
Focus on Health

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MONITORING ESTROGEN REPLACEMENT

There is now and has been for quite some time a lack of understanding in the medical community concerning whether to monitor estrogen replacement with periodic blood levels, and if so, how? In 1942, a new drug appeared on the U.S. market called **Premarin**. It was the first commercially available estrogen. It was manufactured by extraction from pregnant horse urine (PREgnant-MARE's-urINE!). It contained a hodge-podge of estrogenic compounds, pre-dominately estrone, a weak estrogen found in humans, and equilin, a more potent estrogen found in horses but not humans. Neither was really **estradiol**, the most important human estrogen. Blood levels of equilin could not be measured then, and have never been available by commercial medical laboratories since. The mixture of estrogenic compounds in Premarin was so complex and variable that to this day the Federal Drug Administration has not allowed a generic copy of Premarin on the market.

The pharmaceutical company with the patent for Premarin had the market cornered, and, as the concept of estrogen replacement

gained momentum in the 1960's, brilliantly promoted their product. It is, at present, the most widely prescribed estrogen; in fact it is, at present, the most widely prescribed drug of any kind in the United States. The horses used to produce it, however, are all in Canada, since the Society for Prevention of Cruelty to Animals in this country has raised such a fuss about the inhumane treatment of the animals. Nevertheless, the promotion of Premarin that has been and still is being carried out is even better than De Beer's promotion of diamonds. Little wonder that virtually all studies involving estrogen that are done in this country use Premarin, since the company volunteers to supply it at no cost. Consequently, the words "estrogen" and "Premarin" have become synonymous in the U.S., much as "refrigerator" and "Fridgidaire" were in the 1940's. Because blood levels are never measured when Premarin is used, all these studies are of limited (if any) value. The results cannot be extrapolated to mimic those that would be realized if real human estradiol were used and serum blood levels measured and correlated.

Another problem with Premarin deals with route of administration and absorption. Any estrogen taken by mouth (orally) is subjected to the vagaries of intestinal absorption. This is dependent on whether the estrogen is taken on a full or empty stomach and with what liquid.. For instance, alcohol or grapefruit juice may triple the absorption through the intestinal wall. Even more important is the so called "first pass effect" by the liver. Any estrogen taken orally goes from the intestine via the "portal" circulation to the liver. The first time through the liver, the estrogen causes an increased risk of gall stones, hypertension, abnormal blood clotting, and weight gain. Estrogen used non-orally does not cause these problems.

Since Premarin cannot be accurately measured in the blood, a "standard" daily dose of 0.625 mgm, has been agreed upon. Thus, it is the only drug of which I am aware that is given to everyone in the same amount regardless of weight, age, symptoms, cardiovascular or bone status, etc. For a variety of reasons, the best way to replace the declining and fluctuating

blood levels of estradiol coming from the ovaries is with real human estradiol, given non-orally (not by mouth). This makes accurate measurement of blood levels of estradiol essential.

Can estradiol levels in the blood be accurately measured? Yes, now that we have radio-immunoassay (RIA). This technique allows measurement of substances in the blood in amounts of trillionths of a gram (picograms), which are the units used in measuring hormone levels. But, we must be even more precise than that when measuring certain hormones: estradiol, testosterone, cortisol, thyroxin and progesterone.

These hormones are bound, in large part, to globulins (proteins) in the blood. For instance, estrogen binding globulin ties up 98.99% of the estradiol in the blood. It measures on the estradiol test but is completely biologically inactive. What we really need to measure is how much "free" biologically active estradiol is present. The same thing applies to thyroid hormone (free thyroxin and free T3), male hormone (free testosterone) and the adrenal hormone cortisol (free cortisol). The percentage of free estradiol is very constant at any given time in the menstrual cycle or post menopausally. Therefore, after an initial measurement of free estradiol and % of free estradiol, one can follow "total" estradiols, which are cheaper, and multiply by % of free estradiol to determine the free amount. Very few laboratories in this country

have the equipment and personnel to measure free estradiols. No labs in Dallas do so. We, therefore, send the blood to Interscience Institute in Inglewood, California.

There is still an even more confusing situation. The majority of medical laboratories measure estradiol levels using a "kit" test. There are several "kits" available. These were developed about 30 years ago when a fertility drug named Pergonal came on the market. The daily injections of Pergonal required a rapid test for estradiol that could be done in a few hours.

There are three steps necessary to the accurate measurement of total estradiol. They are: 1) Extraction 2) Chromatography separation, 3) RIA. Kit testing leaves out the first two steps, resulting in many impurities and metabolites still being in the blood serum when the third step, RIA, is performed. The result is 8-10 times inaccurate on the high side, which can be corrected for if you are measuring estradiol for fertility, but not if you are using it for hormone replacement. Some labs caution about that in their report (Smith-Kline-Beecham for example); most do not. Doctors who aren't aware of this huge discrepancy are fooled into thinking the patient has a much higher total estradiol level than she actually has, not to mention making the free estradiol level totally incorrect and misleading as well.

The target range for free estradiol in a peri menopausal or post menopausal woman has been determined to be 0.5-1.5 picograms/ml. In a woman with a normal % of free estradiol, 0.8-1.5%, this corresponds to a total estradiol of 50-100 picograms/ml. This level provides the maximum in cardiovascular and bone protection and protection against Alzheimer's disease, and also is the level at which most women feel the best.

The best methods to obtain these blood levels are non-oral estradiol i.e. topical cream, patches, or subcutaneous estradiol pellets. No valid study has ever shown any advantage to adding either of the other two human estrogens: estriol and estrone, neither of which change during menopause. Adding either or both of these (Bi-Est or Tri-Est) increases the cost by one third, with no benefit.

One further word about evaluating estradiol dosage. A blood FSH (follicle stimulating hormone) is not useful. It does not have a reciprocal relationship to estradiol such as TSH does with thyroxin. A third hormone, inhibin, blocks that reciprocal relationship.

If you have further questions concerning monitoring your blood hormone level, feel free to bring them up to me.

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