New Paradigms in Understanding PCOS: Impact of the Microbiome

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Technical Issues & Clinical Questions

Please type any technical issue or clinical question into either the “Chat” or “Questions” boxes, making sure to send them to “Organizer” at any time during the webinar.

We will be compiling your clinical questions and answering as many as we can the final 15 minutes of the webinar.
New Paradigms in Understanding PCOS:
Impact of the Microbiome

Felice L. Gersh, MD
Review what the gut microbiome is, how it develops, and its significance for PCOS patients

Discuss the “unhealthy gut microbiome” and its role in the development of systemic inflammation, insulin resistance, weight gain, hyperandrogenemia, and ovulatory dysfunction (creating the features of PCOS)

Review the laboratory tests available to evaluate the gut microbiome

Understand how to restore a healthy gut microbiome to re-establish metabolic homeostasis through dietary choices
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

- A world-wide epidemic: now found EVERYWHERE!
- The most common endocrine dysfunction of women
- Affects 10-20% of women (some say up to 25%!)  
- 88% are overweight/obese, 20% normal/lean
- Obese carry all the classic issues of PCOS, in addition to the metabolic burdens of obesity
- A LIFE-LONG disease with enormous medical, emotional, and financial consequences
- High risk for diabetes and metabolic syndrome in first degree relatives
Complex Hormonal and Signaling Interactions are Involved

Dysregulation of various **hormonal** and **metabolic** processes
Hormonal/Reproductive Effects of PCOS

PCOS

- Hyperandrogenism
- Acne
- Hirsutism, alopecia
- Chronic anovulation
- Polycystic ovaries
- Infertility
- Pregnancy Complications
- Low libido and sexual problems
- Abnormal hormone receptors
Metabolic Effects of PCOS

- Hyperinsulinemia
- Impaired Glucose Tolerance
- Dyslipidemia
- Visceral Obesity
- Overweight/Obese
- Hypertension
- Fatty Liver
- Endothelial Dysfunction
- Insulin Resistance

PCOS and 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
- Cancers
- Other GYN conditions: fibroids, endometriosis
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

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 lipopolysacharide (LPS) exposure in the fasting state
- Pre-activation contributes to development of insulin resistance and hyperandrogenism in PCOS
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
The GI Tract: An Exquisite Environment Which is Pivotal to Maintain Local and Systemic Homeostasis
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

This figure shows how microbiota species are interchangeable in terms of functions by means of the metabolites produced by the action of gene products contained in the gut bacteria.
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 enterocyte, 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 vein. The resulting gut-to-brain afferent nervous signal is required for activation of IGN, and nerves leaving the brain convey IGN-inducing signals back to the portal vein. It is not known how the efferent signals control IGN.
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
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.

Dysbiosis and Inflammation
High fat/sugar, low fibre diet causes an imbalance between “good” and “bad” gut bacteria.

Dysbiosis of colonic microbiota mucous production and epithelial integrity - resulting in a “leaky gut”

Obesity alters gut microbiota

INSULIN RESISTANCE

Obesity directly increases gut permeability

Insulin drives Testosterone Production in ovary, while impairing follicle development

Gut inflammation initiated State of insulin resistance

Polycystic Ovary Syndrome

Impaired ovulation

Polycystic morphology On ultrasound

Acne/ hirsuitism

Normal tight junction function and mucous barrier preventing the trans-epithelial passage LPS

Macrophages activated by bacterial LPS that passes through gut wall
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 immuno-stimulatory LPS from the colonic lumen into the circulation.

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.

RETURN TO NORMAL OVARIAN FUNCTION
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
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 associated with the pathogenesis of PCOS
- Fecal microbiota transplantation and Lactobacillus transplantation were beneficial as treatments of PCOS rats
New Ways to View Food

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

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
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

Fig. 1 Proposed mechanisms of HAS and Improved healthspan. Ingestion of high-amylose starches increases beneficial microbiota and stimulates the production of butyrate and increases GLP-1 release from the gut.

- Improved appetite
- Enhanced cognitive and motor performance
- Improved gut barrier function
- Reduce markers of oxidative stress and inflammation
- Increase xenobiotic pathways
“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

Best to Start with: Vegan Diet for the Short Term

- 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, organic/unprocessed soy
- 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
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
Fat

• 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

Benefits of Adding High Resistant Starch: High-Amylose Starch

Table 2: Summary of the effects of diet restriction and high-amylose starch

<table>
<thead>
<tr>
<th>Effect</th>
<th>Diet restriction</th>
<th>High-amylose starch</th>
<th>HAS references</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inflammation</td>
<td>↓</td>
<td>↓</td>
<td>Zhou et al. 2008; Shen et al. 2011</td>
</tr>
<tr>
<td>Glucose clearance</td>
<td>Improved</td>
<td>Improved</td>
<td>Robertson et al. 2005; Johnston et al. 2010; Robertson 2012</td>
</tr>
<tr>
<td>Insulin sensitivity</td>
<td>Improved</td>
<td>Improved</td>
<td></td>
</tr>
<tr>
<td>Lipogenesis</td>
<td>↓</td>
<td>↓</td>
<td>Higgins et al. 2006; Higgins and Brown 2013</td>
</tr>
<tr>
<td>Body fat</td>
<td>Reduced</td>
<td>Reduced</td>
<td>Keenan et al. 2006, 2013; Charrier et al. 2014</td>
</tr>
<tr>
<td>Cancer risk</td>
<td>↓</td>
<td>↓</td>
<td>Toden et al. 2007; Clarke et al. 2008</td>
</tr>
<tr>
<td>Oxidative Stress</td>
<td>↓</td>
<td>↓</td>
<td>Kwak et al. 2012</td>
</tr>
</tbody>
</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

Heiman 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
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 bacterocidal/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

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
• **Four Functional Pillars**
  – Infection
  – Inflammation
  – Insufficiency (Digestive)
  – Imbalance (Metabolic)

• **Global Gut Health**
Interpretation-at-a-Glance: 4 Functional Pillars

### Four Functional Pillars Biomarker Map

<table>
<thead>
<tr>
<th>Infection Box</th>
<th>Inflammation Box</th>
<th>Insufficiency Box</th>
<th>Imbalance Box</th>
</tr>
</thead>
<tbody>
<tr>
<td>any parasite present</td>
<td>Calprotectin</td>
<td>PE-1</td>
<td>n-Butyrate</td>
</tr>
<tr>
<td>any pathogen present</td>
<td>EPX</td>
<td>Total Fecal Fats</td>
<td>Total SCFA</td>
</tr>
<tr>
<td></td>
<td>Fecal IgA</td>
<td>Total Protein Products</td>
<td>Beta-glucuronidase</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Lactobacillus</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Bifidobacterium</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>E. coli</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>any potential pathogen</td>
</tr>
</tbody>
</table>
**Digestion and Absorption**

<table>
<thead>
<tr>
<th>Component</th>
<th>Units</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pancreatic Elastase 1 †</td>
<td>&gt;200 mcg/g</td>
</tr>
<tr>
<td>Products of Protein Breakdown (Total*) (Valerate, Isobutyrate, Isovalerate)</td>
<td>1.8-9.9 micromol/g</td>
</tr>
<tr>
<td>Fecal Fat (Total*)</td>
<td>3.2-38.6 mg/g</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>0.3-2.8 mg/g</td>
</tr>
<tr>
<td>Long-Chain Fatty Acids</td>
<td>1.2-29.1 mg/g</td>
</tr>
<tr>
<td>Cholesterol</td>
<td>0.4-4.8 mg/g</td>
</tr>
<tr>
<td>Phospholipids</td>
<td>0.2-6.9 mg/g</td>
</tr>
</tbody>
</table>

- Pancreatic Elastase 1
- Products of Protein Breakdown
- Fecal Fats
## Inflammation & Immunology

<table>
<thead>
<tr>
<th>Substance</th>
<th>Value</th>
<th>Normal Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calprotectin</td>
<td>37</td>
<td>&lt;=50 mcg/g</td>
</tr>
<tr>
<td>Eosinophil Protein X (EPX)†</td>
<td>2.1</td>
<td>&lt;=4.6 mcg/g</td>
</tr>
<tr>
<td>Fecal secretory IgA</td>
<td>2.427 H</td>
<td>&lt;=885 mcg/g</td>
</tr>
</tbody>
</table>

- Calprotectin
- Eosinophil Protein X (EPX)
- Fecal secretory IgA
Tests Relating to Estrogen Detoxification
Beta - Glucuronidase

• Beta-Glucuronidase can effectively reverse detoxification that has taken place in the liver by uncoupling glucuronides
  – Promotes enterohepatic recirculation of toxins, hormones, and drugs
• A moderate level of Beta-Glucuronidase activity is preferred as activity appears to be important for normal enterohepatic recirculation of endogenous compounds and vitamins
• Limited human studies show a relationship to colon and hormone related cancers
  – Calcium-d-glucarate inhibits action of enzyme
Urine Detoxification Report: Estrogen Detoxification Pathways
Wrapping It Up!

So What Does a Woman with PCOS Actually Eat For A Healthy Microbiome and to Maximize Hormonal Health?
How to Eat: PCOS Guidelines

- Eat 2-3 meals a day and no snacks
- Periodic fasting
- Local and home grown
- Old/heritage seeds
- Home cooked
- Avoid refined oils/trans fats/alcohol
- Avoid food allergens and sensitivities - consider elimination diet
- Avoid toxic foods!
- Include phytoestrogens: organic, whole soy, flax seeds
How to Eat for PCOS

- 100% organic
- Sugar free, artificial sweetener free
- Gluten free and Dairy free/reduced
- High fiber/resistant starch
- Non-GMO (data on Roundup and Glyphosate)
- Real foods in natural state
- Variety of colorful fruits and veggies
- Limit processing
Thank You!

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Conferences – Schedule of events we attend
Test Menu – Detailed test profile information
MY GDX – Order materials and get results

Michael Chapman, ND
Moderator

Felice L. Gersh, MD
Presenter
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- Diagnostic profiles featured in this webinar
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- Review a profile that has already been completed on one of your patients

We look forward to hearing from you!
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