 3
N acetyl cysteine
Vitamin D
Resveratrol
Quercetin
Curcumin
Increased consumption of fruits, vegetables (organic), whole grains (no wheat)

Combination NAC, Alpha Lipoic Acid, and Enzymes

Mouse model
Potential therapeutic use in endometriosis
Theory behind the use of enzymes
Theory behind the use of antioxidants

Agostinis et al. Mediators Inflamm. 2015; 918089

Flavonoids: antiangiogenic effects

Uncontrolled angiogenesis is a major contributor to many disease states
Polyphenols in fruits and vegetables inhibit angiogenesis through multiple pathways: regulate VEGF, Matrix metalloproteinases (MMPs), EGFR, inhibit NF kappa B, and other signaling pathways

Aromatase expression and symptoms

Women with endometriosis – higher aromatase expression in endometrial tissue
Aromatase expression is positively correlated with dysmenorrhea severity

Maia et al. Int J of Women's Health; 2012; 4: 61-65

Curcumin and endometriosis

Downregulates matrix metalloproteinase-9 activity
Inhibits MMP-2 activity
Inhibits angiogenesis
Attenuates TNF alpha induced expression of intercellular adhesion molecule-1, vascular cell adhesion molecule-1, and proinflammatory cytokines in endometriotic stromal cells
Reduces estradiol production

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 activation of NF Kappa B in the colon

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

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
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

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
Primate study links organochlorine exposure to endometriosis
Adult exposure to organochlorines has been shown to interfere with both hormonal regulation and immune function and can promote endometriosis

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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

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


My protocol:
start with a modified 4-week detox

DIM Detox: 1 capsule twice a day
NAC 900: 1 daily in evening
Probiotic-5: 1 daily
Detox Pure Pack: 1 pack daily in morning
HM Complex: 1 daily in evening
Pro-Omega Caps: 1 daily in evening
GI Fortify, capsules or powder: 1 heaping scoop in 8 oz water, drink another 8 oz water daily; or 3 capsules daily with 8 oz water
My protocol:
reduce localized inflammation, stabilize mast cells

Green tea extract: 1 daily after breakfast
Quercetin: 2 capsules twice daily
Resveratrol: 1-5 capsules daily (vary with severity)
Alpha Lipoic Acid: 1 twice daily
CurcumaSorb: 2-6 capsules daily, divided into 2-3 doses
Systemic Enzyme Complex: 3 capsules twice daily between meals ….
and/or
AI Enzymes: 3 capsules twice daily between meals

My Protocol: Reduce Systemic and Localized Inflammation

Vitamin D liquid or capsules: 1000-2000 IU daily
Women's Nutrients: 1-2 capsules twice daily with meals
Buffered Ascorbic Acid: 1 rounded scoop daily
B Complex: 1 capsule with a meal
Vitamin A with Carotenoids: 1 capsule with meal
NAC 900 mg: 2-3 daily, divided
UTERINE LEIOMYOMATA

More commonly known as
UTERINE FIBROIDS

Leiomyomata – uterine fibroids
Uterine fibroids

Non-cancerous growths of muscle tissue in the uterus (and occasionally nearby)
Great size variability
According to WebMD – 70-80% of women have fibroids by age 50!
Can cause mild to severe menstrual cramping
Can cause very heavy menstrual bleeding
Can cause fertility issues and pregnancy complications

Uterine fibroids

Not seen prior to puberty
Shrink with estrogen withdrawal (menopause)
Have estrogen and progesterone receptors
Often enlarge during pregnancy
Aromatize – make estrogen themselves in leiomyoma smooth muscle cells
Inflammation upregulates aromatase
Stress can upregulate aromatase
Role of endocrine disruptors

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


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
Fibroids also involve mast cells!

Higher numbers of macrophages inside and close to leiomyomas compared with distant myometrium

Cellular fibroids showed more macrophages and mast cells than the “usual type”

Found large amount of collagen surrounding fibroid – suggestive of myo-fibroblasts producing ECM

Presence of inflammatory cells in fibroid may contribute to excessive ECM production, tissue remodeling and fibroid growth


Nutrients and fibroids

Vitamin D receptors identified in uterine tissue

Only 10% of blacks and 50% of whites had levels of 25(OH)D over 20 ng/ml

Women with sufficient Vitamin D had 32% lower odds of fibroids compared to insufficiency

Baird et al. Epidemiology 2013;24:447-453
Natural therapies:
lower inflammation/toxins, improve gut & metabolic health

Detox – PureWoman + HM Complex  
Green Tea  
Fiber to support gut  
Enzymes  
Vitamin A (carotenoids)  

Resveratrol  
Quercetin  
Curcumin  
Omega 3  
Vitamin D  
Polyphenols

Role of endocrine disruptors

Fibroids are target sites for endocrine disruptors
Endometriosis provides target sites for endocrine disruptors
Atrazine increased aromatase activity: aromatase activity in treated granulosa-lutein cell cultures increased more than 2-fold
Organochlorine pesticides act as estrogen receptor agonists in rat uterine myometrial cells

Holloway et al. J of Applied Tox 2008;28:260-70
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, Phthalates), pharmaceuticals (ethinylestradiol, diethylstilbestrol), dietary components (phytoestrogens).


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

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 neurotransmitter
receptors
EDC’s can impact reproductively-relevant processes and other
functions by mimicking, antagonizing or altering steroidal actions


EDC’s and leiomyoma cells

Promotes growth leiomyoma cells in vitro/in vivo
Dioxins
Phthalates
Bisphenol A
Diethylstilbestrol
Heavy metals
Organochlorine pesticides, DDT
PCBs
Pharmacologic compounds

Walker Cl. Recent Prog Horm Res. 2002;57:277-94
Sharing the same body (a mystery to be unraveled!)

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

Matrix metalloproteinases: playing a large role in ALL of these conditions

There are abnormal functioning MMPs in each condition
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

Matrix Metalloproteinases: expanded view – immune dysfunction

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

Matrix Metalloproteinases: endometriosis

Matrix Metalloproteinases (MMPs) - enzymes that mediate tissue remodeling during the menstrual cycle
Inflammatory cytokines are potent stimulators of MMPs
Estrogen is produced locally in a paracrine manner and under normal conditions, controls the production of MMPs
In endometriosis, E2 is not functioning normally, or endocrine disruptors are a factor
Progesterone can inhibit MMP expression

Osteen et al. 2002: Ann NY Acad Sci; 955:139-146
Matrix Metalloproteinases: endometriosis

Local peritoneal immune environment plays a role in the pathogenesis of endometriosis
Peritoneal fluid: molecules filtered from plasma, ovarian secretions, oviductal fluid, uterine menstrual fragments, various immune cells, including macrophages
Women with endometriosis have increased numbers of activated macrophages, along with higher amounts of inflammatory cytokines

Braundmeier et al. Amer J of Reprod Immun 2006; 56:201-214

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Matrix Metalloproteinases: endometriosis

Elevated cytokines may play a role in establishment of ectopic endometrium in peritoneal cavity by stimulating MMPs to remodel mesothelial lining of peritoneum – allowing for tissue invasion
Stimulation of MMPs by endometrial fibroblasts has been shown to occur through a protein EMMPRIN (Extracellular Matrix Metalloproteinase Inducer)

Braundmeier et al. Amer J of Reprod Immun 2006; 56:201-214
Matrix Metalloproteinases: endometriosis

Progesterone and locally produced differentiation factors work cooperatively to reduce MMP expression by maternal endometrial cells in the pro-inflammatory micro-environment of early pregnancy.

Normally, P exposure reduces MMP expression and limits ability of local inflammatory cytokines to stimulate expression of the MMPs.

Women with endometriosis show altered response to P, allowing continuous expression of MMPs throughout the secretory phase.

Local inflammatory cytokines produced by epithelial cells oppose stromal cell responses to P, altering proper MMP regulation.


Matrix metalloproteinases: uterine fibroids

In patients with uterine fibroids, endometrial polyps, and/or adenomyosis – find significantly higher MMP scores and cytokines than in the normal controls.

In some pathological conditions, specific cytokines were elevated, along with the MMPs.

Matrix metalloproteinases: PCOS

Study comparing serum levels of MMPs in women with PCOS and matched controls

Results: Activity of MMP9 was significantly higher in women with PCOS than in controls

Ranjibaran et al 2016; Soc for Repro and Fertil; 151:305-311

Fibroid incidence and PCOS: in the same body

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
ADENOMYOSIS
Sometimes referred to as endometriosis interna

Adenomyosis

The endometrial cells are found in the muscle of the uterus – like islands of glands in a sea of muscle
Previously called endometriosis interna
Can cause menstrual cramps, heavy or irregular bleeding, lower abdominal pressure, bloating
Adenomyosis

Endometrium has grown into the wall of the uterus.

Adenomyosis and leiomyomata

Women with both adenomyosis and leiomyomata have a number of different clinical features compared to 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
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
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

Treatment goals

Reduce systemic inflammation
Improve sleep and lower levels of stress
Reduce pain and discomfort overall and with menses
Improve nutrient status
Improve gut and metabolic health
Lower overall levels of toxins
Lower levels of endocrine disruptors
Lifestyle therapy

Organic, vegan (or nearly), high in fiber, root vegetables, leafy greens
Add supplements
Exercise: aerobic and resistance
Stress reduction techniques
Grounding
Essential oils
Maintain excellent oral health
Lose excess fat pounds
Live with the Circadian Rhythm

Natural therapies:
lower inflammation/toxins, improve gut and metabolic health

Detox – PureWoman + HM Complex  Resveratrol
Green Tea  Quercetin
Fiber to support gut  Curcumin
Enzymes  Omega 3
Vitamin A (carotenoids)  Vitamin D
Polyphenols
Women with these issues are at risk for many conditions: treat them with TLC!

Environmental toxicants
Chronic low level systemic inflammation, abnormal function of Matrix Metalloproteinases, and immune system dysfunction
Hormonal imbalances
Nutritional deficiencies
Circadian rhythm dysfunction
Gut microbiome dysbiosis
Cancers
Mood disorders

INTERMISSION

SEE YOU AFTER DINNER!!
Part 2:

The Microbiome:
Exploring new paradigms in our understanding of PCOS and inflammation

Polycystic Ovary Syndrome (PCOS)

A hormonal disorder, becoming obvious after puberty, in women of reproductive age - Named for the finding of small cysts developing in the outer edge of each ovary.

PCOS is a global epidemic

The most common endocrine dysfunction of women - affects up to 25% of women

A life-long disease with enormous medical, emotional, and financial consequences

High risk for diabetes, metabolic syndrome, & infertility…and 80% are overweight/obese

Affects women of all ages…actually manifests in childhood

Hormonal/reproductive effects of PCOS

Hyperandrogenism

Abnormal hormone receptors

Low libido and sexual problems

Pregnancy Complications

Infertility

Polycystic ovaries

PCOS

Acne

Hirsutism, alopecia

Chronic anovulation

Metabolic effects of PCOS

Hyperinsulinemia

Insulin Resistance

Fatty Liver

Endothelial Dysfunction

Hypertension

Impaired Glucose Tolerance

Dyslipidemia

Visceral Obesity

Overweight/Obese

Association of PCOS with other inflammatory-related conditions

Autoimmune disease (especially thyroid)

Skin tags and darkened skin (acanthosis nigricans)

Gastrointestinal problems (IBS, leaky gut)

Arthritis and tendinitis

Depression, anxiety, stress

Vaginal infections

Sleep dysfunction and OSA

Cancer
Complex hormonal and signaling interactions are involved

Dysregulation of various hormonal and metabolic processes

Etiology of PCOS

Complex interaction between genetics and the environment – genetic expression
Prenatal hormonal fluctuations within the womb
Exposure to endocrine disruptors, in-utero and subsequently – focus has been on BPA
Abnormal hormone receptor functioning
Oxidative stress beginning in-utero
Gut inflammation: “leaky gut” and systemic inflammation, IR, elevated androgens

Oxidative stress and inflammation are driving risk!

### Inflammation Is the driving force

Enhanced abdominal visceral fat  
Insulin resistance  
Abnormal adipose function with inappropriate adipokine release  
Inflammatory cytokines  
Abnormal glucose-regulation/gut hormones  
Ectopic lipid accumulation and lipotoxicity often occurs

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de Zegher et al. Trends Endocrinol Metabol;2009;20(9): 418-23
Upregulated macrophages: set the scene for inflammation!

Increased cytokine release from MNCs following lipopolysaccharide (LPS) exposure in the fasting state
Pre-activation contributes to development of insulin resistance and hyperandrogenism in PCOS

New Concepts - What is a Human?

We are not quite what we seem!
A microscopic civilization lives within and on us – controlling much more than we ever could have guessed!
The gut microbiome impacts every aspect of our biological systems: digestion, metabolism, neurological, reproductive, cognitive, emotional, immune

Concept of the super-organism

Our microbiome is the most complex ecological system ever discovered!
Our incredible ecosystem consists of hundreds of bacterial species
Controversial! The microbes may outnumber our own cells 10:1 … or maybe they are equal in number!
There is much yet to learn!

Science 2009; Vol. 326 no. 5960 pp. 1694-169
Role of Short-Chain Fatty Acids

Can cause pathogen displacement
  - Secretes antimicrobials and competes for sites of nutrients (colonization resistance)

Development of the immune system
Important for development of regulatory T-cells, T-helper 1 and 2 cells, and T-helper 17 cells
Exert strong immunomodulatory action—release of protective peptides, cytokines, chemokines, and phagocytes – “stuff” to aid our immune system!

The Complex World of the Gut

Moya and Ferrer/Trends in Microbiology 2016

Interactions: Microbiome and Short Chain Fatty Acids

Published online 10 March 2014

Fibers, specific oligosaccharides and resistant starch reach the colon intact, where they induce shifts in the composition and function of intestinal bacteria (shifts indicated by different colors). Intestinal bacteria use these compounds as substrates for the production of the short-chain fatty acids acetate, propionate and butyrate. These microbial metabolites are taken up by intestinal epithelial cells called enterocytes. Butyrate mainly feeds the enterocytes, whereas acetate and propionate reach the liver by the portal vein. Enterocytes can synthesize and release glucose to the portal vein. Propionate and butyrate promote intestinal gluconeogenesis (IGN) in different ways. Butyrate directly activates the expression of gluconeogenic genes in enterocytes by cAMP signaling whereas propionate stimulates gluconeogenesis by functioning as a gluconeogenic substrate and by FFAR3-dependent stimulation of peripheral nerves of the portal veins. The resulting gut-to-brain afferent nervous signal is required for activation of IGF, and nerves leaving the brain convey IGF-inducing signals back to the portal vein. It is not known how these signals control IGF.

Major influences on the microbiome

- Type of birth and infant diet
- Diet, probiotics, and prebiotics
- Medications: antibiotics, NSAIDs, OCPs, PPIs, H2 blockers, laxatives, opioids
- Toxins in meal
- Frequency of meals
- Stress (emotional, social), sleep, hygiene

HORMONES – the forgotten piece


Alteration of estrogen receptor function in women with PCOS

- E2 Receptor Beta expression significantly higher than E2 Receptor Alpha
- E2 Receptor Beta is lower compared to levels of controls
- E2 Receptor Alpha is lower than levels found in controls

Artimani et al. Gynecol Endocrinol. 2015
Old/New views on obesity, insulin resistance, and metabolic syndrome

Formerly thought caused only by a positive caloric balance when caloric intake exceeds caloric expenditure and the excess of energy is stored in adipose tissue

Studies show changes in the gut microbiota trigger the pathogenic mechanisms to promote obesity, T2DM, and metabolic syndrome

Intestinal microbiota in T2DM patients exhibit dysbiosis


Western diet and endotoxemia

Endotoxemia-stems from disruption of intestinal barrier & increase in Gram negative bacterial content of the microbiota

High fat, high simple carbohydrate meal comprehensive endotoxemia and inflammation, increases expression of TLR-4 (specific receptor for endotoxin), and SOCS:- a protein - interferes with insulin signal transduction


Probiotics and/or prebiotic treatment increases the number of beneficial "good" bacteria in the colon.

Beneficial "good" bacteria produce Short Chain Fatty Acids (SCFA) that increase colonic mucous production and tight junction function—decreasing the passage of immunostimulatory LPS from the colonic lumen into the circulation.

Bacterial LPS

Increased production of the satiety hormone GLP-1 by the healthy colon mucosa reduces food intake and results in a Decrease in body fat content.

A reduction in inflammation due to reduced passage of LPS across the gut mucosa results in an improvement in insulin sensitivity, with a drop in serum insulin levels.

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Review

Healthy Gut Microbiota

Composition
Bacteroidetes, Firmicutes

Synergy
Intestinal epithelial integrity
Enzyme activity
Vitamin synthesis
SCFA production

Immune System
Innate and adaptive immune response stimulation

Liver
Acetate and propionate (Gluconeogenesis /lipogenesis)

Obese-Diabetic Microbiota

Composition
Bacteroidetes, Firmicutes

Synergy
Intestinal epithelial integrity
Energy harvest
SCFA production

Liver
Lipogenesis
Inflammation
Oxidative stress
Insulin resistance

Adipose Tissue
Inflammation
Oxidative stress
Macrophage infiltration
Insulin resistance

Figure 1: Compositional and functional alterations in the healthy gut microbiota versus the obese-diabetic microbiota. The metabolic processes in peripheral organs leading to increased adiposity, inflammation, oxidative stress, insulin resistance, and lipogenesis are associated with the altered microbiota profile associated with the obese-diabetic phenotype. IEC, intestinal epithelial cell; LPS, lipopolysaccharide; SCFA, short chain fatty acids.
# PCOS PROTOCOL

4 week detox  
NAC 900  
Inositol  
Metabolic Xtra  
Green tea  
Resveratrol  
Probiotic-5  
Vitamin D 2000 IU  
Women’s Nutrients  
B Complex  
Quercetin – optional

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## My protocol:
Start with a modified 4 week detox

DIM Detox: 1 capsule twice a day  
NAC 900: 1 daily in evening  
Probiotic-5: 1 daily  
Detox Pure Pack: 1 pack daily in morning  
Pro-Omega Caps: 1 daily in evening  
GI Fortify, capsules or powder: 1 heaping scoop in 8 oz water, drink another 8 oz water daily; or 3 capsules daily with 8 oz water
My Protocol for PCOS Patients

- Inositol: 1 scoop with breakfast and dinner
- Metabolic Xtra: 1 capsule 3X daily with meals
- NAC: 1 capsule with breakfast, 2 with dinner
- PureLean Pure Pack: 1 Pack daily
- Vitamin D (liquid or capsules): 1000-2000 IU daily

Serum LBP associated with insulin resistance in women with PCOS

- Compared with controls, PCOS subjects had significantly higher LBP concentration
- Applied to both lean and obese PCOS women compared with controls
- Serum LBP levels significantly elevated in PCOS and independently associated with IR in PCOS

Zhu, Qibo et al. Serum LBP is Associated with Insulin Resistance in Women with PCOS. PLOS One11(1) Jan 2016
Dysbiosis of gut microbiota: clinical parameters

Clear association of altered gut microbiome and PCOS disease phenotypes
Reduced Akkermansia measured
Plasma levels of serotonin, ghrelin, and peptide YY (PYY) were significantly decreased in PCOS patients and had a negative correlation with waist circumference
Reduced gut microbiome diversity
Serotonin made by spore forming gut bacteria – reduced in PCOS
Increase in LPS producing bacteria in PCOS pts


Confirmation of altered gut microbiome in PCOS women

Stool microbiome of PCOS patients showed a lower diversity and an altered phylogenetic composition compared to controls
Alterations in some but not all markers of gut barrier function and endotoxemia
In mouse model, dysbiosis of gut microbiota was associate with the pathogenesis of PCOS
Fecal microbiota transplantation and Lactobacillus transplantation were beneficial as treatments of PCOS rats

Lindheim et al; PLOS One. 2017.12(1)
Guo et al.; PLOS One. 2016
New Ways to View Food: Nurturing the Microbiome - a New Therapy

FOOD AS INFORMATION

FOOD AS MEDICINE

FOOD AS A HORMONE

FOOD AS NOURISHMENT FOR OUR GUT MICROBIOTA
Food as information

Cannot just look at the macronutrient and micronutrient content of food to understand its actions
Think of food differently—identify food and food metabolite-receptor interaction to understand the relationship between the food we eat and diseases, including diabetes
Food components interact with gut flora to induce indirect signals


Food as a hormone

Food can be considered a cocktail of “hormones”… food components travel through the blood and nutrient substrates can act as signaling molecules by activating cell-surface or nuclear receptors, to regulate metabolic health

Food to feed our microbiome

New fields of bio-therapeutics-focus on diet to include nutrients that positively affect the microbiota: key role of probiotics and prebiotics to modulate the human intestinal ecosystem
Diet rich in fiber, prebiotics and probiotics is useful for improving the composition of the gut microbiota

MZ et al. Probiotic carbohydrates reduce intestinal permeability and inflammation in metabolic diseases. Gut 2009; 58: 1044-1045

Diet modulates the microbiome

Low fat/High complex carbohydrate diet improved Metabolic Syndrome by altering the gut microbiome
Low fat/High complex carbohydrate diet-increase in F. prausnitzii
This bacterial strain increases the SCFA - butyrate

Haro, C. et al. Two healthy diets modulate gut microbial community improving insulin sensitivity in a human obese population; J Clin Endocrinol Metab. 1-10; Oct 2015
Importance of the gut microbiome

Genetics
Medicine
Diet/Lifestyle
Early Colonization

Decreased gut diversity
Gut dysfunction

Chronic Disease
• Obesity
• Type II Diabetes
• NAFLD
• Dyslipidemia
• Inflammatory Bowel Disease
• Cardiovascular Disease
• PCOS

Increased gut diversity
Health & Wellness

The composition of gut microbiome can shape a healthy immune response or predispose to disease.


TMAO is gut-derived metabolite formed from dietary nutrients

1
Ingestion of dietary nutrients

2
Gut bacteria metabolize nutrients to TMA

3
TMA converted to TMAO by the liver

Foods rich in dietary TMAO precursors

TMAO precursors: Phosphatidylcholine, Choline, or L-Carnitine

<table>
<thead>
<tr>
<th>Foods Rich in Dietary TMAO Precursors</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Red Meat</strong></td>
</tr>
<tr>
<td>• Beef</td>
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<td>• Pork</td>
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<tr>
<td>• Ham</td>
</tr>
<tr>
<td>• Lamb</td>
</tr>
<tr>
<td>• Veal</td>
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<tr>
<td>• Processed meats</td>
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<tr>
<td><strong>Full-Fat Dairy Products</strong></td>
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<tr>
<td>• Whole milk</td>
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<td>• Eggs</td>
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<tr>
<td>• Yogurt</td>
</tr>
<tr>
<td>• Cream cheese</td>
</tr>
<tr>
<td>• Butter</td>
</tr>
<tr>
<td><strong>Others</strong></td>
</tr>
<tr>
<td>• Energy drinks</td>
</tr>
<tr>
<td>• Dietary supplements</td>
</tr>
</tbody>
</table>

*Note: Certain types of fish are direct dietary contributors of TMAO.*

Estrogens and the gut microbiota and estrogen-like foods for health

When all is “right,” there is a beautiful synergy of estrogen and the microbiome to influence and reduce obesity, cardiovascular disease, diabetes, cancer.

As an amazing “back-up,” the microbiota can even metabolize food containing estrogen-like compounds into biologically active forms.

Estrogen-like compounds (soy products, flax seeds, lignans) can promote the proliferation and growth of certain types of helpful bacteria.
Probiotics and prebiotics

Probiotics: live microorganisms which when administered in adequate amounts confer a health benefit on the host

Prebiotics: a non-digestible food ingredient that beneficially affect the host by selectively stimulating the growth and activity of one or a limited number of bacteria in the colon and improve host health


"Putative mechanisms of action through which prebiotics and probiotic bacteria can impact on host metabolic health in type 1 and type 2 diabetes. Green and red texts indicate hormones, systems and actions that are upregulated and downregulated, respectively. LPS, lipopolysaccharide."

How to build a better microbiome

Hormone balance is essential for a healthy microbiome… though often difficult in women with PCOS

Dietary composition, modification, and interventions have a marked impact on gut microbiota diversity

Plant based fiber is critical in influencing the composition and metabolic activity of the microbiome and determining levels of short chain fatty acids (SCFAs), improve colonic mucosal integrity, reduce gut apoptosis

Agrarian diets high in fruit/legume fiber are associated with greater microbial diversity

A safe strategy to reduce markers of insulin resistance and inflammation!

Rapid improvements in all of the following:
Fasting blood glucose
Glycosylated hemoglobin
Serum lipid profile
Body mass index and percent fat
Body weight
Blood pressure
Reduction in IGF-1

Fallucca F et al. Me-Pi macrobiotic diet intervention during 21 days in adult with type 2 diabetes mellitus. Minerva Endocrinol 2012; 37(suppl. 4):116
Diet fat content

Low levels of saturated fat
Moderate amounts of monounsaturated and polyunsaturated fats
No trans-fats
Omega 6: Omega 3 ratio of 5:1
Fats

Types of fats consumed has a great impact on microbial diversity, composition, and state of overall inflammation.
Mice fed fish oil increased levels of Lactobacillus and Akkermansia.
Mice fed lard increased levels of Bilophila.
Lard-induced White Adipose Tissue (WAT) inflammation is mediated through gut microbial activation of TLR4.


Artificial sweeteners-avoid!

Create compositional and functional alterations to the gut microbiota, promoting glucose intolerance.
They may have directly contributed to the very obesity epidemic they were intended to combat.
Absolutely none permitted!!

Benefits of adding high resistant starch: high-amylose starch

<table>
<thead>
<tr>
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</tr>
</thead>
</table>

Diversity of microbiome requires dietary diversity

The importance of microbiota diversity cannot be overstated! Microbiota produce an abundance of important molecules for host. Each particular macronutrient has the potential to be metabolized into unique metabolic signals

Helman M et al. A healthy gastrointestinal microbiome is dependent on dietary diversity. Molecular Metab 2016;1-4
Eat for diversity-the colors of the rainbow for microbiota diversity

With increased variation comes increased adaptability and increased range of physiological responses
Elimination of one or more macronutrients results in selecting some microbiotic species over others

Heiman M et al. A healthy gastrointestinal microbiome is dependent on dietary diversity. Molecular Metab 2016;1-4

Hormetic effects of phytochemicals

Small amounts have profound effects
Hormone like action
Metabolic performance
Amplification of cell signaling pathways
Enhancing growth of beneficial bacteria
Competitively excluding specific pathogenic bacteria-some have bactericidal/bacterostatic actions

Negative effects of different diets on the microbiome

Ketogenic Diets: diminish total bacterial levels of the gut microbiota
Long term adherence to high protein, low fermentable carbohydrate/fiber “weight-loss” diets increase Bacteroides-likely increasing risk of colonic disease


Best short-term diet for women with PCOS, endometriosis, fibroids, and adenomyosis: high carb vegan diet

Healthy fats-Omega 3 supplementation, Omega 6 and 9 from plants, Saturated fat from coconut oil
Low protein (approximately 12%) 
High Complex carbohydrates (70%)
Low fructose
No animal protein-including no dairy or eggs
No added sugars, No processed foods, Chemical free
Rich in complex carbohydrates: whole-grain cereals, vegetables, legumes
Rich in natural fiber and prebiotic and probiotic products
A safe strategy to reduce markers of insulin resistance and inflammation!

Rapid improvements in all of the following:
Fasting blood glucose
Glycosylated hemoglobin
Serum lipid profile
Body mass index and percent fat
Body weight
Blood pressure
Reduction in IGF-1

Fallucca F et al. Ma-Pi macrobiotic diet intervention during 21 days in adult with type 2 diabetes mellitus. Minerva Endocrinol 2012; 37(suppl. 4):116

It’s not just what you eat, but also when and how often you eat

The benefits of periodic fasting:
Can increase gut bacterial diversity
The benefits of timed eating
Correct the clock: meal timing

Typical American Meal Pattern

Healthier (Circadian-Aligned) Meal Patterns:

A

12 hour overnight fast
12 hour daytime eating period

B

16 hour overnight fast
8 hour daytime eating period

Periodic fasting and grounding

Periodic fasting for 4 days/Fasting mimicking diets for 5 days: shown to increase BDNF

I recommend this form of fasting once monthly for 3 months, then every 1-3 months

Grounding can reset the Circadian Rhythm in a minimum of just 2 days in nature

Cell Metabolism. Volume 22, Issue 1, p86-99, 7 July 2015
Correct the clock: sleep hygiene

<table>
<thead>
<tr>
<th>3 hours before bed</th>
<th>1 hour before bed</th>
<th>Sleeping</th>
<th>Upon awakening</th>
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</thead>
<tbody>
<tr>
<td>• Dim the lights</td>
<td>• Breathing</td>
<td>Cool,</td>
<td>15 minutes of</td>
</tr>
<tr>
<td>• Minimize</td>
<td>exercise</td>
<td>dark,</td>
<td>sunlight</td>
</tr>
<tr>
<td>computer &amp;</td>
<td>• Hot bath</td>
<td>quiet</td>
<td></td>
</tr>
<tr>
<td>electronic use</td>
<td>• Calming tea</td>
<td>room</td>
<td></td>
</tr>
<tr>
<td>• Avoid vigorous</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>exercise</td>
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</tbody>
</table>

Encourage wise choices

100% organic (as close as can be managed)
Local and home grown produce
Old/heritage seeds
Home cooked
Real foods in their natural state
Choose a great variety of colorful fruits and veggies
If eating animal products – choose free range, pastured, wild caught (low mercury), organic
Recognize what needs avoiding

Non-GMO (data on Roundup and Glyphosate)
Gluten free
Dairy free
Sugar free
Artificial sweetener free
Avoid processed foods
Avoid refined oils/trans fats
Avoid alcohol
Avoid food allergens/consider elimination diet

New hope for women with PCOS, endometriosis, fibroids, and adenomysis

Inflammation, immune dysfunction, endocrine disruption, and oxidative stress is the driving force behind all of these conditions
Proper supplementation can be greatly beneficial
Discovery of the huge role played by the gut microbiome in metabolic health offers an innovative therapeutic modality
Modulating the gut microbiota through dietary alterations may enable women with reproductive health and fertility problems to dramatically improve their lives

YOU can make a difference!!
Thank You!

Felice L. Gersh, MD

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