Estrogen Metabolism

A growing body of research shows that it is not simply the amount of total estrogen circulating in the body that is critical to women's health. How estrogen is metabolized in the body may also play an important role in causing various estrogen-dependent conditions, including osteoporosis, autoimmune disorders, and cancer.

After menopause, the metabolism of estrogen can change. Consequently, a woman may respond differently to exogenous estrogen. Estrogen is metabolized in the body in the following ways (Fig. 35-1):

- Two major competing pathways
  - 2-Hydroxyestrone
  - 16-Hydroxyestrone
- One minor pathway
  - 4-Hydroxyestrone

2-Hydroxyestrone is sometimes called the good estrogen. It does not stimulate the cells to divide, which can cause damage to DNA and cause tumor growth. Furthermore, by latching onto available estrogen cell receptors, 2-hydroxyestrone may exhibit a blocking action that

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**FIGURE 35-1**
Steroid hormone metabolism. (Courtesy of Sahar Swidan, PharD, BCPS.)

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**ENZYMES**

1. Cholesterol side chain cleavage (CSCC)
2. 3β-Hydroxysteroid Dehydrogenase (3β-OHSD) AND Δ5,4 Isomerase (reside on same protein)
3. 17α-Hydroxylase**
4. C17,20-Lysase**
5. 17β-Hydroxysteroid Dehydrogenase (17β-OHSD)
6. Aromatase
7. 5α-Reductase AND NADPH
8. 21-Hydrolase
9. 11β-Hydroxylase
10. 18-Hydroxylase AND 18-Hydroxydehydrogenase
11. 16α-Hydroxylase
   (A) Inhibited by Chrysin
   (B) Increased by cruciferous vegetables (Indole-3-Carbinol) and flaxseed
   (C) Decreased by cruciferous vegetables (Indole-3-Carbinol) and flaxseed

**NOTE:** 17α-Hydroxylase and C17,20-Lysase activities reside on a single protein (designated P450C17)
increased levels of 4-hydroxyestrone. This metabolite is much more active and has a strong stimulatory effect. 16-Hydroxyestrone binds to special receptors in side the cells that have increased the rate of DNA synthesis and cell multiplication. Consequently, 16-hydroxyestrone is proposed to have significant estrogenic activity and to be associated with an increased risk of breast cancer. 109 Futhermore, 16-hydroxyestrone permanently binds to the estrogen receptor. Other estrogen metabolites attach briefly and then are released. 114 Other reasons may also exist for the association of 16-hydroxyestrone with a higher rate of cancer. High levels of 16-hydroxyestrone are associated with obesity, hypothyroidism, pesticide toxicity (organochlorines), omega-6 fatty acids, ces, and inflammatory cytokine production. For the body to make a small amount of 16-hydroxyestrone with a higher risk of breast cancer than when the 2-hydroxy pathway breaks down more estrogen. 115

Studies have shown that low 2:16 hydroxyestrogen ratios are associated with elevated breast cancer rate. One study of postmenopausal women who went on to develop breast cancer had a 15% lower 2:16 hydroxyestrogen ratio than did women in control groups. 116 Similarly, in women who already have breast cancer, the survival rate is greater in women with higher ratios. 117–119 2-Hydroxyestrone is protective against cancer only when this substance is methylated by catechol-O-methyltransferase (COMT) in to 2-methoxyestrone. The ratio of 2-methoxyestrone to 2-hydroxyestrone can be measured in the urine and is a good gauge of the body's ability to methylate. Another way of evaluating the body's ability to methylate is by measuring the serum homocysteine level. If it is elevated, this suggests poor methylation. Low ratios of 2:16 hydroxyestrogen are also associated with an increased rate of developing lupus.

Factors that support methylation are numerous:

- S-Aenosyl-1-methionine (SAMe)
- Methionine
- Folic acid (also as folic acid, 5-formyl THF, or 5-methyltetrahydrofolate)
- 5-Methylglycine (TMG)
- Reducing catecholamine production by decreasing stress

A minor pathway of estrogen metabolism is 4-hydroxyestrone. 110 The other ma jor pathway is 16-hydroxyestrone. 116,117 Studies have shown that 4-hydroxyestrone is present in equine estrone causes mutagenic damage five times more rapidly than do other forms of 4-hydroxyestrogens. 118 Therefore, the metabolism of estrone through the 2-hydroxy pathway is of critical importance in lowering the risk of cellular damage and possible development of cancer. It is consequently very important to measure the patient's levels of 2-hydroxyestrogen and 16-hydroxyestrone, as well as the ratio between these two metabolites. Equally important is to measure 4-hydroxyestrone levels. The goal is to normalize estrogen metabolism. Follow-up testing is also suggested to assess the clinical impact of dietary and lifestyle changes, as well as HRT. 119 Even patients not receiving HRT should have an estrogen metabolism test, particularly if they have a family history of breast cancer.

What can elevate 2-hydroxyestrogen levels?

- Moderate exercise 120,121
- Ca s tic vegetables 105,126–135
- Flax 136,137
- Snail 138
- Kudzu (source of isoflavones)
- Rosemary, turmeric
- Exercise
- Weight loss
- Broccoli derivative 139,140
- Indole-3-carbol
- Diindolylmethane (DIM), a breakdown product of indole-3-carbon
- Saliforaphane glucosinolate
- High-protein diet 141
- Omega-3 fatty acids 101,108,148
- Vitamins B6 and B12 and folate 149,150

All the foregoing have been shown to increase the 2:16 ratio significantly and decrease 4-hydroxyestrone production, thus reducing the risk of estrogen-dependent health problems by shifting estrone metabolism toward the less active 2-hydroxyestrone pathway.

Other factors affect how the body metabolizes estrogen. The first is obesity, which increases the action of estrogens in three ways: 151;

- Estrogen production and storage occur in fat cells. 152,153
- Concentrations of sex hormone–binding globulin are decreased in obese patients. This change increases the amount of unbound estrogen available for use by the body. 154
- Obesity decreases the amount of estrogen production.

The second factor is the presence of estrogenic chemicals that interact with estrogen receptors. Researchers have identified 50 chemicals that inhibit estrogen. 155

Third, excessive alcohol intake interferes with the body's ability to detoxify estrogen and increases E2 levels and, consequently, the risk of breast cancer. 156

Equine estrone increases metastasis to the 4-hydroxyestrogens. Equine estrone increases metastasis to the 4-hydroxyestrogens. T studes ha ve sho wn that estrone binds to the estrone receptor. Other estrogen metabolites that react with DNA and cause mutations that can be carcinogenic. 157 In addition, 4-hydroxyestrone is present in greater quantities in patients deficient in methionine and folic acid. Women who have uterine fibroids also may have increased levels of 4-hydroxyestrone.
Finally, even antibiotics found in the food may be associated with an elevated risk of breast cancer development by changing the gut flora involved in the enterohepatic circulation of estrogens.\textsuperscript{161}

Measuring estrogen metabolism (the 2-hydroxyestroneto-16 alpha-hydroxyestrone ratio, 4-hydroxyestrogen) is a key component to therapy.

### Estrogen Receptor Modulators

Selective estrogen receptor modulators (SERMs) are a type of HRT. SERMs decrease total cholesterol by 5% and low-density lipoprotein (LDL) by 10%. They are not as effective in lowering triglycerides, however, and they do not increase high-density lipoprotein (HDL) as effectively as does standard HRT.\textsuperscript{162} Furthermore, because estrogen receptor modulators are not neuroprotective, they do not have the same positive effect on memory and mood as does natural estrogen.\textsuperscript{163}

#### Progesterone

Progesterone is made in the ovaries before menopause. After menopause, some progesterone is made in the adrenal glands (Box 35-5 and Box 35-4e).\textsuperscript{164–169}

Natural progesterone is biologically identical to what the patient's own body produces. Synthetic progesterone, called progestin, is very different from natural progesterone. Consequently, progestins do not reproduce the actions of natural progesterone.\textsuperscript{170} Further information on progesterone is available in the literature.\textsuperscript{171–189}

One study showed that the use of synthetic progesterone increased the risk of breast cancer by 800% as compared with the use of estrogen alone.\textsuperscript{190–193} Furthermore, an article published in JAMA (the official journal of The American Medical Association) discussed a risk of breast cancer that was predicted to rise by nearly 80% after 10 years of use of estrogen-progestin HRT and 160% after 20 years.\textsuperscript{192} Similarly, Dr. Stephen Sinatra, a well-known cardiologist, found that synthetic progestins can lead to serious cardiac side effects in patients, including shortness of breath, fatigue, chest pain, and high blood pressure. Progesterone (bio-identical) does not share the same risk seen with progestins (Box 35-6).\textsuperscript{194–217}

### BOX 35-6. Effects of Bio-Identical Progesterone

- Helps balance estrogen
- Leaves the body quickly
- Improves sleep hygiene
- Stimulates the production of new bone
- Has a natural calming effect\textsuperscript{205}
- Lowers high blood pressure
- Helps the body use and eliminate fats
- Lowers cholesterol
- May protect against breast cancer by inhibiting breast tissue overgrowth
- Increases scalp hair
- Normalizes libido
- Helps balance fluids in the cells
- Increases the beneficial effects of estrogens on blood vessel dilation in atherosclerotic plaques\textsuperscript{206–208}
- Has an anti-proliferative effect on all progesterone receptors, not just receptors in the uterus\textsuperscript{187,188}
- Does not change the good effect of estrogen on blood flow\textsuperscript{177}
- Increases metabolic rate\textsuperscript{209}
- Is a natural diuretic
- Enhances the action of thyroid hormones
- Prevents migraine headaches that are cycle related
- Is a natural antidepressant
- Improves libido
- Helps restore proper cell oxygen levels
- Induces conversion of estrone (E\textsubscript{1}) to the inactive E\textsubscript{15} form
- Promotes helper T-cell (Th2) immunity
- Is neuroprotective by promoting myelination
- Is anti-inflammatory
- Relaxes smooth muscle
- Promotes bone formation or turnover\textsuperscript{210}

The hormonal symphony is very important. If the body has too much synthetic or natural progesterone, then some of the following effects can occur:\textsuperscript{210,211,212}

- Increases fat storage
- Decreases glucose tolerance and increases insulin levels, which may lead to insulin resistance
- Increases cortisol
- Increases appetite
- Increases carbohydrate cravings
- Relaxes the smooth muscles of the gut and thus can cause bloating, fullness, and constipation; can also contribute to gallstone formation\textsuperscript{213}
- Suppresses the immune system\textsuperscript{214}
- Causes incontinence\textsuperscript{215}
- Causes ligaments to relax and can cause backaches, leg aches, and achy hips\textsuperscript{216}
- Decreases growth hormone levels\textsuperscript{217}

### BOX 35-5. Symptoms of Decreased Progesterone Levels

- Anxiety
- Depression
- Irritability
- Mood swings
- Insomnia
- Pain and inflammation
- Osteoporosis
- Decreased high-density lipoprotein
- Excessive menstruation
- Hypersensitivity
- Nervousness
- Migraine headaches before cycles
- Weight gain
- Decreased libido