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HRT in the Fully Menopausal Woman

General Principles: In this group of women, the issues center on **health maintenance** over a long period of time. We are breaking new ground. The Twenty-first Century is the first time in history that large groups of women will be living out substantial portions of their lives after their ovaries have ceased making Estrogen and Progesterone. In addition, their life partners are not only still living, but are **still capable of sexual performance**. The Baby-Boomer generation is not planning to spend the rest of their lives sitting in the proverbial rocking chair or even a chair in front of a TV or computer screen. As long as they are capable, they want to be out, exercising, working, living and enjoying life and even a sexual life. Thanks to modern medicine, they have lived their lives without many of the serious infections that affected their parents. Many of today's fifty year olds are much healthier than their parents were at the same age. They have much **better dental health**. Because of their better teeth and the availability of virtually any food at any time of year, they are far better nourished. They take supplements that also contribute to their better nutrition. Currently, a woman of fifty without any major debilitating disease, has a better than 50% chance of seeing 90 years old. Those odds are likely to continue to rise. **Fifty is the new forty**.

The North American Menopause Society and the American College of Obstetrics and Gynecology now recommends HRT "**at the lowest dose for the shortest amount of time**." This is the result of liability fears following the initial results of the Women's Health Initiative. I feel that this is an over reaction to and a misinterpretation of the data from the WHI.
Most of the problems in the WHI can be attributed to four things:

1. Starting large doses of oral estrogens on older, somewhat obese patients who had previously been off hormones for a long time.
2. Using unopposed estrogens without the benefit of progesterone.
3. Unmeasured and un-measurable hormone doses that do not consider individual patient biologic variations and needs. Not even baseline hormones were measured.
4. **Using Provera instead of bioidentical Progesterone**

Proper dosing depends on the individual woman, her current hormone status, her life style, general health considerations and what she is seeking from HRT. **The "Gold Standard" of a double blind study takes none of these things into consideration. Can you imagine a study of insulin and diabetics where everyone either received the "standard" dose of insulin or received placebo?** No one is stupid enough to suggest such a study. Therapy has to be tailored to the individual. **Hormone replacement therapy should be no different.**

The Fully Menopausal Patient: This section is about the fully menopausal woman. A typical new patient may be in her forties to mid fifties and has not had a period for several years. Usually at this point, hot flashes have decreased considerably. She may even say to her friends that she is "through with menopause". She may be complaining of vaginal dryness that is interfering with intercourse. She may have come to the office because she wants to continue her sexual activity. Perhaps, she is just concerned about osteoporosis, or mental decline, or heart disease or all of these. **Listen to her story. Her needs and her concerns are central. They will guide the course of therapy.**

Initial Laboratory Testing: At the first visit, **I will obtain the usual full set of lab values**. My assumption is that estrogen, and progesterone will either be low or immeasurably low. Testosterone will probably also be low but it may be in the normal range. If the patient has modest abdominal fat or is obese, estrogen may be nearly sufficient for her needs. Since, in all likelihood, she will need both estrogen and progesterone support, I am willing to start the patient on some HRT at the first visit.

Initial Therapy: This woman can begin on low doses of Estrogen and Progesterone. If her hormone levels are very low, she also has very low levels of Estrogen receptors. If you start too high, the Estrogens hitting her few receptors can overwhelm her and she can get hot flashes again. There is an analogy that I tell patients: If someone were outside in the winter in their underwear, freezing cold, you could not immediately place them in a tub of hot water to warm them up. They would burn. They must be warmed in stages, gradually. Estrogen and Progesterone receptors are stimulated to increase by the presence of hormones. There is plenty of time to achieve the ideal dose for that patient. Start slowly with low doses.

I don't give Testosterone immediately. Even if Testosterone is very low on the initial lab work, it will frequently rise once Progesterone is given to the patient. If Testosterone is given without sufficient Estrogen, hirsutism and acne may appear. Wait till the Estrogen and Progesterone are adequate and stable. Testosterone can always be started later if it is still needed. Even in patients without ovaries, I sometimes see Testosterone rise considerably after Progesterone is administered. I assume the Progesterone is being taken up by the adrenals and used as a substrate to make Testosterone. DHEA-S levels can be used as an indicator of adrenal strength and health.

Oral v Non Oral Therapy: One of the functions of Estrogen is to raise HDL and lower LDL cholesterol, which reduces the development of arteriosclerosis. This effect is only preventative. Estrogen does not reverse existent disease. This effect is mediated through Estrogen's influence over liver production of cholesterol. The effect is stronger with oral therapy having first pass through the liver. Estrogen also increases liver production of blood clotting factors, also to a greater extent with oral therapy. Oral Estrogen also raises triglycerides. **For these reasons it makes some sense to**:

1. Use oral Estrogens in young women who are menopausal because of early or premature menopause or bilateral oophorectomy. This will help prevent arteriosclerosis and its multiple consequences.
2. Use non-oral Estrogens for late start women who have been off hormones for a long time.
3. For elderly women and some women with other problems with systemic Estrogen, very small doses of estrogen given directly to the vulva or vagina may be the safest course.

Another note about the WHI: The women with the highest rates of heart attack and non-hemorrhagic stroke were women starting Premarin 0.625 who had been off hormones for over 15 years. They all received **oral therapy** and this level of conjugated estrogens is quite **high a dose** for this age group.

Types of Therapy: I am building another whole section on available forms of therapy, but lets reiterate some points here. As women age, I tend to gradually shift from oral Estrogens to non-oral routes. In addition, patients seem to be comfortable on smaller doses of Estrogen as they age. Progesterone must be given in an appropriate dose to balance Estrogen levels.

1. Oral capsules or tablets have maximum first pass effects. Because more of the hormone is destroyed in the liver, actual milligram doses are higher.
2. Oral/sublingual or buccal troches are mostly absorbed through the skin of the mouth, but I am sure much of the hormone ends up in the stomach. The first pass is probably a mixed effect.
3. Topical creams and gels: Absorption is variable. Some women absorb these very well and some very poorly. Try it and see how it works.
4. Hormone patches: Estrogen is usually well absorbed this way. They are more consistent than the creams. I find that Vivelle-Dot and Climara work very well. There are generics that tend to fall off and work poorly. Note: **Real Progesterone exists in the body and is prescribed in doses fifty to one hundred times those of Estradiol. All the combined patches use synthetic, birth control progestins (norethindrone and levonorgestrel). There are no natural progesterone patches and I doubt there ever will be. The levels required are too high.** Testosterone patches for women would work but none has been FDA approved yet.

Starting Dosages: I usually start with just Estrogen and Progesterone.

1. **Women below 55** or recently off other hormones, active and in good physical condition: Estrogen either Biest 2 mg or 3 mg orally QD in the AM, or Vivelle Dot or Climara 0.05 as directed. The appropriate Progesterone is Oral capsules or tablets, 75-100 mg, PO, HS.
2. **Women 55-65** or off hormones for a long time, I would begin with Vivelle Dot or Climara 0.0375 or 0.025 mg/day and Progesterone 50-75 mg, PO, HS.
3. **Women over 65:** If they have not been on hormones in a long time, I would have a long discussion with the patient to determine her goals. If vaginal dryness is the most important issue, I might give Estriol 0.5mg/ml vaginal cream, one ml in vagina daily X two weeks and then two or three times a week. I would balance this with Progesterone topical cream, 40 mg/ml, one ml on skin HS. **If she has been continuously on estrogen**, continuation of treatment is much less risky. One might consider changing from an oral to a topical route of administration at this age.

Ongoing Management: After six to eight weeks of therapy, we can obtain new blood work. If the baseline FSH and LH were very high and the initial Estradiol and Progesterone were very low, we know this woman is fully menopausal. We don't need to repeat the FSH and LH again. I would, however, follow her with E_2, E_1, Progesterone, Testosterone and DHEA-S. **Ask her how she is feeling on the medication!** Does she have vaginal dryness? A dry vagina indicates too little estrogen. **Weight gain, breast tenderness and fluid retention indicate too much estrogen**. Estrogen levels can be raised or lowered to suit. Progesterone may have to be raised or lowered in tandem.

Uterus Intact or Not? Even if the patient had a hysterectomy, **Progesterone is still important.** See the sections on unopposed Estrogen. If the patient has had the uterus removed, I give Progesterone every night. If the uterus is intact, I like to check on the endometrium from time to time. Initially, I give Progesterone three weeks on and one week off. If there is bleeding after the second round, I will evaluate the endometrium with the usually methods of ultrasound and/or endometrial biopsy. If there is no withdrawal bleeding, I will extend the week off to every six to eight weeks. My experience is that giving progesterone most of the time will thin

the endometrium and protect against endometrial hyperplasia. There will usually be minimal or no withdrawal bleeding. Heavy withdrawal bleeding is an indication of excessive estrogen.

Testosterone: Menopause really means that the Granulosa cells no longer can turn the androgens into estrogens. Women in the early years of menopause may have high testosterone levels. If the Ovaries are intact and the LH levels are high, the Theca Cells are being yelled at to make androgens. If they are still capable, they will. **Remember, the order of failure is Progesterone, then Estrogen and finally Testosterone**. When Estrogen and Progesterone are supplemented, the FHS and LH usually drop by about half. This lower stimulation may reduce the Testosterone output. So, **some women with a normal baseline Testosterone may have a low testosterone after Estrogen and Progesterone supplementation is given.** That is just normal physiologic response. Not to worry. If Testosterone is needed, we can supply that also.
If testosterone is low, it can be added. I find that Testosterone gel is more effective in raising levels than oral Testosterone. If the patient is on compounded Biest, you can have the pharmacist add Testosterone 2 mg or 3 mg to the Biest capsule or tablets. It is best to give both in the morning, as they are brain stimulants. My starting dose of Testosterone Gel is ½ mg/ml, one ml topically in the am. Some women respond strongly to Testosterone and retain it. Some don't. You can always adjust the amount of gel or the concentration as needed.

The New Patient Already On Therapy: This can be a difficult situation. Premarin is very strong stuff and stays around in the body for up to a week. If the patient is under 55 years old, she may have to be off HRT for several weeks to establish her baseline blood levels. For an older woman, we can assume her ovaries are not making Estrogen or Progesterone. If she is on Premarin 0.625 or especially if she is on 1.25, I start the bioidentical hormones at a higher dose. I would begin oral Biest at 3, 4 or even 5 mg capsules and gradually wean the patient down over a few months. Progesterone has to be sufficient to balance the estrogen level.

I saw one woman at age 65 for her first visit. She was having post-menopausal spotty bleeding. I called her after I got back her surprising initial blood work. **Her Estradiol level was 350 pg/dl.** It was then that she told me that **her dermatologist had prescribed Premarin cream to use on her face for wrinkles.** She said it was no problem because, as she was told, it doesn't get absorbed. (I need to note that since that time, the major labs have changed their Estradiol test. The new test is now more specific for Estradiol and does not cross react with the Estrone in Premarin nor the horse estrogens. I now also measure Estrone to help pick up these unexpected cases.) **It is not rare to find that makeup or some other product contains Estrogen, Progesterone or DHEA without being labeled as such.**

When will I stop my hormones? This is a serious question. The Baby Boomers constitute a study in progress. I don't see any particular end point to HRT as long as a patient is healthy. Seriously ill women are usually under the close care of a medical team and HRT is generally discontinued. These patients tend to disappear from gynecologic practices. **I tell patients to re-ask this question every year.** I am not giving them a 20-year prescription. I hope, as time goes on, we will get some data accumulating on physiologic bioidentical hormone use over the long term.

Special Considerations:

The Older New Start: These folks are at higher risk for heart attack and stroke from clotting issues. I usually use topical preparations in small doses. Low dose vaginal preparations are probably OK also. Balancing

estrogen with Progesterone is still important. **Warning: Hormones given vaginally are well absorbed systemically.**

The Young Woman s/p Bilateral Oophorectomy: These women need their womanhood preserved. I will try to restore hormone levels that are age appropriate. I want these women to have enough estrogen to be comfortable. An Estrogen patch of 0.075 or even 0.1 may be required. Progesterone may have to go up to 150mg PO. As she ages, I would gradually reduce the doses.

Not sexually active: If vaginal dryness is not an issue, I find that many of these women are quite happy on lower doses of HRT. The lowest doses of the patch, or topical creams are sufficient. Balance is still important.

Prior Breast Cancer: This is a seriously controversial topic. I am going to be writing on this separately. The chapter in Spiroff, *GYN Endocrine*, 7th edition, Lippencott in an excellent resource. They reviewed hundreds of articles. The short answer is that I try to review the current knowledge with the patient. We than map out a plan that best suits her needs with the lowest tolerable risk. **The public lay literature on this subject is terribly misleading.**

High Breast Cancer risk or patient anxiety about cancer: This situation is like that with prior breast cancer but with somewhat less pressure. I don't think there are any clear answers, but the lay literature and the public reporting of the WHI grossly exaggerates the risk relationship between Estrogen and breast cancer. In addition, the theoretical protection provided by real progesterone is virtually unexplored. It would probably take studies lasting at least 20 years to get any clear answer.

Follow-up laboratory tests: After several rounds of laboratory tests and dosage adjustment, the patient hopefully will be happy with her therapy. Since her ovarian hormone status is probably going to change very little in the future, her medication use should be fairly stable. Seeing these patients once or twice a year with pre-visit blood work should be sufficient to follow them.