Estrogen Treatment ‘Failure':
Hyperexcretion of Estrogen

If your patient doesn’t experience the usual relief of “low estrogen” symptoms when given the same amount of estrogen-including BHRT that works for the large majority of women -- and especially if there’s no change with an increased dose – her body may be “hyperexcreting” estrogens into the urine and stool, retaining too little to achieve symptom relief. Estrogen hyperexcretion can be confirmed (or not) with a finding of higher than anticipated estrogens in a 24-hour urine specimen, while serum estrogens remain low normal or low. In most (but all) instances, there is a history of prior Premarin or other nonbioidentical hormone use.

What to do? Dr. Wright and his colleagues at the Tahoma Clinic have found that estrogen (and other steroid hormone) hyperexcretion is correctable with physiologic quantities of cobalt, one of the relatively “obscure” trace elements. Diet surveys from around the world have found that dietary cobalt intake ranges from 10 to 600 micrograms daily; almost always, “hyperexcretion” of estrogens and other steroids can be corrected with 500 micrograms daily. Symptom relief usually starts within 2 to 3 weeks, and is completely corrected in 2 to 4 months. Correction of hyperexcretion can be confirmed with follow-up 24 hour urine testing, which shows estrogen levels diminished into the expectable range. When symptom relief is accompanied by normalization of laboratory values, cobalt can usually be stopped. Resumption to control both symptoms and lab confirmation of estrogen and other steroid hyperexcretion is rarely necessary.

Other Steroid Hyperexcretion

Dr. Wright and other Tahoma Clinic physicians have occasionally observed hyperexcretion of testosterone and cortisol. As with estrogens, symptoms are usually of underactivity of testosterone or cortisol, with high 24-hour urine values, and low or low normal serum levels of these hormones. Correction is also accomplished with physiologic quantities of cobalt.

Hyperaromatization of Testosterone

- Is your male patient significantly overweight?
- Does he have type 2 diabetes, aspects of insulin resistance such as hyperlipidemia, hypertension, and insulin resistance?
- Does he have type 2 diabetes in his family? If so, be very alert for testosterone hyperaromatization of either endogenous or exogenously administered testosterone. Hyperaromatization is defined as excess conversion of testosterone (and DHEA) into estrogens, and is easily detectable in a 24-hour urine specimen by above-median or high urinary estrogens accompanied by below-median or low urinary testosterone. Confirmation may be found with low or low normal serum total testosterone and free testosterone. “Symptoms” are usually those of low testosterone and relative estrogen excess (low libido, lessening muscle tone, more difficulty losing weight, and possibly gynecomastia) and/or failure of anticipated response to supplemental testosterone.

As noted, testosterone hyperaromatization is almost always accompanied by insulin resistance. This may be confirmed by the 3- to 4-hour insulin resistance testing judged by the criteria established by Kraft.

How to correct hyperaromatization?

Short-term, botanical aromatase inhibitors including Myomin and chrysin are both safe and effective. Myomin is a combination of four Chinese herbs shown to reduce hepatic aromatase. Chrysin is a flavonoid from Passiflora coerulea. Because orally administered chrysin is poorly absorbed, Dr. Wright and Tahoma Clinic physicians usually recommend a liquid liposomal form, Lipo-DC Chrysin. Longer-term, diet, exercise, and supplementation to eliminate insulin resistance is best to not only eliminate any chance of type 2 diabetes, but to drastically slow or eliminate insulin–resistance associated testosterone (and DHEA) hyperaromatization.
Cancer Risk Factors in Women

The 24-hour urine test can provide insight into a woman's estrogen-related cancer risk. The four main markers to consider are the estrogen quotient ("EQ"), the "2/16" ratio, estrone, 4-hydroxyestrone, and 2-methoxyestradiol.

The estrogen quotient (EQ) was derived by Henry Lemon from the 24-hour urinary estrogen determination, and is defined as estriol divided by the sum of estrone and estradiol (EQ = E3 / E1 + E2). In the presence of other estrogens, estriol becomes an anticarcinogen. Lemon theorized, and subsequent evidence has supported, that a preponderance of estriol (EQ > 1) is associated with lower estrogen-related cancer risk.

The "2/16" ratio (the ratio between 2-hydroxyestrogens and 16-alpha-hydroxyestrogens) is firmly established as a relative risk factor for estrogen-related cancer in premenopausal women, and theoretically (although this is not absolutely proven) for postmenopausal women using BHRT. It has been found not relevant in postmenopausal women not using BHRT.

Estrone and 4-hydroxyestrone are individual metabolites that, if elevated, are of concern for increased cancer risk. By contrast, 2-methoxyestradiol is an extremely potent anticarcinogen. As might be expected, there are multiple interrelationships between both individual metabolites and metabolite ratios.

What to look for, what to do:

Low EQ: if EQ is less than 1, the pathway estrone \(\rightarrow\) 16a-hydroxyestrone \(\rightarrow\) estriol (E1 \(\rightarrow\) 16aOHE1 \(\rightarrow\) E3) can be reliably stimulated in women by iodine or iodide. Lugol's iodine 6 to 8 drops daily or SSKI (potassium iodide) 4 to 6 drops daily for 30 to 60 days will usually restore an EQ > 1. Maintenance with Lugol's iodine, 2 drops daily, is recommended not only to support a healthy EQ but also to significantly reduce breast cancer risk. (If more than 2 drops Lugol's are used daily for a sustained period of time, periodic monitoring of thyroid function is advisable.) Obviously, if this pathway is stimulated, the first precursor (estrone) declines. 16a-hydroxyestrone is usually low if estriol is low, but 16a-hydroxyestrone rarely rises to excess as it is mostly metabolized to estriol.

2/16 ratio (2-hydroxyestrone/16a-hydroxyestrogen ratio or 2-OHE1/16a-OHE1 ratio). When this ratio is too low, higher estrogen-related cancer risk exists. This ratio can very frequently be altered by consumption of Brassica (also termed cruciferous and mustard-family) vegetables, commonly including broccoli, cauliflower, cabbage, brussels sprouts, bok choy, mustard greens, kale, and many others, which shift more estrone towards 2-hydroxyestrone and away from 16a-hydroxyestrone. Flaxseed and soy also help this metabolic shift. Supplemental indole-3-carbinol (I3C) and di-indolylmethane (DIM) can also raise the "2/16" ratio. But "overdose" is possible; in some individuals, more than a little can shift so much estrone away from 16 alpha hydroxyestrone that not enough estriol is produced (remember E1 \(\rightarrow\) 16aOHE1 \(\rightarrow\) E3) to maintain a healthy EQ. In this case, reduction of DIM or I3C is indicated.

High estrone (E1). As noted above, high E1 can sometimes be persuaded to "metabolize away" towards 2-OHE1 or 16a-OHE1. High E1 is also a frequent finding in both men and women who take DHEA orally. When switched to transmucosal/transdermal administration, this effect of DHEA almost always vanishes.

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High 4-hydroxyestrone (4-OHE1) and 2-methoxyestradiol (2-MeOE2). The first metabolite has been termed the most potent estrogen carcinogen and precursor of carcinogens, and the second is the very most potent anticarcinogen. As with the "2/16" ratio, 4-OHE1 is "balanced" with 2-methoxyestrone and 2-methoxyestradiol. Supplying more methyl groups to help induce the estrogen methylation pathways can simultaneously raise anticarcinogenic 2-MeOE2 and lower procarcinogenic 4-OHE1. Common methyl donors used to support the methylation pathways are methylcobalamin, methylfolate, SAM-e, glutathione, and betaine.

Cancer Risk Factors in Men

Excess aromatization: See discussion above.

Low "2/16" ratio. Prostate tissue is sensitive to the estrogen produced by men's bodies. Current research indicates that men with a "2/16" ratio less than 2 are also at risk for developing cancer. Prostate cancer development is associated with andropause; the ratio of circulating estrogens to androgens may increase by up to 40% during andropause. As noted above, increasing consumption of Brassica vegetables and flaxseed can also increase the male "2/16" ratio. (It's likely best for men to avoid regular soy consumption.) DIM and I3C can be used if dietary changes aren't sufficient to do the job.

Low androstanediol/DHT ratio (A/D ratio, a hypothetical): It's well known that testosterone metabolizes into the much more potent and procarcinogenic dihydrotestosterone (DHT), a cellular dedifferentiation agent. But the next metabolite after DHT is the frequently ignored androstanediol (testosterone → DHT → androstanediol). Androstanediol is an anticarcinogenic, cellular redifferentiation agent. According to one entirely logical but as yet unproven theory, the reason there fewer cancers overall but a higher percentage of significantly more aggressive cancers among men taking Finasteride and other 5-alpha-reductase inhibitors (compared with men who are not) is that androstanediol can be suppressed even more than DHT by these patent medications, thus setting up an unfavorable and "tilted procarcinogenic" A/D ratio. Because of this relationship, measurement of DHT alone is not as likely to be as accurate an indicator of cancer risk as the A/D ratio.

At present, the reagents necessary to measure the A/D ratio in urine are sufficiently unreliable that Dawn Huo, PhD, head of the steroids department at Meridian Valley Lab, recommends using serum measurements for this ratio instead and is working to return it as part of the overall steroid metabolism panel from a 24-hour urine specimen.

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Notes
The Kraft article is downloadable at: http://www.tahomaclinic.com/DrKraftInsulinGlucoseArticle.pdf.
A summary of "Kraft's criteria" is downloadable at http://www.tahomaclinic.com/DrKraftGlucoseInsulinSummary.pdf.


Jonathan V. Wright, MD, has degrees from both Harvard University (cum laude) and the University of Michigan. More than any other doctor, he practically invented the modern science of applied nutritional biochemistry, and he has advanced nutritional medicine for nearly three decades. Dr. Wright is credited with introducing the nutritional remedy for benign prostate disease (BPH), the first successful treatment to reverse macular degeneration, the safe medical use of DHEA therapy, natural hormone replacement therapy for women, and many other revolutionary natural cures.

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