Sex Hormone Essentials: Estrogen Metabolism

Stephen L. Goldman, DC
Genova Diagnostics
Technical Issues

Clinical Questions

Clinical Questions will be answered during the final fifteen (15) minutes of the webinar.
Goals of Presentation

Review the components of the **Sex Hormone Pyramid** as they apply to estrogen metabolism:

- Anabolic/ Catabolic Balance review
- Estrogen metabolism
- Other steroidal enzyme activity
• Urine Test (FMV or 24 Hour) – provides comprehensive evaluation of hormone metabolism
  
  – Unbound hormones and circulating metabolites
  – Assess hormone metabolism
  – Assess steroidal enzyme activity
  – Hormone Therapy (HT), use 24 hour collection method
  – “Adding up receipts”
Estrogens

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<td>Estradiol (FMV urine)</td>
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<td>Estriol (FMV urine)</td>
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Estrogen Metabolites

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<th>Estrogen Metabolites</th>
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<tr>
<td>2-Hydroxyestrone (FMV urine)</td>
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<td>16α-Hydroxyestrone (FMV urine)</td>
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<td>4-Hydroxyestrone (FMV urine)</td>
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<td>2-Methoxyestrone (FMV urine)</td>
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<td>4-Methoxyestrone (FMV urine)</td>
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Ratios

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<td>Anabolic/Catabolic Balance (FMV urine)</td>
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<td>11β-HSD Index (FMV urine)</td>
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<td>2-Hydroxyestrone/16α-Hydroxyestrone Ratio (FMV urine)</td>
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<td>2-Methoxyestrone/2-Hydroxyestrone Ratio (FMV urine)</td>
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Anabolic/Catabolic Balance
An Overview
Anabolic/Catabolic Balance

- If you don’t maintain an anabolic/catabolic balance, you will find overall sex hormone balance very difficult to achieve.
Cholesterol

<table>
<thead>
<tr>
<th>Pregnenolone</th>
<th>17-OH-Pregnenolone</th>
<th>DHEA</th>
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<tr>
<td>Progesterone</td>
<td>17-OH-Progesterone</td>
<td>Androstenediol</td>
</tr>
<tr>
<td>Corticosterone</td>
<td></td>
<td>Testosterone</td>
</tr>
<tr>
<td>Aldosterone</td>
<td></td>
<td>DHT</td>
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Cortisol (Glucocorticoids)

Estrone (E1) ↔ Estradiol (E2)

2-OHE1 → 2-MeOE1

16α-OHE1 → Estriol (E3)

4-OHE1 → 4-MeOE1

Cortisol & DHEA derive from same precursors

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Adrenal Dysfunction/ “Cortisol Steal”

- The adrenal glands produce the hormones cortisol and DHEA.

- Over secretion of cortisol triggered by daily stress from work, family or other sources can wear down the internal system and cause fatigue.

- During this process DHEA may be compromised, causing other functions to suffer.

- “Cortisol Steal” describes the imbalance leading to DHEA compromise.
# Androgens

## 17-Ketosteroids

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<tbody>
<tr>
<td>DHEA (24hr urine)</td>
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<tr>
<td>Androsterone (24hr urine)</td>
<td>0.60-5.50 micromol/24 hr</td>
</tr>
<tr>
<td>Etiocholanolone (24hr urine)</td>
<td>1.20-6.10 micromol/24 hr</td>
</tr>
<tr>
<td>11-Keto-androsterone (24hr urine)</td>
<td>0.30-1.90 micromol/24 hr</td>
</tr>
<tr>
<td>11-Keto-etiocholanolone (24hr urine)</td>
<td>0.30-1.60 micromol/24 hr</td>
</tr>
<tr>
<td>11-Hydroxy-androsterone (24hr urine)</td>
<td>1.30-4.10 micromol/24 hr</td>
</tr>
<tr>
<td>11-Hydroxy-etiocholanolone (24hr urine)</td>
<td>0.50-2.60 micromol/24 hr</td>
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<tr>
<td><em><em>17-Ketosteroids, Total</em> (24hr urine)</em>*</td>
<td><strong>6.0-22.2 micromol/24 hr</strong></td>
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### Androgens

<table>
<thead>
<tr>
<th><strong>17-Ketosteroids</strong></th>
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<td>17-Ketosteroids, Total* (24hr urine)</td>
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### Glucocorticoids

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<th><strong>17-Hydroxysteroids</strong></th>
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<tr>
<td>allo-Tetrahydrocortisol, a-THF (24hr urine)</td>
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<td>Tetrahydrodeoxycortisol, THS (24hr urine)</td>
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<tr>
<td>Tetrahydrocortisone, THE (24hr urine)</td>
<td>22.50</td>
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<tr>
<td>Tetrahydrocortisol, THF (24hr urine)</td>
<td>7.78</td>
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<td>17-Hydroxysteroids, Total* (24hr urine)</td>
<td>33.7</td>
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* Total values equal the sum of all measurable parts.
## Androgens

### 17-Ketosteroids

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<td>1.30-4.10 micromol/24 hr</td>
</tr>
</tbody>
</table>

### Anabolic/Catabolic Balance

**17-Ketosteroids/17-Hydroxysteroids Ratio**

- Anabolic/Catabolic Balance (24hr urine) 0.2
- Anabolic/Catabolic Balance (24hr urine) 1.0-3.9

Catabolic (Wear & Tear) ↔ Anabolic (Growth & Healing)

### Catabolic

<table>
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<th>Value</th>
<th>Reference Range</th>
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<tbody>
<tr>
<td>17-Hydroxysteroids Total*</td>
<td>33.7</td>
<td>8.8-22.4 micromol/24 hr</td>
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### Anabolic

<table>
<thead>
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<th>Test</th>
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<tr>
<td>17-Ketosteroids Total*</td>
<td>5.9</td>
<td>6.0-22.2 micromol/24 hr</td>
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</tbody>
</table>

- Tetrahydrocortisone, THE (24hr urine) 22.50
- Tetrahydrocortisol, THF (24hr urine) 7.78
- 17-Hydroxysteroids, Total* (24hr urine) 33.7

* Total values equal the sum of all measurable parts

- Cortisol, Free (24hr urine) 76

Cortisol, Free (24hr urine) 20-90 mcg/24 hr
SEX HORMONE ESSENTIALS
Anabolic/ Catabolic Balance:
Stress and Steroid Metabolism

Patrick Hanaway, MD
Genova Diagnostics
Estrogen Metabolism

Phase I and Phase II Detoxification
Two Major Pathways of Detoxification

Fat Soluble Toxin → Activated Intermediate → Water-Soluble Compound

Phase I: Hydroxylation Reactions
- Cytochrome P450 enzymes

Phase II: Conjugation Reactions
Two Major Pathways of Detoxification

Fat Soluble Toxin → Activated Intermediate → Water-Soluble Compound

Genomic Variations

Toxins
Drugs
Foods

Phase I: Reactive Intermediate
Phase II: Elimination

Oxidative Stress
2:16α-OHE1 Ratio

• Post-menopausal women at baseline who went on to develop breast CA showed 15% lower 2:16-OHE1 ratio than controls (Meilahn EN 1998)

• Lower premenopausal urinary 2:16α-OHE1 may play a role in breast carcinogenesis. Protective association of higher postmenopausal 2:16α-OHE1 may be modulated, obesity may modify associations (Int J Biol Markers. 2012 Aug 1:0. doi: 10.5301/JBM.2012.9353.)

• Women with breast CA at all ages show increased 16α-hydroxylation (Zumoff B 1994)
2:16α-OHE1 Ratio

• **Low ratio** = associated with increased risk of breast and prostate cancer, lupus (Kabat GC 2006, Muti P 2002, Weidler C 2004)

• **High ratio** = associated with increased risk of bone loss in women with low estrogen (e.g., menopause); however, women on HT with high ratio actually show superior bone mineral density response to estrogen (Armammento-Villareal RC 2004)
2-Hydroxyestrone (2-OHE1)

• Very weak estrogenic activity

• Methylation of 2-OHE1 provides protection against breast cancer (NIH trials for 2-MeOHE1 & Br Cancer)

• Highest levels associated with osteoporosis risk (Napoli N 2007)

• Potent antioxidant (Nakano 1987)
16α-Hydroxyestrone (16α-OHE1)

- Strong estrogenic activity
- Turns on estrogen receptor
- Greater likelihood of estrogen-dependent conditions
Normal Human Breast Tissue stained for 16α-Hydroxyestrogen (845X)
Near Adjacent Cancerous Human Breast Tissue Stained for 16α-Hydroxyestrogen (845X)

Klug TL, US Patent 5,854,009
4-Hydroxyestrone (4-OHE1)

- Very potent
- If not inactivated by COMT, 4-OHE1 can be oxidized to 3,4 quinone compounds → DNA adduct formation in tissues such as breast
- Higher 4-OHE2:2-OHE2 ratios in tumor tissue compared to adjacent healthy breast tissue (Meilahn EN 1998)
- Increased 4-hydroxylation of estrogen in uterine fibroids (Reddy VV 1981)
- Link between CYP1B1 SNP (increased 4-OH-estrogen production) and prostate CA (Tang YM 2000)
Estrone (E1) → 2-OHE1 → 16α-OHE1 → 4-OHE1 (pro-carcinogenic) → 4-MeOE1 (neutralized)

Estradiol (E2) → 2-MeOE1 (protective) → Estriol (E3)
Estrogen Metabolites

Estrogen Metabolism
2-Hydroxyestrone/16α-Hydroxyestrone Ratio

16α-OHE1
Higher Risk of Breast / Prostate Cancer

2-OHE1
Lower Risk of Breast / Prostate Cancer

Methylation Activity
2-Methoxyestrone/2-Hydroxyestrone Ratio

Less Methylation

More Methylation

RR = 1.7 - 2.8

RR >= 0.2
COMT: Phase II Methylation

• Increasing breast CA risk with decreasing COMT activity

• Risk higher in women…
  – With prolonged estrogen exposure (HRT, early menarche, or high BMI) \( (\text{Huang CS 1999}) \)
  – Low folate or high homocysteine \( (\text{Goodman JE 2001}) \)
  – Co-existing GST polymorphisms (especially if on HRT) \( (\text{Mitruten K 2002}) \)
To support healthy metabolic pathways...

- Increase production of 2-OH Estrone
  - CYP1A1...
2-Hydroxylation Support

- Broccoli derivatives: Indole-3-carbinol (I3C), diindolylmethane (DIM), sulforaphane glucosinolate
- Soy isoflavones
- Flaxseed lignans
- Omega-3 fats
- Rosemary, turmeric, chrysin
- Exercise
- Weight control
- Vitamin D
- ETOH/smoking
To support healthy metabolic pathways...

- Increase production of 2-OH Estrone
  - CYP1A1
- Decrease production of 4- and 16α-OH E1
  - CYP1B1
16α-Hydroxylation

- Obesity
- Hypothyroidism
- Pesticide toxicity (e.g. organochlorines)
- Omega-6 fatty acid excess
- Inflammatory cytokines
To support healthy metabolic pathways...

- Increase production of 2-OH Estrone
  - CYP1A1
- Decrease production of 4- and 16α-OH E1
  - CYP1B1
- Increase production of 2-MeOE1
  - COMT
Methylation Support

COMT uses SAMe as its methyl donor; therefore, maintaining SAMe availability will encourage COMT activity

- Methionine
- Magnesium
- B2, B6, B12
- Folic acid (also as folinic acid, 5-formyl THF, or 5-methyl THF)
- TMG (betaine)
- Reduce catecholamine production by minimizing stress
Role of Methylation

- 2-OHE1 is only protective against cancer when methylated by catechol-O-methyltransferase (COMT)
  - 2-methoxy-estrogens are being researched for therapeutic use in breast cancer and CV disease
- 4-OHE1 is less likely to oxidize to carcinogenic compounds if neutralized by COMT
- 2-MeOE1:2-OHE1 ratio in urine provides a gauge of methylation capacity in a given patient
To support healthy metabolic pathways...

- Increase production of 2-OH Estrone (E1)
  - CYP1A1
- Decrease production of 4- and 16α-OH E1
  - CYP1B1
- Increase production of 2-MeOE1
  - COMT
- Decrease production of carcinogenic quinones
  - GST
Glutathione Support

- N-acetylcysteine
- Glycine, glutamine
- Magnesium
- Vitamins B2, B6, B12, folic acid
- Anti-oxidants (to discourage formation of quinone compounds)
ENZYMATIC STEPS:
3β-HSD = 3β-Hydroxysteroid dehydrogenase
5α = 5α-reductase
5β = 5β-reductase
CYP11B1 = 11β-Hydroxylase
11β-HSD = 11β-Hydroxysteroid dehydrogenase
17β-HSD = 17β-Hydroxysteroid dehydrogenase
17,20 Lyase = 17,20 Desmolase
CYP17 = 17α-hydroxylase
CYP19 = Aromatase
CYP21 = 21-hydroxylase

ESTROGEN METABOLISM:
1A1 = Cytochrome P450 1A1 (CYP1A1)
3A4 = Cytochrome P450 3A4 (CYP3A4)
1B1 = Cytochrome P450 1B1 (CYP1B1)
COMT = catechol-O-Methyl transferase

This sample pie-chart represents the optimal balance of estrogen metabolites. The metabolites in green are considered protective, whereas metabolites in red are associated with increased risk of auto-immune disease, breast & prostate cancer. The dark line separates Phase 1 and Phase 2 detoxification pathways.
5α-Reductase Activity
Etiocholanolone/Androsterone (E/A) Ratio

More 5α-Reductase
Less 5α-Reductase

RR = 0.55 - 2.45
5a-Reductase Activity

• We cannot measure DHT in urine, though it can be measured in serum.
• Evaluation of 5-alpha reductase activity provides insight into possible conversion of testosterone into DHT.
• Elevated DHT increases risk of BPH and prostate cancer. LiJ, Ding Z, Dept of Systems Biology, University of Texas MD Anderson Cancer Center, Epub 2011
5α-Reductase Activity
Etiocholanolone/Androsterone (E/A) Ratio

More 5α-Reductase

Less 5α-Reductase

RR = 0.55 - 2.45
ENZYMATIC STEPS:
3β-HSD = 3β-Hydroxysteroid dehydrogenase
5α = 5α-Hydroxysteroid dehydrogenase
5β = 5β-Hydroxysteroid dehydrogenase
11β-HSD = 11β-Hydroxysteroid dehydrogenase
17β-HSD = 17β-Hydroxysteroid dehydrogenase
17,20-Lyase = 17,20-Lyase
CYP17 = 17,20-Lyase
CYP19 = aromatase
CYP21 = 21-Hydroxylase

ESTROGEN METABOLISM:
1A1 = Cytochrome p450 1A1 (CYP1A1)
3A4 = Cytochrome p450 3A4 (CYP3A4)
181 = Cytochrome p450 181 (CYP1B1)
COMT = Catechol-O-Methyltransferase
11β-HSD Index
(a-THF + THF)/THE

Less Cortisol 0.33 More Cortisol

RR = 0.59 - 1.42
11β-HSD Index

• Provides insight into active cortisol and its metabolites relative to inactive cortisone and its metabolite
Concluding Thoughts

• The Endocrine Pyramid & Steroidogenic Pathway provide an important framework for understanding hormonal health.

• Metabolic pathways and clinical presentation guide us to personalize recommendations for treatment.
Concluding Thoughts

Review the components of the **Sex Hormone Pyramid** as they apply to estrogen metabolism:

• Anabolic/ Catabolic Balance review

• Estrogen metabolism

• Other steroidal enzyme activity
Questions & Answers

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Essential & Metabolic Fatty Acids Analysis
Amino Acids

Case Studies

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Depression - NutrEval
Optimal Health - ONE

In-Depth Modules

Antioxidants, Interpretation At-A-Glance
B-Vitamins, Interpretation At-A-Glance
Minerals, Interpretation At-A-Glance
Digestive Support, Interpretation At-A-Glance
Functional Imbalances, Interpretation At-A-Glance

Oxidative Stress - Biomarkers
Metabolic Analysis - Biomarkers
Amino Acids Plasma - Biomarkers
Amino Acids Urine - Biomarkers
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Sex Hormone Essentials

- 9/26/12 – Personalizing Hormonal Therapy
  » Right Test → Right Treatment
Sex Hormone Essentials: Estrogen Metabolism

Stephen L. Goldman, DC
Genova Diagnostics