Quantitative values vs. Relative values

When deciding how to incorporate or modify estrogen therapy, 2 things must be considered; the actual amount of each analyte (quantitative) and the ratios of each analyte relative to one another (relative).

Each PhyL hormone profile includes quantitative values for:
- Estrone
- Estradiol
- Estriol
- 16 – alpha-hydroxyestrone
- 2-hydroxyestrone
- 2-methoxyestrone
- 4-hydroxyestrone
- 4-methoxyestrone

Additionally, the report includes 3 estrogen ratios:
- Estrogen Quotient
- 2:16 Ratio
- Methylation Ratio
- Total Estrogen Load
- Progesterone Ratio
- These ratios show the balance between the quantitative values
Estrogen in Cycling Women

Progesterone levels rise after ovulation. If progesterone levels are too low or estrogen was not detoxified, PMS results.

Estrogen falls, liver must work hard to detoxify it— if it has enough nutrients.

Butternutrition.com
Estrogen Metabolism

Estrone ↔ Estradiol

Estriol

Intended for internal use – Confidential - do not distribute
Estrogen Metabolism 2-Pathway

Estrone → CYP1A1 → 2-Hydroxylase → 2-OHE1 → COMT → 2-OMeE1 → Estradiol

- Good reaction: 2-OMeE1
- Poor reaction: 2-OHE1
Estrogen Metabolism – 16-Pathway and E Quotient

Estrone ↔ Estradiol

CYP1B1

16α Hydroxylase

16α-OHE1 BAD 

16α Hydroxylase

Estriol GOOD 

Intended for internal use – Confidential - do not distribute
Estrogen Metabolism – Inflammation

2-OHE1 Decreases

16-aOHE1 Increases

2-OMeE1 Decreases
Estrogen Metabolism 4-Pathway

Estrone ↔ Estradiol

CYP1B1 → 4-Hydroxylase

4-OHE1
BAD

COMT

4-OMeE1
GOOD

Intended for internal use – Confidential - do not distribute
Estrogen Metabolism

**Estrone**
- 4-Hydroxylase (CYP1B1)
- 2-Hydroxylase (CYP1A1)

- 4-OHE1 (BAD)
- 2-OHE1 (GOOD)
- 16α-OHE1 (BAD)

**Estradiol**
- 16α-Hydroxylase

- Estriol (GOOD)

**Metabolic Enzymes**
- COMT
- 4-OMeE1 (GOOD)
- 2-OMeE1 (GOOD)
# Monitoring Estrogen Dosing vs. Metabolism

<table>
<thead>
<tr>
<th>TEST</th>
<th>RESULT</th>
<th>UNITS</th>
<th>TARGET RANGE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregnanediol - FMV ( FMV - Female (supplemented - bedtime dose range 2000-8000) )</td>
<td>4448.6</td>
<td>ug/mg CR</td>
<td>1000-6000</td>
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<tr>
<td>Total Estrogen Load ( Female )</td>
<td>145.6</td>
<td>Total</td>
<td>40-150</td>
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<tr>
<td>Estrone - FMV ( FMV )</td>
<td>8.9</td>
<td>ug/mg CR</td>
<td>1-12</td>
</tr>
<tr>
<td>Estradiol - FMV ( FMV )</td>
<td>1.6</td>
<td>ug/mg CR</td>
<td>0.6-5</td>
</tr>
<tr>
<td>Estriol - FMV ( FMV )</td>
<td>10.3</td>
<td>ug/mg CR</td>
<td>2.5-25</td>
</tr>
<tr>
<td>E Quotient (E3/(E1+E2) ( Optimal = greater than 1 )</td>
<td>Optimal 1.0</td>
<td></td>
<td>&gt;=1</td>
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<tr>
<td>16 Alpha-hydroxyestrone</td>
<td>5.8</td>
<td>ug/mg CR</td>
<td>0.2-15</td>
</tr>
<tr>
<td>2 Hydroxyestrone</td>
<td>15.0</td>
<td>ug/mg CR</td>
<td>4.2-15.6</td>
</tr>
<tr>
<td>4 Hydroxyestrone</td>
<td>&lt;0.5</td>
<td>ug/mg CR</td>
<td>&lt;3.5</td>
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<tr>
<td>2:16 Ratio</td>
<td>Low 2.6</td>
<td>Ratio</td>
<td>&gt;4</td>
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<tr>
<td>2 Methoxyestrone</td>
<td>1.1</td>
<td>ug/mg CR</td>
<td>0.5-8.1</td>
</tr>
<tr>
<td>Methylation Ratio</td>
<td>(low) 7.2</td>
<td>Ratio</td>
<td>&gt;10</td>
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## Monitoring Estrogen Dosing vs. Metabolism

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
<th>Units</th>
<th>Target Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregnandiol (Female Cream/No supplemented range)</td>
<td>3324.0</td>
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<td>Total Estrogen Load (Female)</td>
<td>(High) 253.3</td>
<td>Total</td>
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<tr>
<td>Estrone</td>
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<td>ug/mg CR</td>
<td>1-12</td>
</tr>
<tr>
<td>Estradiol</td>
<td>(High) 5.1</td>
<td>(High)</td>
<td>0.6-5</td>
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<tr>
<td>Estriol</td>
<td>(High) 47.8</td>
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<td>2-Hydroxyestrone</td>
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<td>(Elevated)</td>
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<td>4-Hydroxyestrone</td>
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<td>Favorable 22.9</td>
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# Monitoring Estrogen Dosing vs. Metabolism

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<th>TEST</th>
<th>RESULT</th>
<th>UNITS</th>
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</tr>
</thead>
<tbody>
<tr>
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<td>Estrone</td>
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<td>Estradiol</td>
<td>1.8</td>
<td>ug/mg CR</td>
<td>0.6-5</td>
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<tr>
<td>Estriol</td>
<td>(high) 28.0</td>
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<tr>
<td>E Quotient (E3/(E1+E2) (Optimal = greater than 1)</td>
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<td>ug/mg CR</td>
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<tr>
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<td>ug/mg CR</td>
<td>&lt;3.5</td>
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<tr>
<td>4-Hydroxyestrone</td>
<td>&lt;0.5</td>
<td>ug/mg CR</td>
<td>&lt;3.5</td>
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<td>2:16 Ratio</td>
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<td>2-Methoxyestrone</td>
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<td>ug/mg CR</td>
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<td>Methylation Ratio</td>
<td>(low) 0.8</td>
<td>ug/mg CR</td>
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# Monitoring Estrogen Dosing vs. Metabolism

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<tr>
<td>Pregnandiol (Female Supplemented range)</td>
<td>4137.0</td>
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<td>Total Estrogen Load (Female)</td>
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<td>Estrone</td>
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<td>ug/mg CR</td>
<td>1-12</td>
</tr>
<tr>
<td>Estradiol</td>
<td>1.2</td>
<td>ug/mg CR</td>
<td>0.6-5</td>
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<tr>
<td>Estriol</td>
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<td>Optimal 11.2</td>
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<td>16-A Alpha-hydroxyestrone</td>
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<td>ug/mg CR</td>
<td>0.2-15</td>
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<td>Methylation Ratio</td>
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**Monitoring Estrogen Dosing vs. Metabolism**

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<tr>
<td>Pregnanediol - FMV (FMV - Female (Cream or non-supplemented range))</td>
<td>3143.0</td>
<td>ug/mg CR</td>
<td>400-2000</td>
</tr>
<tr>
<td></td>
<td>(High) 162.0</td>
<td>Total</td>
<td>40-150</td>
</tr>
<tr>
<td>Estrone - FMV (FMV)</td>
<td>8.1</td>
<td>ug/mg CR</td>
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<td>16-Acetahydroxyestrone</td>
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</table>
2-Hydroxyestrone

When within range and with proper methylation, 2-hydroxyestrone is considered a “good” estrogen metabolite and the 2-hydroxyl pathway is considered the most favorable path for detoxification of estrogen.

**LOW 2-OHE1**

- Low 2-OHE1 + Low 16-aOHE1 + Low Primary Estrogens
  - consider an increase in estrogen therapy

- Low 2-OHE1 + Low 16-aOHE1 + High Primary Estrogens
  - Support Phase I metabolism

- Low 2-OHE1 + High 16-aOHE1 + Low Primary Estrogens
  - Consider bi-est to treat
  - Inflammation indicator – support gut health and Phase I + Phase II

**HIGH 2-OHE1**

- High 2-OHE1 + High 16-aOHE1 levels
  - consider reducing estrogen therapy is TEL is high
  - Increase 2:16 Ratio

- High 2-OHE1 + Low 16-aOHE1
  - Make sure primary estrogens and TEL are good, otherwise consider changing to bi-est or reducing therapy

- High 2-OHE1 + Low 2-OMeE1
  - See therapies for increasing methylation ratio (Slide 14)

Methylation not as critical
16-alpha-Hydroxyestrone

Considered a “bad” estrogen. Can increase the rate of existing cancer growth and is found at higher levels than 2-OHE1 in breast cancer patients.

LOW 16alpha-OHE1

- Considered favorable
- Low levels combined with low 2-OHE1 can indicate the need for primary estrogen therapy – patients who are already on a treatment plan may consider an increase in estrogen therapy.

HIGH 16alpha-OHE1

- High levels of 16-aOHE1 combined with high 2-OHE1 levels
  - consider reducing estrogen therapy
- High levels of 16-aOHE1 combined with low 2-OHE1 levels
  - Increase the 2:16 Ratio
4-Hydroxyestrone

Considered a “bad” estrogen, 4-hydroxyestrone is reported to have carcinogenic effects on estrogen–sensitive tissues and may even indicate when a tumor exists. During Phase I detoxification, 4-hydroxyestrone can be metabolized into quinone estrogens that can cause genetic mutations and further increase the risk of cancer.

<table>
<thead>
<tr>
<th>LOW 4-OHE1</th>
<th>HIGH/ANY 4-OHE1</th>
</tr>
</thead>
</table>
| • Considered favorable | • High levels of 4-OHE1 combined with high 2-OHE1 levels  
• consider reducing estrogen therapy  
• Increase Phase II detoxification by up-regulating COMT (increasing Methylation)  
• Stop Oral Estrogen therapy |
| | • High levels of 4-OHE1 combined with low 2-OHE1 levels  
• Do not supplement without addressing COMT activity by increasing Phase II detoxification |
2-Methoxyestrone

Considered a “good” estrogen with anti-carcinogenic effects. 2-methoxyestrone both decreases the risk of developing cancer and slows proliferation of existing cancer cells.

LOW 2-OMeE1

- Plus Normal/elevated 2-OHE1
  - Increase methylation through diet, supplements, lifestyle
- Plus Low 2-OHE1
  - Not relevant

HIGH 2-OMeE1

- High levels of 2-OMeE1 combined with high 2-OHE1 levels
  - Consider reducing estrogen therapy
- High levels of 2-OMeE1 combined with low 2-OHE1 levels
  - Considered Favorable
  - If symptoms are present and primary estrogen levels are low, estrogen supplementation can be considered
Low 2:16 Ratio (ratio less than 4)

Risks Associations: Cancer, PCOS

Possible causes:

- INFLAMMATION
- Reduced CYP1A1 activity (inhibiting 2–OHE1 production)
- Estrogen therapy dosing is too high (when combined with a high 2-OHE1)
- Oral estrogen supplementation
- Decreased Methylation activity
- Caffeine/coffee consumption
- Poor GI health

Treatments to consider:

- GI DETOX supporting Phase I and Phase II metabolism
- Increase methylation
- Supplement with I3C or DIM
- Increase fruit and vegetable intake, especially cruciferous vegetables or supplement with cruciferous veggie drinks/capsules
- Change to a non-oral estrogen therapy
- Increase omega-3 fatty acids
- Avoid caffeine/coffee in diet
- Increase detoxification and methylation with folic acid, B vitamins, as well as SAMe and sulfur supplements
- Encourage a Paleo-like diet
- Regulate sleep
- Increase exercise
2:16 Estrogen Ratio

High 2:16 Ratio (ratio more than 35)

**Risks Associations:** Although a 2:16 ratio above 4 is associated with reduced risk of breast cancer, when a patient presents with a HIGH 2-OHE1 AND a HIGH 2:16 ratio, this can be associated with some cancers and increases as the 2-OHE1 value increased above norms.
Methylation Ratio

Low Methylation Ratio (ratio less than 10)

Risks Associations:

If quantitative values of 2-OHE1 are low, the risk is also lower and the patient may require estrogen therapy (check the primary estrogen levels).

Possible Causes:
• Decreased Methylation due to:
  • Low COMT activity
  • Inflammatory responses (stress)
  • Diet

Treatments to consider:
• GI DETOX Supporting Phase and Phase II detoxification
• Increase methylation by the following:
  • Supplement with I3C or DIM
  • Increase fruit and vegetable intake, especially cruciferous vegetables or supplement with cruciferous veggie drinks/capsules
  • Increase omega-3 fatty acids
  • Avoid caffeine/coffee in diet
  • Increase detoxification and methylation with folic acid, B vitamins, SAMe and sulfur-containing supplements
• Encourage a Paleo-like diet
• Reduce stress
• Identify possible COMT mutations
Methylation Ratio

High Methylation Ratio

**Risks Associations:** A High Methylation ratio is favorable and is associated with a decreased risk in developing certain cancers.

When the Methylation ratio is high AND the level of 2-OHE1 is Low, the ratio can be ignored.

When the Methylation ratio is high AND the level of 2-OHE1 is also high, the patient may be at greater risk for inflammation due to estrogen dominance.

Look for signs/symptoms of methyl trapping.
Methyl Trapping

Risks Associations:

If someone has an MTHFR mutation, methyl trapping can occur during therapy with folate, SAMe, B-Vitamins or other methyl donor supplements.

Some other causes of methyl trapping:
- Infection
- Autoimmunity
- Toxic body burden
- Problems with blood sugar and fat metabolism
- Other inflammatory indications

Treatments to consider:

Non-methylating nutritional support should be provided for mutations in:
- MTR/MTRR, BHMT, SHMT2, MAT1A, CBS, QDPR, OTC, CPS, ARG2, PCBD1, MAOA or B, COMT, HNMT, DHPR, NOS1, 2, 3, SOD1, SOD2, PEMT, PON1, ABCB1, cytochrome P 450 genes and Soluble Carrier Family transporter protein SNPs
Cortisol Testing

Stacy J Cocilova – Physicians Lab
Intended for internal use – Confidential - do not distribute
Cortisol Metabolites

- Cortisone
- Corticosterone
- DHEA-S
- Pregnanetriol
- Tetrahydroaldosterone
- αTHF (allo-tetrahydrocortisol)
- αTHB (allo-tetrahydrocorticosterone)
- THA (tetrahydro-11-dehydrocorticosterone)
- ACTIVE: THF (tetrahydrocortisol)
- INACTIVE: THE (tetrahydrocortisone)
- THB (tetrahydrocorticosterone)
- THS (tetrahydrodeoxycortisol)
- 11-Deoxycorticosterone
- 11- Deoxycortisol
Cortisol Metabolites

Cortisol, which is the active hormone, can convert into cortisone, the inactive form.

Cortisol and Cortisone convert back and forth in various places in the body.

By looking at whether cortisol metabolites (aTHF, bTHF) or cortisone metabolites (bTHE) are made more (compared to what is normal), we can report a total cortisol vs a total cortisone.
There are certain lifestyles and disease states that drive cortisol metabolism to cortisone metabolism more often and we can use this information to make some changes to the patient that continues to have low cortisol.

**More Cortisone:**
- Hyperthyroidism, hGH, E2, ketoconazole, quality sleep, magnolia, scutellaria, izyphus, testosterone, citrus peel extract

**More Cortisol:**
- Hypothyroid, licorice, grapefruit, inflammation, visceral obesity, high insulin, excess sodium

**VS.**
Why Cortisol vs Cortisone?

Addison Disease patient

Obesity patient
Why Cortisol vs Cortisone?

- Hypothyroid?
- Sluggish Metabolism?
- Inflammatory Response/
  Elevated ACTH?
Transdermal Progesterone
Saliva/blood spot vs Urine

Levels well above baseline for >12 weeks!

Patient testing shows elevated levels sometimes >6 MONTHS later!

INTERNATIONAL JOURNAL OF PHARMACEUTICAL COMPOUNDING
June 1998