Estrogen Metabolism
Tara Scott, MD. FACOG, FAAFM, ABOIM

Webinar 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.
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WHO Am I?

- Tara Scott, MD
- Board certifications in: OB/GYN, Integrative Medicine, and Anti-Aging, Functional and Regenerative Medicine
- Lecture around the world teaching doctors a functional approach to women’s health
- Medical Director of Integrative Medicine at Summa Health in Akron, OH
Objectives

- Review the basics of estrogen metabolism
- Define SNPs and how they affect metabolism
- Discuss which SNPs affect the risk of breast cancer
- Review a case and demonstrate the information the DUTCH test provides

Why is it so important to check estrogen metabolism?

- Is it really possible to have a randomized placebo controlled trial with hormone therapy?
- You need to consider:
  - Weight, age, oophorectomy status
  - Pharmacokinetics- what the body does to the drug
  - Pharmacodynamics- what the drug does to the body
Suppose I tell all my patients to drink 2 liters of water

Marathon Runner in 80 degree weather

Dialysis Patient

Menstrual Cycle

- Developing egg makes Estrogen-causes growth
- After its released, progesterone balances estrogen
What do we Know

This was our Endocrinology Bible in residency!!

Menstrual Cycle

- Developing egg makes Estrogen—causes growth
- After its released, progesterone balances estrogen
Estrogen causes proliferation

Progesterone Inhibits proliferation, decline in DNA synthesis, interferes with the estrogen receptor

Estrogen stimulates many oncogenes that mediate estrogen induced growth. Progesterone antagonizes this action—suppresses transcription of oncogene mRNA

STEROIDOGENIC PATHWAY
Estrogen- Functions

• Promotes growth
• Body development
• Slows bone loss
• Three main types
  • Estradiol- good for heart and bones
  • Estriol - good for skin
  • Estrone- goes to breast- sort of the bad one

Estrone (E1)
Predominant estrogen in postmenopausal women.

Estradiol (E2)
Predominant estrogen in premenopausal women. Most biologically active estrogen in women.

Estriol (E3)
Predominant estrogen in pregnant women. Most abundant estrogen in urine.

Samavat & Kurzer, 2015
Estrone (E1)
Primarily synthesized from androstenedione by aromatase conversion in the ovaries. Reversibly converted into estradiol by enzyme, 17β-hydroxysteroid dehydrogenase Type II.

Estradiol (E2)
Primarily synthesized by developing follicle in the ovaries. Reversibly converted into estrone by enzyme, 17β-hydroxysteroid dehydrogenase Type I.

Estriol (E3)
Synthesized from estrone, which can be converted from the hydroxylation of estradiol or 16-Hydroxyestrone.

I think of Estrogen like three sisters

<table>
<thead>
<tr>
<th>Estrogen Receptor- Alpha</th>
<th>Estrogen Receptor- Beta</th>
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</thead>
<tbody>
<tr>
<td>17- Beta-estradiol</td>
<td>100</td>
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<tr>
<td>17- alpha-estradiol</td>
<td>58</td>
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<tr>
<td>Estriol</td>
<td>14</td>
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<tr>
<td>Estrone</td>
<td>60</td>
</tr>
<tr>
<td>4-OH-Estradiol</td>
<td>13</td>
</tr>
<tr>
<td>2-OH-Estrone</td>
<td>2</td>
</tr>
<tr>
<td>Tamoxifen</td>
<td>4</td>
</tr>
<tr>
<td>Raloxifene</td>
<td>69</td>
</tr>
</tbody>
</table>

Other sources of Estrogens
PHASES OF DETOXIFICATION

Healthy Estrogen Metabolism

Specific Phytonutrients
Specific Supplements
Specific Vitamins
Specific Diet
Healthy Intestine
Minerals
Correct Insulin Resistance
Estrogen Metabolism

More simplified . . .

The "Good" Estrogens

2-HYDROXYESTROGENS:

• Considerable weak with overall low hormonal potency and low binding affinity to estrogen receptors\(^1\).

• 2-hydroxyestrogen have anti-proliferative effects in breast tissue\(^1,2\).

1. Samavat & Kurzer, 2015
2. Gupta et al., 1998
The “Good” Estrogens

**METHOXYESTROGENS:**

- Methoxyestrogens are deactivated forms of estrogen formed from methylation of catechol estrogens.

- This methylation conjugation prevents the biotransformation of hydroxyestrogens into quinone-DNA adducts (DNA damage) and the byproduct formation of reactive oxygen species.

- Methoxyestrogens also inhibit cell proliferation by inhibiting mitosis\(^1,2,3\).

The “Bad” Estrogens

**4-HYDROXYESTROGEN QUINONE METABOLITES**

- Lead to the formation of depurinating adducts\(^1\).

- Women with or at high risk for breast cancer had high levels of adducts in their urine\(^2\).

- In cellular preparations of adenocarcinoma, 4-hydroxyestradiol was 4x higher than 2-hydroxyestradiol\(^3\).
The “Bad” Estrogens

16α-HYDROXYESTRONE

- 16α-Hydroxyestrone is the intermediate between estrone and estriol.
- Higher urinary concentrations of 16α-Hydroxyestrone were associated with mammary cell proliferation in animals.
- 16α-Hydroxyestrone has been found to be higher cancer breast tissue relative to normal breast tissue.
- 16α-Hydroxyestrone is inversely proportional to 2-hydroxyestrone.
- Recent evidence has drawn into question the significance in the 16α-Hydroxyestrone breast cancer relation.

Estrogen Metabolites

Preventing Negative Estrogen Burden

INSECTICIDES (e.g., endosulfan) has been found to inhibit the expression of CYP-1A1, resulting in reduced activity of the 2-hydroxyE pathway.

1. Telang et al., 1992
2. Castagnetta et al., 2002
3. Obi et al., 2011
4. Huang et al., 2012

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**RESVERATROL** prevents the formation of depurinating estrogen DNA adducts in human breast cells treated with E1.

Resveratrol inhibits peroxidase activity, reducing the formation of catechol estrogen quinones1.

Resveratrol also increases NDPH quinone reductase activity2.

**N-ACETYLCYSTEINE** prevents electrophilic damage to DNA by inhibiting the formation electrophilic quinones.

It has been found that the consumption of N-acetylcysteine for a 1-month period resulted in 55% reduction in urinary levels of estrogen DNA adducts1.
IODINE plays a critical role in the maintenance and functioning of mammary gland tissue.

There exists high rates of breast cancer among women with thyroid abnormalities\(^1,2\).

Women with breast cancer tend to have larger thyroid volumes than controls, indicating an association between iodine deficiency and breast cancer\(^1,2\).

IODINE supplementation is effective at diminishing ductal hyperplasia in rats\(^1\).

Patients with benign breast disease that received iodine treatment experienced significant bilateral breast reduction\(^2\).

Japanese communities that consume high amounts of seaweed (high [I]) have reported lower incidences of benign and malignant tissue\(^3\).

Iodine is thought to exhibit its beneficial effects by modulating estrogen metabolism\(^4,5\).
Preventing Negative Estrogen Burden

Increase 2-HydroxyE Pathway Activity

- Increase CYP 1A1
- Increase COMT
- Increase quinone reductase
- Increase glutathione conjugation

Reduce 4-HydroxyE Pathway Activity

- Reduce CYP-1B1
- Reduce Peroxidase
- Decrease β-glucuronidase activity
**BIFIDOBACTERIUM** significantly decreases glucuronidase activity\(^1\).

**CALCIUM-D-GLUCARATE** is a potent beta-glucuronidase inhibitor that has been shown to exert anticarcinogenic effects\(^1\).

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**Estrogens & Estrogen Metabolites**

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**Urinary Hormone Results**

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DUTCH sample report

Genetics 101
What is DNA?
What is a Single Nucleotide Polymorphism (SNP)?
A SNP (pronounced “snip”) is a DNA sequence variation that occurs when a single nucleotide (A, T, C, or G) in the genome sequence is modified.

SNPs do not necessarily cause disease, but they can help determine the likelihood that someone will develop a particular illness.

Not all SNPs are significant
It depends on where it is located.
Genetics 101

Effects of SNPs on protein shape

Some SNPs change the meaning but not the function
Some SNPs are of no consequence.

Are you coming too? Are you two coming?

Some SNPs just denote ethnicity.

Color
Personalize

Colour
Personalise
Some SNPs totally change the meaning

Genetic Inheritance

• Heterozygous - one variation

• Homozygous - two variations

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Genetic Polymorphisms

MTHFR C677T

Methylenetetrahydrofolate

- MTHFR is responsible for reducing folate into its active form.
- MTHFR C677T involves a base change from cytosine to thymine at base 677.
- MTHFR C677T is the most common SNP in the folate cycle.

1. Hiraoka & Kagawa, 2017
2. Miller 2008

Treatment of MTHFR C677T

MTHFR C677T can be enhanced by treatment with folate and/or vitamin B12.

- E.g., In a study that assessed individuals with high dietary folate intake (>225 mcg/day), serum folate levels were significantly lower in individuals with 677TT that those with 677CC.

- Authors recommended that individuals homozygous for 677TT consume approximately 1.4 times more folate to reach levels seen in individuals with 677CC of 677TC genotypes.

1. Nishio et al., 2008
What is Methylation?

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COMT is responsible for the metabolism of monoamines and catechol estrogens.

COMT V158M involves a base change from valine to methionine at base pair 158.

Reduced COMT activity is associated with higher dopamine and norepinephrine levels, lower pain tolerance, and catechol estrogen accumulation (DNA damage). E.g., Individuals with homozygous 158MM genotype administered significantly more morphine post-surgery.

Genetic Polymorphisms

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1. Kotyuk et al., 2015
2. Tan et al., 2016
3. Ashton et al., 2006
Genetic Polymorphisms

**COMT**

- Converts Androgens (androstenedione and testosterone) into estrogens (estradiol and estrone)
- If this is a fast version, it will make estrogen dominance worse
**CYP 1B1** Metabolizes estrogen in 4-OH estrogens
If this is FAST, will increase the risk of estrogen dominance, especially if coupled with a slow COMT

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**Diagram:**
- **Estrone (E1)**
  - Metabolized by CYP 1B1
  - Converted to Estradiol (E2)
  - Converted to Estriol (E3)

**Factors:**
- **17β-HSD**
- **2-OHE1**
- **2-MeOE1**
- **16α-OHE1**

**Inhibitors:**
- Excess sugar, n6 fats, cimetidine, OCs
- Hypothyroidism, pesticide exposure, smoking, caffeine, various medications
- Grapefruit, peppermint oil, rosemary, wild yam, anti-fungals & other medications

**Activators:**
- Crucifers, berries, I3C, DIM, soy, flaxseed, caffeine, rosemary, exercise, thyroid

**Actions:**
- **COMT**
  - 4-OHE1
  - 4-MeOE1

**Support:**
- Adequate methionine, B6 vitamins, GSH, reduce stress, rule out Hg toxicity & oxidative stress
Case – Part 1

Emma was a new patient, and her main complaint was severe PMS and anxiety. She has a lot of stress with 3 young children. The oldest was born prematurely at 28 weeks and has mild cerebral palsy.

Her main complaints were anxiety, poor sleep, and stress.

Medications: Vitamin D
Multivitamin

Family history: Thyroid disease- mother
Celiac disease- sister
Case – Part 1

- CORTISOL - PM: 6.8
- FERRITIN, SERUM: 40
- PROGESTERONE: 13.0
- TRIIODOTHYRONINE,FREE,SERUM: 2.8
- DHEA-SULFATE: 361.1 High
- VITAMIN D, 25-HYDROXY: 21.3 Low
- TSH: 2.080
- T4,FREE(DIRECT): 1.00
- REVERSE T3, SERUM: 13.8
- PREGNENOLONE, MS: 135
- DIHYDROTESTOSTERONE: 3.2 Low
- IRON BIND.CAP.(TIBC): 355
- UIBC: 272
- IRON, SERUM: 83
- IRON SATURATION: 23
- ENDOMYSIAL ANTIBODY IGA: NEGATIVE
- T-TRANSGLUTAMINASE (TTG) IGA: <2
- T-TRANSGLUTAMINASE (TTG) IGG: <2
- IMMUNOGLOBULIN A, QN, SERUM: 290

Saliva Hormone Results 2015
Saliva Hormone Results 2015

Pt was treated with cyclic oral Progesterone 100mg days 14 until the next cycle begins

Vitamin D was replaced with D3 drops

Adaptogens were suggested for high cortisol
CASE FOLLOW-UP

PT presented back to review serum labs- done mid luteal

<table>
<thead>
<tr>
<th>Lab</th>
<th>Results</th>
<th>Normal Range</th>
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</thead>
<tbody>
<tr>
<td>Estrone:</td>
<td>86</td>
<td>54-179</td>
</tr>
<tr>
<td>Estradiol:</td>
<td>122</td>
<td>43-211</td>
</tr>
<tr>
<td>DHEAS</td>
<td>312 H</td>
<td>57-297</td>
</tr>
<tr>
<td>Total Testosterone</td>
<td>20</td>
<td>8-48</td>
</tr>
<tr>
<td>Free Testosterone</td>
<td>2.6</td>
<td>0.0-4.2</td>
</tr>
<tr>
<td>Progesterone</td>
<td>11.0</td>
<td>1.8-23.9</td>
</tr>
</tbody>
</table>
CASE FOLLOW-UP

Pt had previously been seen for stool results

Digestive Issues

Poor Diversity

Decided to change to Progesterone troche for better absorption – 75mg

CASE Follow Up- DUTCH TESTING
Androgens and Progesterone

Estrogen Metabolism

- Important to assess the balance and ratio between the different types of estrogen
- Assess phase 1 and phase 2
- Pay attention to quantity of 4 OH Estrone
Organic Acids

<table>
<thead>
<tr>
<th>Category</th>
<th>Test</th>
<th>Nutritional Organic Acids</th>
<th>Result</th>
<th>Units</th>
<th>Normal Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin B12 Marker</td>
<td>- (Urine)</td>
<td>Above range</td>
<td>2.4</td>
<td>ug/mg</td>
<td>0 - 2.2</td>
</tr>
<tr>
<td>Methylmalonate (MMA)</td>
<td>- (Urine)</td>
<td>Within range</td>
<td>0.4</td>
<td>ug/mg</td>
<td>0 - 1.4</td>
</tr>
<tr>
<td>Xanthurenone</td>
<td>- (Urine)</td>
<td>Within range</td>
<td>2.4</td>
<td>ug/mg</td>
<td>0 - 7.3</td>
</tr>
<tr>
<td>Kynurenate</td>
<td>- (Urine)</td>
<td>Within range</td>
<td>45.7</td>
<td>ug/mg</td>
<td>32 - 60</td>
</tr>
<tr>
<td>Glutathione Marker</td>
<td>- (Urine)</td>
<td>Within range</td>
<td>6.4</td>
<td>ug/mg</td>
<td>4 - 13</td>
</tr>
<tr>
<td>Pyroglutamate</td>
<td>- (Urine)</td>
<td>Within range</td>
<td>4.9</td>
<td>ug/mg</td>
<td>2.4 - 6.4</td>
</tr>
<tr>
<td>Dopamine Metabolite</td>
<td>- (Urine)</td>
<td>Within range</td>
<td>26.1</td>
<td>ng/mg</td>
<td>10 - 85</td>
</tr>
<tr>
<td>Norepinephrine</td>
<td>- (Urine)</td>
<td>Within range</td>
<td>1.3</td>
<td>ng/mg</td>
<td>0 - 5.2</td>
</tr>
</tbody>
</table>
Treatment options

- HOW WOULD YOU CHANGE PROGESTERONE DOSE?
- HOW WOULD YOU SUPPORT METHYLATION?
- WHAT WOULD YOU GIVE FOR ADRENAL SUPPORT?

Conclusions

- Estrogen metabolism should be monitored for any premenopausal patient with risk factors.
- Epigenetic modulation of estrogen metabolism is effective!
- Consider genetic testing for patients with symptoms of poor methylation.
- DUTCH test is a comprehensive test to look at estrogen metabolism and methylation.
...and that concludes our talk
Thank you for listening.

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