What’s going on in America?
Infertility: Endometriosis and PCOS

Bethany M. Hays, MD, FACOG
London, UK
May 6, 2017
Outline

• What happened and why you don’t want to be like us!
• A few words on Functional Medicine, the therapeutic encounter and creating an environment for insight
• STAIN- methodology and a checklist for addressing complex illness
• Environmental Toxins-pivotal in women’s health
US Health Status

- US makes up 5% of the world’s population but consumes more than 50% of the world’s pharmaceutical drugs
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• US ranks last or near last among developed nations on infant mortality and life expectancy.
THIS IS THE NEW CHILDHOOD IN AMERICA:

1 in 3 is overweight
1 in 6 has learning disabilities
1 in 9 has asthma
1 in 10 has ADHD
1 in 12 has food allergies
1 in 20 has seizures
1 in 54 males has autism
1 in 88 has autism

50% (half) of all children have chronic illness or are overweight.

This is the NEW NORMAL in our country.

Are you concerned yet?! Because if you’re not, then you are not paying attention!
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• We also suffer from more chronic illnesses
Medical error—the third leading cause of death in the US


Abstract  Translate

Medical error is not included on death certificates or in rankings of cause of death. Martin Makary and Michael Daniel assess its contribution to mortality and call for better reporting.

Full text  Translate

The annual list of the most common causes of death in the United States, compiled by the Centers for Disease Control and Prevention (CDC), informs public awareness and national research priorities each year. The list is created using death certificates filled out by physicians, funeral directors, medical examiners, and coroners. However, a major limitation of the death certificate is that it relies on assigning an International Classification of Disease (ICD) code to the cause of death. As a result, causes of death not associated with an ICD code, such as human and system factors, are not captured. The science of safety has matured to describe how communication breakdowns, diagnostic errors, poor judgment, and inadequate skill can directly result in patient harm and death. We analyzed the scientific literature on medical error to identify its contribution to US deaths in relation to causes listed by the CDC.
So WHY would anyone want to know what an American doctor has to say about women’s health?
Institute for Functional Medicine
US Health Status

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- We also suffer from more chronic illnesses.

- *We consume 25% of the world supply of glyphosate*
Breast Cancer

Health

Alzheimer’s
Today’s Plan

• Infertility- what is keeping us from getting pregnant
• Pregnancy- why is it the pivotal point in our health
• Perimenopause- hormone balance and oestrogen dominance
• Menopause- why oestrogen levels matter and should determine our treatment of menopause
If you don’t remember anything else…

- Stressors
- Toxins
- Antigens, Allergens
- Inflammation, Infections
- Nutrition
- Sleep. Sedentary lifestyle
If you don’t remember anything else…

- Stressors
The Brain

Senses, Perception, Processing, Transduction
Response to Danger

- **Freeze** - increased sensory acuity
- **Flight** - the second option is to escape increased blood supply to muscles, heart rate, urge to urinate or defecate
- **Fight** - if there is no way to escape-increased clotting
- **Fright** - Tonic incapacitation (also called freeze by some)- HR remains high, muscles are prepared to leap
- **Faint** - Parasympathetic overload? BIITS syndrome

Triggers of Adrenaline

- Lack of sleep
- Low blood sugar
- Heat and cold
- Pain
- Life threats - accidents, war, attacks by others
- Emotions and imaginings - anger, response to injustice, fear
- Drugs
Symptoms of Too Much Adrenaline

- Insomnia- can’t fall asleep, awakening with hot flashes or night sweats
- Elevated HR, palpitations
- Anxiety
- Intermittent systolic hypertension
- Low insulin with low blood sugar
- Tremor
- Headache
- Hot Flashes
Symptoms of Too Much Adrenaline

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- Headache

- Hot Flashes
Balancing Adrenaline

- Cortisol\(^1\)
- GABA
- Endorphins
- Oxytocin\(^2,3\)
Ways to Lower Adrenalin

- Breathe
- Heart rate Variability Training
- Improve Sleep
- Avoid hunger
- Avoid stressful people and situations
- Massage
- Change your mind!
Resiliency vs. Adaptation

Cortisol Levels vs. Time

Stressor
Cortisol Steal

Cholesterol

Pregnenolone

Progesterone

11-deoxycorticosterone

Corticosterone

18-OH-corticosterone

Aldosterone

17-OH-pregnenolone

17-OH-progesterone

11-deoxycortisol

Cortisol

Cortisone

DHEA

Androstenedione

Testosterone

Estrone

Estradiol
Symptoms of Too Much Cortisol

- Memory loss
- Depression
- Elevated blood sugar/eventually insulin
- Awakening at 2AM
- Low DHEA, Progesterone, oestrogen, Testosterone (Cortisol Steal)
- Susceptibility to infections
- Central adiposity
High cortisol may keep an overactive immune system under control,

But it may cause depression, hypothyroidism, and memory loss…
Cortisol Levels

Time

HPA Adaptation...to Exhaustion
If you don’t remember anything else…

- Stressors
- Toxins
Toxic Exposures

- **Exotoxins**
  - Heavy metals
  - Pesticides – organophosphates, atrazine
  - Flame retardants
  - Solvents
  - Pharmaceuticals
  - Air pollution
  - Phthalates, BPA
  - PFOS, PFOA
  - Acrylamide, dioxins

- **Endotoxins**
  - Intestinal bacteria (Endotoxemia from LPS)
  - Yeast/candida (acetaldehyde)
  - Other infectious diseases
  - Food chemicals/additives
  - Stress
  - Emotions
Total Toxic Body burden

Bucket fills and overflows as disease...
- Cancer
- Autoimmune conditions
- Neurodegenerative Disease
The average baby has over 200 chemicals in their cord blood.
What makes up Total Body Burden?

- Standard American Diet
- Exposure to heavy metals
- Petrochemicals, residues, pesticides, and fertilizers.
- Food allergies, environmental allergies
- Molds and mycotoxins
- Medications
- Internal toxins: bacteria, fungus, viruses, and yeast
- Metabolic toxins that aren’t eliminated properly.
- Mental, emotional, and spiritual toxins
  - Isolation, loneliness, anger, jealousy, and hostility
Synthetic Organic Chemical Production (billions of kilograms)

Diabetes Prevalence (%)
Pesticides throughout the world are used as mixtures which note their active ingredients but keep their adjuvants confidential and call them “inert”. Testing is usually done on the active ingredient alone.

“8 formulations out of 9 were up to one thousand times more toxic than their active principles. Despite its relatively benign reputation, Roundup was among the most toxic herbicides and insecticides tested.”

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3955666/
Atrazine

- An insecticide being used in increasing amounts since Roundup is creating "super weeds".
- An aromatase inducer - stimulates conversion of testosterone to estradiol.
- Banned by the European Union in 2003.
- Contaminates water in 9/10 states being monitored by EPA with spikes 9-18X the limit approved by EPA which considers them "not a health hazard".
- 33 million Americans exposed to contaminated drinking water.
- Highest contamination in Hispanic farm workers.
- Associated with birth defects, premature birth and low birth weight at levels of .1ppb (estradiol is effective at levels 100 to 1,000X lower than that).
- Reduced 33/43 immune endpoints in meta-analysis.

Age-adjusted mortality rate, by county, 2005

### Table 1

Possible mechanisms of endocrine disruption

- Affect synthesis of hormones
- Block/bind hormone receptors on target tissues
- Alter amount or activity of hormone receptors on target tissues
- Change signaling cascades by altering one or more steps in path
- Alter hormone metabolism
Figure 4: Potential molecular mechanisms implicated in chemical-induced autoimmune reactivities.
Western-style Diet And Endotoxemia

“Placing 8 healthy subjects on a Western-style diet for 1 month induced a 71% increase in plasma levels of endotoxin activity (endotoxemia), whereas a prudent-style diet reduced levels by 31%.”

Advice for women

- Never microwave plastic
- Avoid glyphosate (eat organic)
- Don’t drink from BPA containing containers
- Look into the chemistry of your make-up
- Check water for toxins
Toxic Burden: Women Put Over 150 Chemicals on Their Faces Every Day

Environmental Working Group
Limit or Avoid Animal Fat$^{1,2}$
Chemical Industry Says: “doses too low to matter”.....?!?

<table>
<thead>
<tr>
<th>Substance</th>
<th>Concentration (ppb)</th>
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</thead>
<tbody>
<tr>
<td>BADGE-4OH</td>
<td>97.5 ppb</td>
</tr>
<tr>
<td>PFCs</td>
<td>45 ppb</td>
</tr>
<tr>
<td>Cialis</td>
<td>30 ppb</td>
</tr>
<tr>
<td>Paxil</td>
<td>30 ppb</td>
</tr>
<tr>
<td>Lead</td>
<td>21 ppb</td>
</tr>
<tr>
<td>Mercury</td>
<td>11.1 ppb</td>
</tr>
<tr>
<td>Albuterol</td>
<td>2.1 ppb</td>
</tr>
<tr>
<td>PBDEs</td>
<td>0.29 ppb</td>
</tr>
<tr>
<td>Nuvaring</td>
<td>0.0035 ppb</td>
</tr>
</tbody>
</table>

Video: 10 Americans by Ken Cook  EWG.org
What can I do?

- Drink more (clean) water
- Take out “the garbage” every morning
- Get a GOOD air filter
- Eat more vegetables (organic)
- Identify toxins in your environment and remove them
- Shoes off at the door
- Non-toxic cleaning products
- Adequate sleep
Daily Detox

- Diet organic, low in processed food
- Daily Sweating
- Daily exercise
- Daily water intake
- Regular bowel function
- Daily supplements that support detox: Curcumin, Glucosinolates, Ellagic Acid, Catechins, organic sulfates, silymarin
Depending on need, can be dietary or supplement

- **Artichoke:** 6 oz whole artichoke or 150-600 mg of leaf extract
- **Pomegranate:** 6 oz of juice, 1 fruit, 30-100 mg of ellagic acid
- **Watercress:** 6 oz or 125-500 mg of whole plant extract
- **Green tea:** 2-4 cups or 50-150 mg catechins

Many companies have detoxification support products… go with a trusted company.
The dangers of sudden detox

- Sudden weight loss
- Severe detox diets and “cleanses”
- Failing to take into account total body burden of toxins
- The need to “have it now”!
1. Avoid Toxins
2. Improve detoxification
3. Go slowly
Diagnosis of Toxins

- GGT
- Various tests for environmental toxins—if you know what to test for…
“Genes load the gun
Environment pulls the trigger”
Things to keep in mind

- **Stressors** (including prenatal)
- **Toxins**
- **Antigens, Allergens**
If you don’t remember anything else…

- Stressors
- Toxins
- Antigens, Allergens
- Inflammation, Infections
Oestrogen

- COX 2
- PGE2
- Inflammation
- Aromatase
- Genetics
- Insulin
If you don’t remember anything else…

- Stressors
- Toxins
- Antigens, Allergens
- Inflammation, Infections
- Nutrition
Healthy Food— and how to get our patients to eat it.
If you don’t remember anything else…

- Stressors
- Toxins
- Antigens, Allergens
- Inflammation, Infections
- Nutrition
- Sleep, Sedentary lifestyle
Sleep Deprivation and Elevated Cortisol


Chronic sleep deprivation:

- Increases evening cortisol levels;
- Increases insulin and blood glucose;
- Decreases parasympathetic and increases sympathetic tone;
- Increases appetite and energy expenditure;
- Increases levels of proinflammatory cytokines;
- Increases blood pressure
If you don’t remember anything else…

- Stressors
- Toxins
- Antigens, Allergens
- Inflammation, Infections
- Nutrition
- Sleep, Sedentary lifestyle
What do Endometriosis and PCOS have in common???
Endometriosis
Trying to Find Patterns In Complexity
Definition: A complex disorder that is characterised by the presence of endometrial tissue in ectopic sites outside the uterus and is linked to pelvic pain and infertility.

Bulun, E, Zeitoun K, Takayama, L et al oestrogen Production in endometriosis and the use of aromatase inhibitors to treat endometriosis. Endocrine-Related Cancer 1999;6:293-301.
“Endometriosis is being reported in younger age women and manifesting with increasing severity”

S. Gupta, A. Agarwal, N. Krajcir, J.G. Alvarez
Role of oxidative stress in endometriosis
Endometriosis-what is it?

- The presence of endometrial GLANDS and STROMA outside of the uterine lining

- Several theories of how this happens\(^1,2\)

- Rare in postmenopausal women-it is oestrogen related

- Can be asymptomatic (or highly symptomatic with minimal disease)-cause or co-incidence??

- Estimated to be present in 3-10% of women in the reproductive age group and in 25-35% of infertile women
Associations

- Infertility 41%
- Pain 99%
- Sexual dysfunction
- Oestrogen related cancers
- Allergy and Asthma 61% v12%
- Fibromyalgia 5.9% v 3.4%
- CFS 4.6% v0.03%
- Autoimmune disorders
  - Hypothyroid 9.6% v 1.5%
  - RA 1.8% v 1.2%
  - SLE 0.8% v0.04%
  - Sjogren’s 0.6% v 0.03%
  - MS 0.5% v0.07%
Theories on Aetiology

- Retrograde flow and implantation of endometrial cells doesn’t explain different genetics in endometrium vs endometriosis and its presence in women after tubal ligation (Sampson’s theory)

- Transformation of “totipotential” peritoneal cells (Coelomic metaplasia) (Oral and Arici)

- Lymphatic dissemination and hematologic spread (Halban theory)

- Developmentally displaced endometrial cells
Newer theories

- Oxidative stress
- Inflammation
- Genetics
- Environmental toxins
Endometriosis differs from normal endometrium

- Presence of aromatase with elevated E2
- Reduced 17-β HSD-2 increased E3/E1
- Higher ER-β with unchanged ER-α'
- Decreased Progesterone signalling or “Progesterone Resistance”
- COX-2, TNF-α, PGE2, various cytokines are elevated-inducing ligand independent activation of receptors
Genetic Risk factors

- DNA Methylation/epigenetics
  - HOXA10
  - COX2
  - Aromatase
  - Hormone receptors

- Familial/genetic
  - PON-1
  - GST-M1
  - GPX
Endometriosis is an Inflammatory Disease
Pain

- While endometriosis may predict pelvic pain (59% in those with endometriosis vs 44% in those without), pelvic pain does not predict endometriosis 54% with endometriosis vs 40% in those without
Inflammation

- Endometriosis is an inflammatory disease
- Pelvic fluid contains increased activated macrophages
- Pelvic fluid contains increased TNF-alpha, IL1-Beta, IL-6, IL-8 and chemoattractants which recruit macrophages
- Inducible inflammatory cytokines and PGE2 are upregulated
- These findings are seen in endometriosis and ovarian cancer
Endometriosis and the Gut
- A higher prevalence of antinuclear antibodies has been reported for women with endometriosis.

- Endometriosis is associated with changes in both cellular and humoral immunity, suggesting that impaired immune function may contribute to the development of the disease.

- Altered immune function may predispose some women to develop endometriosis, or influence the severity.

- Although the peritoneal fluid of women with endometriosis contains increased numbers of immune cells, evidence suggests that their actions do more to promote the disease than to prevent it.
Extracellular matrix (ECM)

- ECM can control the differentiation by influencing the intracellular gene expressions via signal transduction.
What is cell differentiation?

Pluripotent Stem Cells

- In vivo fertilized egg
- Totipotent
- 8 cell embryo
- Cultured undifferentiated stem cells
- Blastocyst
- Neural cells
- Cardiac muscle
- Blood cells
Endometriosis and the Gut
Dysbiosis and Disease

Bacterial cell wall
Lipopolysaccharide
inducing NFκB, gene transcription and cell signaling via cytokine production.
The translocation of bacterial products from the intestinal lumen to the mesenteric circulation and its lymphatics induces regional and systemic production of TNF-alpha and other proinflammatory cytokines.

NEJM 2000. Vol 343; No. 20: 1467-1476
Control of Cell Differentiation

- Gene control
- Cell interaction
- Hormones
- Environmental factors
Nutritional Insufficiencies
Vitamin D

- Vitamin D inadequacy has been reported in approximately 36% of otherwise healthy young adults and up to 57% of general medicine inpatients in the United States and in even higher percentages in Europe.

- Recent epidemiological data document the high prevalence of vitamin D inadequacy among elderly patients and especially among patients with osteoporosis.

- Factors such as low sunlight exposure, age-related decreases in cutaneous synthesis, and diets low in vitamin D contribute to the high prevalence of vitamin D inadequacy.

Oestrogen

- We have known since at least 1999 that endometriosis produces its own oestrogen via an “autocrine feedback mechanism” which produces oestrogen and prostaglandin from the endometriosis stromal cells.

Bulun, E, Zeitoun K, Takayama, L et al oestrogen Production in endometriosis and the use of aromatase inhibitors to treat endometriosis. Endocrine-Related Cancer 1999;6:293-301.
Oestrogen

+ COX 2

+ Inflammation

+ PGE2

+ Aromatase

+ Genetics

+ Insulin
Hormonal changes in endometriosis:

1.) higher levels of aromatase = more oestrogen production
2.) feed-forward production of E2 via COX2
3.) inability to make 17βHSD2 = less E2 → E1
4.) progesterone resistance
Natural Products as Aromatase Inhibitors

Marcy J. Balunas\textsuperscript{a,†}, Bin Su\textsuperscript{b,‡}, Robert W. Brueggemeier\textsuperscript{b}, and A. Douglas Kinghorn\textsuperscript{b,*}

\textsuperscript{a}Program for Collaborative Research in the Pharmaceutical Sciences and Department of Medicinal Chemistry and Pharmacognosy, College of Pharmacy, University of Illinois at Chicago, Chicago, IL 6061, USA

\textsuperscript{b}Division of Medicinal Chemistry and Pharmacognosy, College of Pharmacy, The Ohio State University, Columbus, OH 4321, USA

Abstract

With the clinical success of several synthetic aromatase inhibitors (AIs) in the treatment of postmenopausal estrogen receptor-positive breast cancer, researchers have also been investigating also the potential of natural products as AIs. Natural products from terrestrial and marine organisms provide a chemically diverse array of compounds not always available through current synthetic chemistry techniques. Natural products that have been used traditionally for nutritional or medicinal purposes (e.g., botanical dietary supplements) may also afford AIs with reduced side effects. A thorough review of the literature regarding natural product extracts and secondary metabolites of plant, microbial, and marine origin that have been shown to exhibit aromatase inhibitory activity is presented herein.
Natural Product Compounds with Aromatase Inhibitory Activity: An Update

Marcy J. Balunas\textsuperscript{1,2,3,4} and A. Douglas Kinghorn\textsuperscript{5}

\textsuperscript{1} Division of Medicinal Chemistry, Department of Pharmaceutical Sciences, School of Pharmacy, Storrs, CT 06269, USA

\textsuperscript{2} Center for Marine Biotechnology and Biomedicine, Scripps Institution of Oceanography, University of California San Diego, La Jolla, CA 92093, USA

\textsuperscript{3} Instituto de Investigaciones Científicas y Servicios de Alta Tecnología, Clayton, Panamá

\textsuperscript{4} Smithsonian Tropical Research Institute, Ancón, Panamá

\textsuperscript{5} Division of Medicinal Chemistry and Pharmacognosy, College of Pharmacy, The Ohio State University, Columbus, OH 43210, USA

Abstract

Several synthetic aromatase inhibitors are currently in clinical use for the treatment of postmenopausal women with hormone-receptor positive breast cancer. However, these treatments may lead to untoward side effects and so a search for new aromatase inhibitors continues, especially those for which the activity is promoter-specific, targeting the breast-specific promoters I.3 and II. Recently, numerous natural product compounds have been found to inhibit aromatase in non-cellular, cellular, and \textit{in vivo} studies. These investigations, covering the last two years, as well as additional studies that have focused on the evaluation of natural product compounds as promoter-specific aromatase inhibitors or as aromatase inducers, are described in this review.
• **Grape seed extract** (proanthocyanidins)
  - Eng et al., Cancer Res. 2003; 63:8516.
  - A potent form is undergoing a clinical trial right now.

• **Red Wine** (particularly French Cabernet and CA Pinot Noir).
  - Eng et al., Breast Cancer Res. Treat. 2001; 67:133.

• **White Button Mushrooms**
Natural Aromatase Inhibitors

- Tanglewood Cabernet Savignon France
- Green tea extract
- Coffee
- Cocoa
- Collards, mustard greens, kale, beet greens, parsley, dandilion greens, spinach
- Tobacco
- White button, crimini mushrooms
- Green onions
Natural Aromatase Inhibitors

- Green onions
- Celery
- Asparagus, turnips, endive, escarole
- Peppers, bell peppers
- Turmeric, ginger root
- Tomato, avocado, carrot
- Peach, plum pomegranate, apple, black raspberry
- Beer
Supplements Inhibiting Aromatase

- Red clover
- Grape seed extract
- Willow herb
- Noni
- Licorice
- Cat’s claw
- Mistletoe
- Many flavones
Decreasing oestrogen Production

- **Minimise VAT** since VAT has aromatase

- **Address hyperinsulinaemia** because insulin stimulates aromatase

- **Achieve Ideal Body Weight**
  - The adipocyte produces adiponectin to increase insulin sensitivity, burn fatty acids, and reduce triglycerides and inflammation.
  - *If the adipocyte is too full of fat, it makes less adiponectin which DECREASES insulin sensitivity - and leads to more insulin and more oestrogen.*
“Higher BMI is associated with higher CRP concentrations. These findings suggest a state of low-grade systemic inflammation in overweight and obese persons.”

Another reason to achieve ideal body weight!
Toxic exposure\textsuperscript{1} and Endometriosis

- Dioxin\textsuperscript{2}
- TCDD\textsuperscript{3,4}
- Heavy Metals\textsuperscript{5}
- PCB’s\textsuperscript{6}
- Glyphosate\textsuperscript{7}
What Disrupts Hormonal Balance?

- Nutritional Insufficiencies
- Inflammation, Aging
- Acute and Chronic Stress
- Adiposity
- Altered Biotransformation
- Trauma
- Toxins
- Genetic Propensity
- Food/Diet
- Smoking
- Food Allergy, Sensitivity and/or Intolerance

Hormonal Dysfunction

Signs and Symptoms
We will see this again when we discuss... Perimenopause.
Possible aggravating impact of gene polymorphism in women with endometriosis.

“The study results suggested that women having higher concentration of PCBs and GSTM1 null (*0/*0) polymorphism might have an increased susceptibility of endometriosis.”

Allopathic Approach to Endometriosis

- OCP’s (Progesterone dominant)
- GNRH Agonists
- Surgery
  - Laser Vaporisation
  - Removal of Ovarian Endometrioma
  - Hysterectomy if severe.
Where would you go?

- Genetic predisposition
- Inflammatory disease
- Associated with oxidation
- Environmental toxins found
- Associated with autoimmunity
- Found in the pelvis
A Theory of Endometriosis

Altered gut flora or food sensitivity

GALT up-regulation

Cytokine production in peritoneal fluid

Transformation of totipotential cells

Up-regulation of oestrogen

Growth of ectopic endometrium

Retrograde flow provides nutrients
STAINS

- Stress
- Toxins
- Antigens, allergens
- Infections (dysbiosis), Inflammation
- Nutrition
- Sleep, sedentary lifestyle
Does endometriosis CAUSE infertility?

- In a 1992 study of 2080 infertile women (1263 with endometriosis) patients who failed to conceive with conventional therapy were enrolled in IVF. Conception rates were virtually identical regardless of the presence or absence of endometriosis (30.7% vs 30.0%) leading to the conclusion that endometriosis had nor impact on fertility unless pelvic anatomy was severely distorted.

Causes of infertility

- Ovarian Function-poor oocyte quality
  - Altered follicular environment
  - Elevated oxidative stress
  - Altered hormone milieu

- Tubal function-impaired fertilisation
  - Altered peritoneal environment
  - Altered immune function
  - Altered hormone milieu

- Uterine receptivity-failure of implantation
  - Altered hormone milieu
  - Oxidative stress
  - Clock genes
Medical vs surgical treatment

- Medical treatment has been universally unsuccessful\(^1\)
- Surgical treatment has been inconsistent in both mild cases and those ultimately treated with assisted reproduction.\(^2,3,4,5\)
Why does surgery work

During both laparoscopic and open surgery, the endometrial implants are removed along with the local production of oestrogen, and the pelvis is irrigated, removing inflammatory cytokines. Anesthesia and pain medications are given. Often, surgery is followed by hormone suppression.
So how do we address endometriosis

- 1. The earlier the better
- 2. Avoid toxins and improve detox pathways
- 3. Lower oestrogen and oestrogen effects
- 4. Address gut issues, and lower inflammation
Interventions to support Detoxification

- Artichoke
- Pomegranate
- Watercress
- Green tea
- Cruciferous Vegetables (Indole-3-Carbinol)
- N-Acetyl Cysteine
- Glutamine
- Vitamin C
- Sulfur (onions, shallots, glucosamine sulfate)
- Adequate protein intake
Why some people retain more toxins than others

1. Increased exposures
2. Genetic differences in Phase I & II enzymes (polymorphism)
3. Nutrient deficiencies (B6, Mg, Se)
4. High sugar, low protein diets
5. Heavy metals
6. Stress, emotional trauma
7. Intestinal dysbiosis/overgrowth
Diet and Endometriosis

- Vegetables OR 0.3
- Fruits OR 0.6
- Red meat OR 2.0
- Ham OR 1.8
Interventions to lower Oestrogen effect

- Flax lignans – kill two birds with one stone
- EPA
- Magnesium to bowel tolerance
- Probiotics
- 5R program when needed
- Treat yeast
Intestinal bacteria play a major role in biotransformation and detoxification and may explain some of the differences in xenobiotic metabolism between individuals.
Food Plan to Support Hormone Balance

<table>
<thead>
<tr>
<th>Food Group</th>
<th>Foods to Include</th>
<th>Foods to Exclude</th>
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</thead>
<tbody>
<tr>
<td>Legumes</td>
<td>All legumes and legume products, especially soy products</td>
<td>None</td>
</tr>
<tr>
<td>Vegetables</td>
<td>All, especially cruciferous and sea vegetables (various seaweeds)</td>
<td>None</td>
</tr>
<tr>
<td>Fruits</td>
<td>All whole and dried fruits, especially citrus</td>
<td>None</td>
</tr>
<tr>
<td>Grains</td>
<td>All whole grains and whole-grain products, especially rye</td>
<td>Non-whole grains, refined flours and refined flour products</td>
</tr>
<tr>
<td>Nuts/Seeds</td>
<td>All nuts and seeds and their butters, especially flaxseed, walnuts, and pumpkin seeds</td>
<td>None</td>
</tr>
<tr>
<td>Fish</td>
<td>All, especially cold-water fish: salmon, sardines, tuna, and halibut are an excellent source of omega-3 fatty acids(^1)</td>
<td>Salted or cured fish</td>
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<tr>
<td>Eggs</td>
<td>From organically raised hens</td>
<td>Non-organic eggs(^2)</td>
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<tr>
<td>Poultry/Meat</td>
<td>Organic meats and poultry</td>
<td>Non-organic meats and poultry, salted and cured meats(^3)</td>
</tr>
<tr>
<td>Dairy</td>
<td>Organic dairy products, and soy, nut, and grain dairy substitutes</td>
<td>Non-organic dairy products(^3)</td>
</tr>
<tr>
<td>Oils</td>
<td>Cold-pressed unrefined seed and nut oils, especially flaxseed, walnut, sesame, canola, olive, and soy oils(^1)</td>
<td>Refined vegetable oils, butter, lard, margarine, shortening, and saturated or hydrogenated fats</td>
</tr>
<tr>
<td>Beverages</td>
<td>Mineral or filtered water, herbal tea and decaffeinated herbal tea, fruit juice, and coffee substitutes, especially mint teas and decaffeinated coffee, black tea, cocoa, and beverages with lemon or lime juice soft drinks</td>
<td>Alcohol (beer, wine, spirits), coffee</td>
</tr>
<tr>
<td>Sweeteners</td>
<td>Brown rice syrup, fruit sweetener, molasses, stevia</td>
<td>Refined or artificial sweeteners</td>
</tr>
<tr>
<td>Spices and herbs</td>
<td>Especially nutmeg, anise, thyme, sage, fennel, caraway, and turmeric; and lemon and lime juice</td>
<td>Chocolate, high sodium foods, salt</td>
</tr>
</tbody>
</table>

\(^1\) Cruciferous vegetables include: broccoli, cauliflower, all cabbages, Brussels Sprouts, kale, bok choy, arugula, mustard greens, and watercress.

\(^2\) Non-organically raised livestock are often given hormones to improve their growth; unfortunately, these hormones can be passed on to the consumer and negatively influence hormone balance.

\(^3\) Omega-3 and some omega-6 fatty acids help to counteract symptoms associated with hormone imbalance and should be consumed daily.

\(^4\) Important: Do not cook with oils that are not specified for cooking or baking, such as flaxseed or walnut oils. Olive, canola, soy, and sesame oils are good choices. For cooking or baking, use flaxseed, olive, sesame, or walnut oils for homemade salad dressings. These provide valuable omega-3 and omega-6 fatty acids. Refrigerate all oils and dressings.
A conclusion is the place where you got tired of thinking!
Conclusions
Conclusions

- Endometriosis is an inflammatory disease
- Found in close proximity to the gut and associated with inflammatory processes there
- Endometriosis makes its own oestrogen
- Local inflammation increases oestrogen production which stimulates growth
- Toxins are largely fat soluble, oestrogen-like molecules found in increasing levels in humans
Treatments are therefore:

- Address the gut
- Address inflammation
- Decrease exposure to toxins
- Improve detoxification of oestrogens and toxins
- Decrease body burden of toxins by addressing obesity and VAT
PCOS
PCOS

- Incidence (2004): between 6 and 10% of reproductive age women
- First described by Stein and Leventhal in 1935
- “A complex genetic disease reflecting the interplay of genes and environment” (Sam et al. 2003)

Genes and Environment

• “We propose that the heterogeneity of clinical and biochemical features in PCOS can be explained by the interaction of a small number of key genes with environmental, particularly nutritional, factors.”

PCOS

- **Clinical:** menstrual abnormality, hirsutism, acne, alopecia, anovulatory infertility, recurrent miscarriage

- **Endocrine:** elevated androgens, LH, oestrogens and prolactin

- **Metabolic:** Insulin resistance, obesity, lipid abnormalities and increased risk for DM2
Rotterdam Criteria:

- Requires two of the following:
  - Androgen excess
  - Ovulatory dysfunction
  - Polycystic ovaries on ultrasound

However among 58 specialists there were no single criteria endorsed as definite or probable by more than 64%
Theories:

- A unique defect in insulin action and secretion that leads to hyper-insulinaemia and insulin resistance.
- A primary neuroendocrine defect leading to an exaggerated LH pulse frequency and amplitude.
- A defect of androgen synthesis that results in enhanced ovarian androgen production.
- An alteration in cortisol metabolism resulting in enhanced androgen production.
Causes of Insulin Resistance

- Inadequate clearance of insulin in the liver
- Poor production of insulin by the β-cell
  - Increased secretion when fasting
  - Decreased secretion in response to meal
- Decreased insulin sensitivity in peripheral target tissues
  - Serine vs tyrosine phosphorylation
- Obesity is additive to insulin resistance
Hyperinsulinemia and Hyperandrogenism

- Which comes first “the chicken or the egg”?
- Decreasing androgens by oophorectomy or anti-androgen therapy or GnRH-agonist therapy does not lower insulin levels
- Insulin may:
  - Increase LH through stimulation of IGF’s
  - Enhancing the amplitude of the LH pulses- important in fertility
  - Steroidogenesis via insulin receptor increase in CYP17 activity
  - Decrease SHBG production in the liver
PCOS

Genetics → Insulin Resistance of PCOS → Compensatory Hyperinsulinemia

Liver: ↓ SHBG, ↓ IGFBP-1

VAT: ↑ FFAs

↑ Pituitary LH

Ovary (theca cells): ↑ Androgens

Hyperandrogenemia

What is PCOS then?

- A syndrome which is the result of a “vicious cycle” which can be initiated at any one of many entry points… leading to androgen excess and anovulation.”

Causes of Imbalance: Lessons from PCOS

Genetics: 20-40% occurrence in first degree female relative. Candidate genes include HSD17B6.

Intrauterine Exposure: Animal studies show intrauterine exposure to androgen predisposes to PCOS, including impaired GnRH pulsing, HPA negative feedback mechanisms.

Environment: BPA and other endocrine disruptors accumulates at greater extent in PCOS due to decreased hepatic clearance; this in turn induces androgen production and IR

Obesity: present in 30-75% of PCOS; adipose dysfunction contributes to IR, which can exaggerate hyperandrogenism; sedentarism associated with metabolic dysfunction
Lessons from PCOS

Genetics, Obesity, Sedentarism, Intrauterine Androgen exposure

Insulin Resistance

↑GnRH Pulsing

↓SHBG

Androgen Excess

Antral Follicle Arrest/Anovulation

No corpus luteum/decreased Progesterone

Unopposed (↑) oestrogen

↑Endometrial CA Risk

Metformin?

- The insulin-sensitising agents, metformin and troglitazone, not only reduce circulating insulin concentrations, but also reverse the metabolic and endocrine anomalies (decreased androgens, increased SHBG, decreased PAI-1 consistent with improved fibrinolytic capacity and decreased LH), and more recently, restoring menstrual abnormalities and improving the reproductive outcome in anovulatory PCOS women.

- (Nestler et al., 1998b; Mitwally et al., 1999; Pirwany et al., 1999; Moghetti et al., 2000; Vandermolen et al., 2001)
Additional questions that emerge are: what predicts a good response to metformin - the effect can vary greatly; how safe is metformin in pregnancy and lactation; could metformin reduce the higher prevalence of miscarriage or gestational diabetes in PCOS?
Laboratory Workup

- FSH/LH
- Oestradiol, Testosterone, SHBG (or free Testosterone)
- Fasting and post prandial glucose and insulin
- Ultrasound of ovaries
## Modulators of ovarian androgens

<table>
<thead>
<tr>
<th>Stimulators</th>
<th>Inhibitors</th>
</tr>
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<tbody>
<tr>
<td>- Prostaglandins</td>
<td>- CRF</td>
</tr>
<tr>
<td>- Angiotensin</td>
<td>- TGF-β</td>
</tr>
<tr>
<td>- Inhibin</td>
<td>- EGF</td>
</tr>
<tr>
<td>- IGF1</td>
<td>- TNF</td>
</tr>
<tr>
<td>- Insulin</td>
<td>- Cytokines</td>
</tr>
<tr>
<td></td>
<td>- Activin</td>
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</tbody>
</table>
Figure 3. The Diabetes Epidemic Correlates With Release of POPs Into the Environment.
Conventional Treatment

- Lowering insulin-metformin
- Lowering androgens-OCP’s
- Life-style interventions
Insulin, Oestrogen and Inflammation

- Rigid Cell Membranes (from SAD)
  - Are resistant to insulin leading to increased insulin levels

- Insulin
  - leads to rigid cell membranes (increases AA)
  - Decreases SHBG leading to more free oestrogen
  - Stimulates aromatase leading to more free oestrogen

- Oestrogen
  - Stimulates COX 2 to produce PGE2

- PGE2
  - Stimulates aromatase to produce more oestrogen
Nutrients Known to Modify Insulin Responsiveness at the Cellular Level

- Chromium
- Alpha-lipoic acid
- CoQ10
- Vitamin D
- Magnesium
- Vitamins C and E and other antioxidants
- Omega-3 fatty acids
- Vanadium
Coeliac Disease and PCOS

- Associated with irregular periods, delayed puberty and early menopause\(^1\)
- Three-fold increase in coeliac disease in infertile women\(^2\)
- Coeliac disease by biopsy 0/52, but IgG anti-gliadin antibodies 8/50 infertile vs 1/50 control\(^3\) (Study done in Turkey)
Autoimmunity and PCOS

- Autoimmune mechanism at work?\(^1\)
- Threefold increase in AITD in PCOS patients vs general population.\(^2\)
Inflammation

- Elevated hsCRP in meta-analysis

If you don’t remember anything else…

- Stressors
- Toxins
- Antigens, Allergens
- Inflammation, Infections
- Nutrition
- Sleep. Sedentary lifestyle
Sensitivity: ED, LPD, PCOS

Insulin and FSH-signaling Sensitizers

- Myoinositol (MI) and D-chiro-inositol (DCI) work synergistically
  - DCI mediates insulin activity on non-ovarian tissue
  - MI displays specific effects on ovary by modulating glucose metabolism and FSH-signaling
  - MI may also improve ovarian functions by modulating steroid metabolism via non-insulin dependent pathways
  - Some studies showed clinical improvement measured by more regular menstrual cycles, ovulation or pregnancy.

- Study Doses:
  - DCI 1,000mg to 1,200 gram qday
  - MI 2,000mg qday
  - Combined MI 3,300mg plus DCI 84mg qday

Reference: See Ref. Sensitivity
Why I don’t have a doctor!

- When a doctor himself needs doctoring so that another doctor doctors the doctor, does the doctor doing the doctoring doctor the doctor the way the doctor being doctored wants to be doctored or does the doctor doing the doctoring of the doctor being doctored doctor as he wants to doctor.