

HORMONE THERAPY: MALE-TO-FEMALE HRT

There is some stuff I have learned about hormones that may be of interest to you if you are contemplating HRT for the purposes of feminization.

GO BIO-IDENTICAL

Where possible try to use "bio-identical" hormones. These are the ones that are molecularly identical to those which are produced naturally by the human body. **Synthetic hormones** are purposely designed to be more difficult for the body to metabolize and break down so they will remain active for longer periods in the bloodstream. There are additional problems with these drugs as they can place undue stress on the liver and cause the build up of "molecular junk" made up of left-over bits the body cannot metabolize. For example the popular HRT drug Premarin (conjugated estrogen) is derived from pregnant mare urine - hence the name "Premarin." The estrogen are HORSE estrogens, not HUMAN estrogens. There are elements to the molecule that are normally metabolized by enzymes in a horse's body that simply do not exist in a human being. Where possible use REAL "17-beta Estradiol" and "Micronized Progesterone."

GO TRANSDERMAL

Administration is another important consideration. Most of the synthetic estrogens are an oral administration, which must first pass through the liver before entering the blood stream. This is the complete reverse of the way the body processes estrogen it makes itself, which travels through the blood stream and only the left-over hormone passes into the liver where it is broken down and cleaned from the body. Oral estrogens are given in high doses because they must be able to "overwhelm" the liver's ability to break them down. A portion of them will make it through the liver into the blood stream, but what doesn't puts stress on the liver and produces byproducts which are known to be "liver toxic" thus damaging the liver. The most effective means of absorption is via injection. However there is the added risk of infection and large doses must be given that wear off over time, causing a "roller coaster" of peaks and valleys in hormone levels. There is no advantage to recreating a woman's cycle if one doesn't have ovaries or a uterus! The second most effective means of delivery is "transdermal." For 17-beta Estradiol there are a number of transdermal patches (Climera, Vivelle, Estraderm) on the market that fit the bill. They provide a steady dose over time of bio-identical estrogen. The FDA recently approved an Estradiol Lotion (Estrasorb) that may be a promising alternative to the patches. A similar product, an Estradiol Gel called "Sandrena" has been available in Europe for a while. Some oral estrogens may be slowly dissolved under the tongue for sublingual usage, though this is not the intended nor recommended method by the manufacturers and data relating to the effectiveness is largely anecdotal. A final option is to take estradiol nasally. There is one estrogen nasal spray on the market (Aerodiol) for which the manufacturer claims good absorption through the mucous membranes in the sinuses.

NOTE: *The aforementioned methods of administration work fine for smaller doses (i.e., "beginner" doses to see how well you tolerate the medication or maintenance doses post-operatively). For higher dosing these methods of delivery can be cumbersome. For example, to get the equivalent of 6mg Oral Estradiol from a patch you'd have to wear four Climera 100 Patches concurrently. Since you aren't supposed to place a patch on the same spot two weeks in a row, and you're only supposed to put them on your buttocks or abdomen, most people would quickly run out of locations on their body to place the patches. Nasal sprays and gels could be applied several times over the course of a day, but most people find intramuscular injections or dissolving oral estradiol pills under their tongues (or between the cheek and gum) preferable alternatives when a higher actively "feminizing" dose is desired. Lower doses tend not to cause*

much feminization and transdermal patches in particular are often reported to be inadequate for that purpose. Nonetheless many doctors like to start people out on the patch because there are very low incidence of side effects reported from them and it is nearly impossible for patients to overdose on them (doctors are well aware that TS patients are often impatient to be feminized and tend to "mega-dose" on orals, which is not only dangerous but also costly and wasteful).

For progesterone there are lotions and "breast creams" which are infused with Micronized Progesterone. Some of these are available without a prescription from compounding pharmacies. Even if they are "prescription strength" the dosage levels can be inconsistent if the progesterone is not thoroughly mixed with the cream and the amount used exactly the same each time. Another option may be Prometrium, which is an oral administration that has micronized progesterone in a gel cap suspension of peanut oil.

BLOCK ANDROGENS

Aldactone/Spirolactone: The preferred general anti-androgen is Spironolactone (Aldactone). This drug is primarily used as an anti-hypertensive and shouldn't be used by people with low blood pressure. Another side-effect is that it increases the amount of intracellular potassium, which can lead to the potentially life threatening problem called Hyperkalemia. This can usually be managed with diet and regular blood monitoring. It is also a diuretic so remaining properly hydrated is also crucial to maintaining good health. Okay, so what does it DO? A couple of things: first and foremost it competes with Dihydrotestosterone (DHT) at hormone receptor points. DHT is believed to be the cause of non-genetic male-pattern baldness and excess facial/body hair. The other thing Spironolactone does is block the expression of the P-450 gene¹ that, among other things, stimulates progesterone to testosterone conversion [see the section titled "**Hormone Chain Explained**"]. I have also found information claiming that the topical form of Spironolactone (available as a foam) is the preferable method of delivery for blocking DHT at the skin - if the primary purpose of using the drug is to hamper body/facial hair growth and/or male pattern balding.

***A word of caution.** I've heard of people trying to take Spironolactone sublingually by dissolving it under their tongue. First of all the pills taste absolutely terrible so that should be enough incentive not to try dissolving them in your mouth. The other thing is that the few people who've tried it have reported bleeding gums and sores afterwards. It is not intended to be taken this way and you would seriously risk overdosing by doing so, which could lead to a heart attack.*

Finasteride: Probably better known by the brand name versions, Propecia and Proscar. This drug is popular as a treatment for male-pattern baldness. Like Spironolactone it targets DHT hormones, however it doesn't block DHT receptor points as Spironolactone does. Instead it does what Natural Progesterone does - blocks the activity of the 5-alpha-reductase enzyme in an effort to prevent the conversion of testosterone into DHT. For patients seeking to reverse a receding hairline, they often use Minoxidil (Rogaine) as well. This may be undesirable to M2F TS patients, however, because Minoxidil can often have a systemic effect (i.e., it causes hair growth elsewhere on the body, not just where it was applied). For most M2F patients the object of DHT reduction is to slow/reduce unwanted facial and body hair. If that is the objective, Spironolactone has been shown in studies on women with Hirsutism to be more effective at reducing unwanted hair than Finasteride [**source**]. Finasteride used in conjunction with Spironolactone is more effective, but alone it is not a good general anti-androgen. However, in patients for whom Spironolactone or Flutamide (discussed below) are problematic, Finasteride is often prescribed as an anti-androgen that's better than taking nothing at all.

There is some argument over whether or not Natural Progesterone (also discussed below) is more efficient than Finasteride at blocking 5-alpha-reductase activity. The dosages and methods seem to be a very important factor in end result as one study found progesterone to be 97%

efficient [source] at blocking 5-AR, while another found it only 24-62% effective [source]. The latter study found Finasteride to be 59-82% effective (a combination of Pg and Finasteride was 68-78% effective) [source]. However, a different study showed Finasteride to be only 20% effective [source]. So it remains unclear whether one is more effective than the other or if they are roughly equal in effectiveness at blocking the enzymatic conversion of testosterone to DHT. The only thing that IS clear, is that Finasteride provides none of the other health benefits of natural progesterone, which may be a major factor to consider when selecting an HRT regimen. Note that these numbers refer to SERUM levels of 5-AR. The enzyme is also produced at localized points in the skin, where the efficiency of Finasteride is roughly cut in half!

Androcur/Cyprotone Acetate: A popular anti-androgen outside the United States is Cyprotone Acetate (it has not been approved by the FDA for use in the USA). There is a commonly held belief among many transsexual people that Cyprotone Acetate is the most powerful general antiandrogen available. There are a number of pharmacological studies that have shown Spironolactone to be the most powerful of the anti-androgens available, especially when delivered transdermally. That being said, there are many dermatologists who claim Cyprotone Acetate is more effective, possibly because it is absorbed into adipose (i.e. "fat") tissue nearer the skin and slowly released, while Spironolactone must travel to hormone receptors in the skin via the bloodstream if taken orally. Suffice it to say that one can potentially be more effective than the other depending on what the application and desired chemical action is. Spironolactone is available worldwide by prescription and there is more data behind it's use, especially in TS HRT. Cyprotone Acetate was developed to treat testicular cancers in men as part of their chemotherapy. There have been no studies of the effects of long-term use of Cyprotone Acetate that I could find.

If you are switching to or from Spironolactone (Aldactone) and Cyprotone Acetate (Androcur) be aware that Androcur is much more powerful as an anti-androgen than Spiro, therefore you don't need to take as much of it. The general rule of thumb for conversion between the two is that Androcur is FOUR TIMES as strong as Spironolactone. So, if you were taking 200mg/day of Spiro that would mean you'd only need 50mg/day of Androcur. It is also suggested that you ramp down off of or up onto Spiro over the course of two to three weeks and start with no more than 25mg/day of Androcur until you are certain you do not have any negative reactions to it. It is important to have your liver function monitored while taking Androcur. Also be aware that people who switch from Spiro to Androcur also often notice a weight gain of between 5 and 20 pounds. Some of it is water weight returning once the diuretic effects of Spiro dissipate.

Flutamide vs. Spironolactone: It seems more and more Male-to-Female TS patients are opting for (or are being placed on) a drug called "Flutamide." This is a powerful, systemic anti-androgen with a chemical action very similar to Cyprotone Acetate in that it blocks the receptors for testosterone. Flutamide may be given together with injections of another type of hormonal therapy drug (goserelin, buserelin or leuporelin). These drugs block the production of a hormone produced by the pituitary gland (luteinising hormone) which normally stimulates the production of testosterone. Flutamide should not be taken as a monotherapy (i.e. by itself) by pre-op M2F transsexuals because of the way it interferes with the normal negative feed-back action of androgens, Flutamide stimulates gonadotropin production and subsequently androgen production. Meaning, on it's own, it can potentially INCREASE androgen levels! As for how Flutamide stacks up against the other anti-androgens, in one study of women with hirsutism (excessive facial/body hair growth) it was compared to Spironolactone:

Treatment with the pure antiandrogen flutamide caused a rapid and significant decrease ($P < 0.05$) in the hirsutism score, which became significant after only 3 months of therapy. The maximal 50% inhibitory effect ($P < 0.01$) was observed after 6 months of therapy, with a hirsutism score similar to values found in normal premenopausal women. In contrast, spironolactone caused an inhibition ($P < 0.05$) that became significant after 5 months of therapy with an approximately 30% decrease in the hirsutism score ($P < 0.01$, flutamide versus spironolactone).

No further decrease in the hirsutism score was observed up to the last time interval studied, namely, 9 months. [source]

That being said, For a small subgroup of women flutamide and other oral antiandrogens are highly toxic. Between February 1989 and December 1994 the Food and Drug Administration (FDA) received reports of 20 patients who died and 26 who were hospitalized for hepatotoxicity due to flutamide, a rate around 3 per 10,000 flutamide users. Early symptoms of hepatotoxicity include nausea, vomiting, fatigue and jaundice and if such symptoms occur they must be immediately reported to a doctor. Dermatologists generally recommend that serial blood aminotransferase levels should be monitored during the first few months of flutamide treatment. Any adverse aminotransferase level changes suggest that hepatotoxicity is a significant risk and flutamide use should be stopped. For this and other reasons, some dermatologists do not use flutamide to treat hirsutism however, the side effect risk of flutamide is no better or worse than other oral antiandrogens

Studies that compare flutamide to spironolactone or cyproterone acetate suggest that overall the beneficial effects on reducing hirsutism are similar. Some suggest flutamide is slightly superior and others say it is slightly less superior. Initially flutamide was given to patients at high dose rates of up to 250mg three times a day. However more recent studies indicate that a similar improvement in hirsutism can be obtained with flutamide doses as low as 62.5mg a day. The reduction in dose significantly reduces the risk of side effects.

Flutamide vs. Finasteride: Another study concerning male pattern balding compared Finasteride and Flutamide. The effect on hair growth and regrowth (on the head) showed Flutamide to be more effective at stimulating the length of hair shafts. Both agents were similar in effectiveness on diameter of the hair shafts. Also of interest to M2F transsexuals would be the effectiveness of Flutamide on DHT inhibition as compared to Finasteride. The following table shows the results of that study on blood testosterone and DHT levels. The drugs were delivered transdermally by a hydroalcoholic solution and a gel (the third item on the table checked levels after administration of the carrier medium alone, without any of the drugs).

Serum T/DHT Levels (in nmole/L)

Group	T	DHT
Finasteride	7.2±6.9	0.91±0.57
Flutamide	5.8±3.1	1.06±1.62
Vehicle (control)	8.9±7.4	1.10±1.02

Clearly flutamide is more effective than finasteride at reducing serum testosterone levels, but flutamide was similar to the non-medicated carrier medium in reduction of serum DHT. [source]

CONSIDER ADDING PROGESTERONE

Usually TS HRT consists of just an estrogen and an anti-androgen. Most endocrinologists consider progesterone "optional" but there are very good reasons to consider it "essential." First and foremost progesterone is the body's natural way to block an enzyme called 5-ARD (5-alpha-reductase) which converts testosterone into DHT. Many TS patients choose to use Finasteride (Propecia/Proscar) for this purpose, and it is quite good at blocking the conversion, but Finasteride doesn't offer the other benefits progesterone does. [more on Pg benefits] [other effects

of progesterone] The bone-building enzymes called "Osteoblasts" have a hormone receptor for progesterone. In post-menopausal women on HRT who have been given estrogen it only helps combat loss of bone density if their adrenal glands are still capable of producing high levels of progesterone (a normal chemical response to high estrogen is to produce more of the "balancing hormone" progesterone). However, if the body isn't capable of countering the estrogen with enough progesterone the person becomes "estrogen dominant" and the estrogen may actually DECREASE bone density by acidifying blood (which causes calcium to be pulled from bone stores to neutralize it) and estrogen can also create "microclots" in bones that create weakening "voids." What the pharmaceutical industry has been slow to admit is that doctors have been prescribing the WRONG hormone to women for over half a century! Why? Because nobody owns the patent on natural micronized progesterone. There's simply no profit in it for them. Other natural progesterone benefits include lowering "bad" cholesterol and countering rampant estrogen-driven cellular division (particularly crucial if one has an estrogen-sensitive tumor). Testosterone can also counter this cellular growth, by the way. There is anecdotal evidence that progesterone is necessary for rounder, fuller, breast growth as some of the tissues in the breast are progesterone sensitive. Many TS women have reported additional breast growth and "fullness" after taking progesterone - even years after they had believed they had achieved all the growth possible under estrogen-only HRT. [source 1] [source 2 summary page 1 / source 2 summary page 2 / full book at Amazon]

Part of the problem in verifying things where TS HRT is concerned is that virtually no broad studies have been done. Almost all the data is co-opted from studies done on post-menopausal women, which may very well be an "apple to oranges" type comparison. The truth is nobody knows if the data is transferable or not.

I should also mention that, though the terms are used interchangeably even by doctors, "progesterone" and "progestins" are NOT the same thing! Many TS people take Medroxyprogesterone (Provera) as part of their HRT, believing it will give them the same benefits as micronized progesterone. Provera is NOT a substitute for Prometrium!

Prometrium & Liver Toxicity: As far as Prometrium goes, about 75% of what you ingest is broken down in the liver before any ever hits the bloodstream. While this gives your liver some extra work, I haven't seen any studies indicating progesterone or its metabolites are particularly "liver toxic." I'd be more inclined to say the polar opposite. One study I've read found that progesterone increased the amount of a protein (called Metallothionein or MT) that binds with heavy metals, thus improving detoxification after exposure to things like Cadmium [source] That pretty well says to me that progesterone moving through the liver actually INCREASES its ability to detoxify, so I'm not going to worry about whether the Pg is trucking through my liver or not!

SUMMARY: *The Ups and Downs of Progesterone*

Studies: The "Up" Side

General Benefits

Mayo Clinic researchers surveyed 176 women taking natural micronized progesterone who had previously taken synthetic progestins. After one to six months, the women reported an overall 34% increase in satisfaction on micronized progesterone compared to their previous HRT, reporting these improvements: 50% in hot flashes, 42% in depression, and 47% in anxiety.

Cardiovascular Health

Studies at Wake Forest University School of Medicine have concluded that synthetic medroxyprogesterone, in contrast to bio-identical progesterone, increases the risk of

coronary vasospasm. This narrowing of major blood vessels surrounding the heart could potentially lead to a heart attack. On the contrary, bio-identical progesterone plus estradiol protected against vasospasm.

Skin Health

Though progesterone does not increase skin thickness (1), it does increase blood flow to the skin (2) resulting in an increased ability to sweat and lose the extra heat through the skin (3). Progesterone can also raise body temperature, enhancing the ability to tolerate cold (4).

Bone Density

Progesterone has stimulating effect on the bone building osteoblasts resulting in increased bone building activity (4, 5, 6, 7, 8, 9, 10). This is due to a direct stimulation of the progesterone receptors in osteoblast bone cells (11, 12), as well as an increased secretion of IGF-1 and other growth factors by the bone cells exposed to progesterone (13, 14, 15). The most positive effect is seen when estrogen & progesterone are used in combination (16).

"Good" Cholesterol

Natural micronized progesterone will not reduce the good HDL levels that are enhanced by estrogen replacement (17), and will result in higher HDL than when synthetic progestogens are used (18).

This lipoprotein (a) benefit of estrogen is not diminished by either synthetic (medroxyprogesterone acetate) or natural micronized progesterone (19, 20).

Epithelial Breast Cancer

Cancers often develop in epithelial cells [which make up one of the several tissues in breast composition]. All cells have a finite life span, and there is a balance between cell division and cell death. When stimulated by estrogen, the BCL2 gene causes breast cells to grow rapidly and prevents cell death. In ovarian carcinoma cell lines and in breast epithelial cells, Progesterone induces apoptosis [disintegration of the cell membrane] and upregulates the P53 gene - a tumor suppressing gene (34,35). Tests have demonstrated that "progesterone at a concentration similar to that seen during the third trimester of pregnancy exhibited a strong antiproliferative effect on at least two breast cancer cell lines (36,37).

It is also noteworthy to mention how synthetic progestins such as medroxyprogesterone acetate (Provera) or norethindrone occupy the progesterone receptor site and inhibit the binding of endogenous progesterone to the receptor. Synthetic progestins do not activate the P53 gene and also prevent the production of the body's own progesterone (the brain is tricked into thinking there is enough already). This chemically induced progesterone deficiency, like natural progesterone deficiency, may increase the risk of breast cancer because the BCL2 gene is upregulated by estradiol and no corresponding downregulation opposes that action.

General Tumor Suppression

As mentioned above, progesterone can upregulate the P53 tumor suppressing gene. This gene is present in tissue outside the breast as well, so there can be a systemic suppression of cancerous cell divisions.

Hair Growth/Hair Loss

Finasteride (Propecia/Proscar) was found to be a major inhibitor of dihydrotestosterone (DHT) formation. Even 1 nM finasteride inhibited DHT synthesis in dermal papillae by 86% and 1 nM progesterone by 75%. Estrogens were less able to inhibit the synthesis of DHT in dermal papillae (e.g. 100 nM 17alpha-E: 20%; 100 nM 17beta-E: 60%). Measurements were made on cultures done from scalp biopsies with high-performance liquid chromatography analysis, which is why test levels are reported in "nanometers." [As reported in the European Journal of Dermatology. Vol. 11, Issue 3, May - June 2001: 195-8, Investigative Reports. "Influence of estrogens on the androgen metabolism in different subunits of human hair follicles" S. Niiyama, R. Happle, R. Hoffmann: Department of Dermatology, Philipp University, Deutschhausstraße 9, D-35033 Marburg, Germany. full article text: www.john-libbey-eurotext.fr/articles/ejd/11/3/195-8/]

And to be fair and impartial, I think I should say that there ARE some risks or negative side effects that have ALSO been observed and studied in relation to micronized progesterone:

Studies: The "Down" Side

Sex Drive

Excessive progesterone may decrease libido due to antiestrogen and anti-androgen effect (21, 22). As well as decreasing libido, excessive levels may induce depression (23).

Blood Sugar

While estrogens help the cells of the body utilize glucose more efficiently by making them more sensitive to insulin, progesterone can cause a decrease in insulin sensitivity, having an effect on blood sugar that is similar glucocorticosteroids 12. This interference with the action of insulin can interfere with normal glucose uptake and cause insulin resistance (24, 25, 26, 27, 28) .

The ability of progesterone to interfere with proper function of insulin and glucose has since been associated with gestational diabetes (29, 30, 31) as well as hormone replacement therapies (32,33, 34, 35) and has been observed in both synthetic & non-synthetic progesterone (36, 37, 38, 39). Even the high progesterone levels which occur naturally during the luteal phase can induce insulin resistance in some women (21, 28) .

Progesterone-sensitive Breast Cancer

Progesterone insufficiency may play a role in the development of breast cancer (29), however progesterone may also play a role in the proliferation of some progesterone receptor forms of breast cancer - referred to as "PR+" breast cancer. There is a test to determine whether breast cancer cells are estrogen or progesterone sensitive. (30). This increased risk is associated with the increased production of IGF-1 by breast cells stimulated by excessive progesterone (31, 32) - resulting in the proliferation of several forms of breast cancer cells (33).

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PROMETRUIM vs. PROVERA: A study was done on the effectiveness of Provera vs. Progesterone on 5-alpha-reductase inhibition (which prevents Testosterone to DHT conversion). The study checked [natural] progesterone, medroxyprogesterone acetate [i.e. Provera],

levonorgestrel, norethindrone, 17-beta estradiol [natural estrogen], and ethinyl estradiol [i.e., synthetic estrogen].

The results on 5-ARD inhibition:

Drug Tested	Effectiveness on 5-AR	Margin of Error
Progesterone	97%	(+/- 5.3%)
Norethindrone	59%	(+/- 4.6%)
levonorgestrel	47.9%	(+/- 6.3%)
17-beta Estradiol	40.8%	(+/- 14.2%)
Medroxyprogesterone	0%	n/a
Ethinyl estradiol	0%	n/a

[concentrations between 10^{-8} to 10^{-4} mol/L were used] [**PubMed source**]

Conclusion: Natural progesterone (i.e. Prometrium) is the most effective at preventing T-DHT conversion while medroxyprogesterone (i.e., Provera) is completely ineffective. Even natural estrogen was more effective.

So, if the HRT regimen is ethinyl estradiol and Provera the patient should supplement with Finasteride (Propecia/Proscar) to inhibit T-DHT conversion. Obviously taking Provera isn't going to inhibit the formation of DHT at all, so there's no reason to take it.

I should note that the above effectiveness percentages refer to SERUM levels. 5-AR and DHT are also active at localized places within the skin, where effectiveness is roughly halved. This makes a strong argument in favor of using a topical form of progesterone if the purpose of taking Pg is to combat the effects of DHT on hair follicles. As progesterone tends to collect in fatty tissues any infused cream/lotion/gel/foam should be applied at points on the body with high levels of blood circulation and low levels of fat (a the wrists and hands for example).

Long-term use of progestins like Provera have been more closely associated with the development of breast cancer, while long-term use of progesterone appears to offer a protective effect against breast cancer, possibly due to an insulin-related effect that is present with natural progesterone, but is not present when using progestins or just estrogen.

Q. Will Provera or Prometrium increase breast size?

A. Depends on what you mean by "increase." Among the side-effects listed for both progestin and progesterone is "breast-enlargement." This is a TEMPORARY condition that mimics the swelling of the breasts when a woman is ovulating or when she is pregnant. Progesterone and progestin cause fluid retention in tissues, which may be responsible in part for the breast enlargement, but it is more likely due to a downstream effect that increases the level of Prolactin. Once the progesterone (or progestin) influence is removed the swelling effect will reverse. HOWEVER, there is another factor to consider for someone who is still developing breasts. Progesterone is the hormone that promotes development of the lobules and alveoli in the breasts (i.e., the "glandular tissues"). It causes the alveolar cells to proliferate, to enlarge, and to become secretory in nature. Estrogen stimulates the non-glandular tissues (fatty tissues and fibrous tissue

called "Cooper's Ligaments"). [source]. Progestins, however, are sometimes prescribed to counteract precocious breast development in adolescent girls (i.e., breast development that is too soon or too much). Progestins are considered a successful therapy for Benign Fibrocystic Breast Disease (FBD) to counter estrogenic stimulation of Coopers Ligaments that can make breasts lumpy and dense. Whether or not progestins stimulate the growth of glandular tissues appears to be unknown. [source 1] [source 2] [source 3] [source 4] [source 5]

About Progesterone Creams

Progesterone creams purchased over the counter usually have very low amounts of the hormone added. Anything less than 3% USP is considered "non prescription strength" but also possibly ineffective as the primary ingredients are basically lotion (skin moisturizers) that are not absorbed through the skin into the bloodstream. The skin is a very effective barrier to absorption, that's one of it's jobs. Prescription strength creams are available using proven "carrier mediums" that CAN cross the skin barrier into the bloodstream, but they are usually only available as special orders through a "compounding pharmacy." I'm unaware of any standard commercially available transdermal progesterone product from a major pharmaceuticals company that could be purchased at your local drug store. If you DO plan to try transdermal prescription strength progesterone creams, effective amounts for F2M transsexuals should contain 20-30mg of micronized progesterone per dose (this, when absorbed into the skin, will yield roughly the same amount of useful progesterone as a 200mg Prometrium pill.

Why use a transdermal delivery? One is to prevent any chance of liver problems (though as noted above, progesterone doesn't appear to be liver toxic itself). The other is to focus 5-alpha-reductase blocking in the skin instead of in blood serum. A certain amount of testosterone in the skin will be converted to DHT at the skin level. That DHT is far more likely to affect male pattern balding or unwanted facial and body hair growth. I have seen references to alleged studies indicating that a blood serum increase in progesterone is only 50% as effective at blocking skin-level DHT formation as a prescription transdermal cream [source unknown, sorry]. If this is true a M2F using progesterone to prevent male pattern hair problems might find a topical delivery system yielding better results than either oral or injectibles (I'm not saying there's any proof of that, however).

Oh, in Canada they made sale of creams with ANY progesterone by prescription only. Also, see the end of this section for information indicating the OTC creams sold in the United States may be in violation of Federal regulations too.

About Micronized Progesterone Injectables

Q. *What is the typical dosage for progsterone in oil IM injections? The only dosage information I can find is on the Anne Lawrence/TS roadmap sites. I [am] interested in frequency of injections as someone. . . .insisted that pio IM injections would completely seep out into the blood within a day and be largely broken down by the liver and expelled by the body, and that I would have to take IM pio injections on a daily bases.*

A. The short answer is there IS no "typical dosage" for Progesterone in oil for IM injections. Here's why:

Dosages are different depending on what is being treated and the amount of fatty tissue the patient has.

Here's how it works: the micronized Pg is suspended in oil. The oil is a "carrier medium" that is readily absorbed - like a sponge - by fatty tissues. This "stores" the Pg in the fat where it is slowly released into the bloodstream over time (I've never seen figures for the absorption rate nor the release rate). It is usually "cycled" with doses off and on because you can reach a point of "super-saturation" of fatty tissue with it and, like a waterlogged sponge, the tissue simply cannot absorb anymore. So you have to have some "downtime" that allows the Pg in fat stores to be released into the bloodstream before you can administer more (think of it like letting the sponge dry out a bit for a while before soaking it again).

Most Endos still consider Pg completely unnecessary or optional for TS HRT - which is something with which I seriously disagree, given what a potent 5-alpha-reductase blocker it is with additional health benefits for bone building and cholesterol. Feminizing affects are minimal, and that's based largely on anecdotal evidence because no studies have been done with TS women. Though in natal females it is known to stimulate the growth of one of the three kinds of breast tissue that firms and rounds the breast structure, so I'd say any Endo that didn't include Pg wasn't doing everything they could for the patient's breast development.

Anne Lawrence's suggestion sounds like a "minimum starting dose" to me. Based on what I've read of Pg supplementation, a woman sees best benefit from a "maintenance dose" of about 20 mg/day into the bloodstream. For other methods of delivery this would require dosing much higher to compensate for the loss of some Pg to destruction and enzymatic conversion to other substances (about 90% for oral, 20 - 30% for transdermal or sublingual). Injections, though, generally are close to 100% efficient in delivering Pg into the bloodstream. If 50mg was injected in, say, saline it would all move right into the bloodstream. In oil, however, most of it is carried into fatty tissues and only a portion of it is released into the bloodstream each day thereafter. As I said, I've never seen figures for the release rate.

I've also read that you probably wouldn't want to take the 100mg injections because they reportedly cause "excessive burning and aching" at the injection site - so much so I found doctors on one Endocrinology message board advising 100mg Pg in oil be injected with Lidocaine to mitigate the pain!

The only real way to know how much to use would be to get a baseline Pg test done, then do a minimal injection regimen, have the level re-tested and see how much it boosted the serum level and adjust the injection amount and/or frequency up or down until it's close to the "target level."

Ideally for a TS woman (and this is just my non-doctorly opinion) the target level should be above that of a post-menopausal woman (which would be the same as for a male), but below the range for a woman's luteal phase of her cycle (so kind of in the upper portion of follicular or inbetween follicular and luteal). For example, the generic reference range I have indicates that the range would be between 1 - 4 ng/ml, so a good "target" would be about 2 - 2.5 ng/ml. But labs use their own reference ranges to compensate for the methods and calibration of their equipment, so it's important to use THEIR numbers.

Even though the manufacturer of Pg in oil for IM injections say the max daily dosage is 200mg, there are a couple of reasons that a TS woman wouldn't want to mega-dose on progesterone:

- 1) In a natal female the level of Pg goes up during ovulation and skyrockets during pregnancy. If a non-pregnant person (physiologically male or female) takes huge amounts of progesterone it "tricks" the brain into thinking that the person is pregnant and starts "priming the body" for gestating a fetus and milk production. This is called a "Prolactin Response" because the person's body starts producing prolactin hormones (the ones that cause lactation). If a person is cycling with large amounts of Pg, repeated "Prolactin Responses" can lead to the formation of a

"Prolactinoma" in the brain, which is a benign, non-cancerous enlargement of the anterior pituitary gland that can disrupt other hormone levels in the body.

2) The body generally tries to make good use of what hormones are available. In the case of Pg it stores excess in fatty tissues or enzymatically converts Pg into other hormones. Leftovers are either broken down by the liver and expelled from the body (usually in urine) or some of it just oozes out of the body in other fluids (like saliva). If you have HUGE amounts of Pg in your system and there isn't any more room in fat to store it (because it's already saturated from supplements), you can over-tax your liver and waste a bunch of it as it is broken down or otherwise simply expelled from the body, but more importantly, your body will likely first try to enzymatically convert it to testosterone. This is likely the underlying cause of the "virilization" (mostly unwanted facial or body hair growth) reported by some men and women who've taken Progesterone supplements - and what likely has also led to the general belief that it is undesirable as part of TS HRT.

In lower doses, though, this enzymatic conversion is less of a problem and can be further mitigated by combining Pg supplements with Spironolactone, which happens to suppress expression of the P-405 gene responsible for signalling enzymatic conversion of progesterone into testosterone.

Because Pg in oil that is injected is moved into fatty tissue, the dosage is often also adjusted based on the amount of fat the person has. A skinny person without much fat would have less tissue to absorb the oil - if you gave them the same dose as a fatter person a larger portion of the injection would be swept into the bloodstream directly, rather than absorbed.

Frankly, transdermal or oral are a little easier to figure out how much you'll be getting into the bloodstream - even though some of it is destroyed in the process of getting there. The other advantages to transdermal or oral administration are that you don't have to cycle on and off (which can create PMS-like symptoms, as it essentially mimics the fluctuations of a woman's menses - there is no medical advantage for a TS woman - or a post-menopausal woman for that matter - to duplicate the menstrual cycle). Other methods of delivery may be a bit more "wasteful," but they provide means for a persistent, stable level while injections (by their nature) cause an initial "surge" in levels that tapers off over time until another injection creates another surge, and so on and so on.

So the answer is - there ISN'T a "typical dosage" and blood tests for Pg will have to be done and various regimens tried until serum levels are close to the target level. That's the nature of Endocrinology, though. It's an inexact science requiring repeated testing, monitoring, and adjusting to "tailor" the drugs to the unique chemistry of the individual patient. "Typical dosages" for any HRT drugs are merely "suggestions" within a "safety zone" of minimal and maximum amounts.

Probably not the answer you want to hear, but that's why you probably can't find a solid number. There isn't one.

That person who told you intramuscular injections would seep out in a day is wrong. These injectibles are specifically designed (by suspension in oil to carry it into fat stores or by the addition of an ester) to remain in your body for extended periods of time and gradually become bio-active over the course of a few days (you may find you'll need to juice yourself with the estrogen more often than the progesterone, since it appears it metabolizes and expells from your system faster than the progesterone will).

PROGESTERONE COUNTERPOINT:

In the interest of remaining objective and giving time to both sides of an issue, I am obligated to inform you that much of what the creams promise is based on the work of the late Dr. John Lee, who was widely regarded as an authority on the subject of progesterone supplements. However, if you look at **this collection of information** (much of it referenced to the **OB/GYN.net** message board) you'll see that he's pretty well considered in some circles to have been a quack with allegations that his "research" findings can't be reproduced in a strictly controlled study. Almost every web site I've seen selling a progesterone cream refers to Dr. Lee's work. The only thing that's obvious is that many claims about progesterone (specifically in relation to OTC creams) are hotly contested. Furthermore that it appears that the OTC creams may actually be illegal in the United States too, according to FDA guidelines (though they don't seem to be cracking down on it because the evidence sorta indicates that the creams aren't actually HURTING anyone).

Because there is some question concerning verifiable benefits of progesterone supplementation I have chosen to focus primarily on known biochemical reactions such as 5-alpha-reductase blocking, osteoblast enzyme stimulation, and P-53 gene down regulation rather than on vague and largely anecdotal "evidence" regarding how it made someone feel. I should point out that biochemical reactions observed in a lab may not translate directly to biochemical reactions in the human body in terms of end effect. For example, if a reaction is seen to affect 90% of a sample in the lab that doesn't necessarily mean the same effectiveness will be seen in the human body where there will be other variables that may decrease the efficiency of the chemical reaction.

HELP! I'M LEAKING!

Occasionally M2Fs taking hormones will experience fluid (usually kind of yellowish in color) leaking from their nipples. This usually occurs subsequent to an orchiectomy or SRS where the person hasn't changed their pre-operative dosages, or if they suddenly lower their dosages dramatically (specifically dropping progesterone and/or estrogen). Don't freak, the leak is normal!

What has happened is the person inadvertently tricked their brain into thinking a couple of things about their body that aren't true.

First, when they have had an orchiectomy their estrogen and progesterone levels were no longer "opposed" by testosterone or any amounts of the "downstream" androgens that were competing with for hormone receptors. The result was the same as if the person had suddenly, and dramatically, increased estrogen and progesterone intake.

This tricks the brain into thinking the body was pregnant. Especially the progesterone, in biological females the levels go through the roof during pregnancy. It doesn't matter whether you're born male, female, or intersexed, the wiring for all this is "primitive" and not gender-specific. It's why males still have nipples, even though they generally don't serve any purpose - except possibly in at least one species of Malaysian bat, where the males may nurse the young [see sidebar].

During a woman's pregnancy, the high level of progesterone

Natural Male Lactation

"In 1992 eighteen Dayak fruit bats [*Dyacopterus spadiceus*] were captured from a rainforest in the Krau Game Reserve, Pahang, Malaysia. Of the 10 mature males captured, each had functional mammary glands from which small amounts of milk were expressed. It is not known whether the males actually feed young. The reason this could happen is that a breast is a breast is a breast. Male lactation is physiologically possible and has been observed in some domesticated mammals and even humans. Dr. Robert Greenblatt says that milk production in human males can be stimulated by letting a baby suckle for several weeks. Indeed some males, either at birth or puberty, secrete milk. Historically male lactation has been noted by the explorer Humbolt, who spoke of a 32 year old man who breastfed his child for five months. It was even observed in a 55 year old Baltimore [Maryland] man who had been the wetnurse of all the children of his mistress!"

- Professor Patty Stuart-Macadam of the Department of Anthropology at the University of Toronto.

triggers an increase in the amount of another hormone called prolactin. There are hormone receptors on the milk glands in the breasts that react to prolactin, which stimulates them to start producing milk.

The first thing a M2F will probably notice (and may actually, initially, be quite pleased with) is a swelling in size of their breasts as they become laden with fluid from Stage One Lactogenesis. Even if there are high levels of prolactin, the "release" of the milk is inhibited by the presence of high levels of progesterone. The Stage One Lactogenesis can be triggered either by suddenly, and dramatically increasing estrogen and/or progesterone intake, or by maintaining pre-operative dosages post-operatively (i.e., post-SRS or post-orchectomy).

When a M2F person then cuts their dosages, specifically the progesterone, they inadvertently mimicked the sudden drop in progesterone that happens when a woman gives birth. That triggers Stage Two Lactogenesis (also called "copious milk production"). This typically begins 30-40 hours after the drop in progesterone, but actual lactation usually doesn't start for 50-73 hours (2-3 days) after birth, so the M2F experiencing breast leakage most likely won't notice it until more than two days later, and may not make the connection that cutting their dosage triggered the lactation. As mentioned at the beginning of this section, the fluid is often yellowish. This is because it's what is called "foremilk" which is very high in fat content, and fat is yellow in color.

After that first few days, the endocrine system no longer controls the lactation. It enters what is called Stage Three Lactogenesis (Autocrine, or Local, milk production). Removal of the milk and stimulation of the nipple (i.e., as in via nursing a baby) triggers additional releases of prolactin that perpetuate milk production. If you don't remove the milk/fluid your body will absorb it and the prolactin levels will drop and your endocrine system will stabilize. **The breasts will begin to shut down milk production within several days if milk is not regularly and effectively removed** (like by a nursing baby).

Since the body has been tricked into thinking it has given birth, it is also possible that the sudden drop in hormone levels could mimic post-partum depression, another side-effect M2Fs often suffer generally that might worsen so they may not immediately associate it with their hormone therapy.

One last thing to consider if you are lactating is that lovemaking (sexual stimulation) releases a hormone called oxytocin, which has been associated in both biological females and M2F transsexuals with an ejection of liquid from the nipples (either a spray or a flow, depends on the person). You may want to issue your partner a set of swim goggles! Seriously, though, stimulation of the breasts during sex could actually prolong the lactation (see Stage Three Lactogenesis above).

THE TRUTH ABOUT PROLACTIN

I've heard a number of M2F TS people discussing the "benefits" of increasing their prolactin levels or how lactation (or leakage) from their nipples is a "good sign." I'm afraid I'd have to beg to differ. Increased levels of prolactin in anyone other than a nursing mother are not a good sign at all!

First of all, if you aren't taking any hormone medications and are experiencing lactation get yourself to a doctor post haste! It's a symptom of a pituitary tumor or prolactinoma in your brain.

If you're taking progesterone supplements see the information above about how that could potentially stimulate a release of prolactin as well as potentially cause the formation of a prolactinoma. Yes, in your brain. Generally I don't like any sentence to end with ". . . in your brain." You shouldn't either.

One drug some M2F TSs take trying intentionally to stimulate prolactin, under the belief that it will stimulate breast growth, is Domperidone. No, it isn't wine. That's *Dom Perignon*. The drug (not the wine) is also called Motillum and Evoxin. One place people seem to have gotten the idea of using this was from Annie Richard's "Birth of Venus" web site (and to be fair, other places online where TS HRT info is shared). Annie's site is wonderful, but I have to take issue with the following statements from her web site:

"...transsexual women gain considerable benefits from the breast developing effects of prolactin even if its not initiating lactation because of their high oestrogen intake, and thus should not be deterred from early use. . . . Generally, start at 20 milligrams (two 10 mg tablets) four times a day, i.e. about every 6 hours. After starting domperidone, it may take three or four days before any effect is noticed, though sometimes women notice an effect within 24 hours. It appears to take two to three weeks to get a maximum effect. Most women take the domperidone for 3 to 8 weeks."

I find the claims dubious at best. Prolactin has no breast developing effects. The key word there is "developing."

Progesterone is the hormone that promotes development of the lobules and alveoli in the breasts (i.e., the "glandular tissues"). It causes the alveolar cells to proliferate, to enlarge, and to become secretory in nature. Estrogen stimulates the non-glandular tissues (fatty tissues and fibrous tissue called "Cooper's Ligaments"). [source].

The aforementioned hormonal actions on breast tissue development are why I maintain that you cannot achieve "female breasts" on estrogen alone! Estrogen-only HRT will cause a "side-effect" increase in progesterone up to a point, which will stimulate *some* glandular tissue growth, but female bodies produce progesterone in the adrenal glands AND the ovaries. M2F TS's can only produce it in the adrenal glands. Since we're pushing for pubescent girl levels of hormones to stimulate initial breast development I don't think it's physically possible, without progesterone supplementation, for a M2F TS to get the full, firm breast development biological females have [source].

All Prolactin does is stimulate those alveoli to swell and secrete milk. If you don't have all that much prolactin stimulation OR if you don't have that many alveoli (as M2F TSs often don't) it is unlikely that what they secrete will ever build up in sufficient quantities to come out of the nipples in the same way as a nursing mother - a fluid swelling of the breasts may be all that happens or a small amount of clear (or nearly clear) liquid may leak from the nipples. Progesterone also causes some fluid retention in breast tissues so if no liquid is being secreted from the nipples it would be hard to say whether the fluid swelling was due to prolactin or progesterone (especially if you're also taking progesterone supplements).

I should also note that Domperidone (Motillum, Evoxin), while often prescribed for increasing breast milk production in nursing mothers, was not developed for that purpose. It is a drug for treating gastrointestinal disorders like gastroenteritis. [source] It's actually a dopamine-receptor blocking agent that has as a side-effect stimulating the Pituitary Gland to produce prolactin. In general the drug is considered quite safe, even for use over a course of several months.[source] However, incidence of gynecomastia and lactation have been reported in biological males taking the drug - though it is listed as a "less common" or "rarely occurring" side-effect.[source 1] [source 2] This suggests to me that the increased prolactin levels may be effecting OTHER hormones, primarily progesterone, that in turn causes growth of glandular breast tissue. People tend to forget that these hormones are all inter-linked with feedback loops and enzymes that convert them to other things.

What this means for a M2F TS is anybody's guess. Here's my guess:

I suppose it's possible it could stimulate an increase in breast-building hormones (those would be estrogen and progesterone), though I think it would be FAR more effective to just take extra estrogen and progesterone if that's what you're really shooting for. More than likely it is simply causing whatever alveoli you've got to start cranking out fluid, which will probably be contained in your breast tissues because you won't produce "nursing level" amounts of it, and the fluid swelling (i.e., the increase in breast size) will probably go away shortly after you stop taking Domperidone just as it does for nursing mothers taking it.

So, in short, I'm not denying it could probably swell your breasts, but I'm inclined to believe that swelling will reverse as soon as you stop taking the drug just as they do for those nursing mothers taking it.

Q: If it's actions are temporary in biological females, why would they be permanent in transwomen?

A: They wouldn't be. Plus, increasing prolactin levels is unlikely to achieve the long-term results M2F TSs desire.

ESTROGENS

ESTER ESTROGENS EXPLAINED

Estradiol Valerate - I looked up what the difference is between it and Estradiol. Regular Estradiol is listed as "17-beta-Estradiol" while Estradiol Valerate is called "Ester of 17-beta-Estradiol." This made me wonder what the heck an "ester" was. I learned it is a molecule attached onto the steroid backbone that prevents it from latching onto hormone receptor points immediately, especially right around the injection site. The body has to first break off the "ester" that was added before the hormone can become "fully functional" and bind with estrogen receptors. Different esters take different amounts of time to be broken off the steroid backbone, which determines how long the injection remains "active" in your system. According to Schering Pharmaceuticals the Pharmacokinetics of Estradiol Valerate are:

"Estradiol valerate is rapidly and completely absorbed. The steroid ester is cleaved into estradiol and valeric acid during absorption and the first liver passage. At the same time, estradiol undergoes extensive further metabolism, e.g. into estrone, estriol and estrone sulphate.

Maximum concentrations of estradiol in plasma are generally reached between 4-6 hours after tablet intake. In relation to the single dose, approximately two times higher serum levels of estradiol are observed after multiple administration. On average, the concentration of estradiol varies between 30 (minimum levels) and 60 pg/mL (maximum levels). Estrone, as a further estrogenic metabolite, reaches about 8-times higher concentrations in plasma. After stopping the treatment, pre-treatment levels of estradiol and estrone are reached within 2-3 days.

Estradiol binds to albumin and the sex hormone binding globulin (SHBG). The unbound proportion of estradiol in plasma is about 1-1.5 % and the SHBG-bound proportion is in the range of 30-40 %.

After the ester cleavage of the exogenously administered estradiol valerate, the metabolism of the drug follows the biotransformation pathways of endogenous estradiol. The metabolic clearance of estradiol has been found to be about 30 mL/min/kg. The metabolites of estradiol are excreted with a half-life of about 1 day; by about 90 % via the kidneys and by about 10 % with the bile."

Understanding "Synthetic" Estrogens

One thing that confused the heck out of me at first was how the pharmaceutical industry uses the word "synthetic" in regard to hormones like estrogen. It has nothing to do with the original SOURCE of the drug, nor does it have anything to do with the process. The terms refer exclusively to whether or not the end product is chemically different from what the human body produces.

For example, Premarin - though it comes from a natural source (pregnant mare urine) - is biochemically different from what the human body produces (because it is horse estrogen). Technically it is a "synthetic." However, Wyeth-Ayerst Laboratories decided to market Premarin as "natural" because of the animal source, rather than on its biochemical nature. When they aren't selling a bill of "natural" goods Premarin is simply called "conjugated estrogen" because it is a mixture of TEN different estrogens - including *equilin* and *equilenin*; both of which the human body has no enzymes to metabolize (because those are the horse estrogens). The main "human estrogen" in it is the weaker estrogen called Estrone (E1), which is normally the metabolized result of Estradiol (E2), though there is reportedly a little bit of Estradiol in Premarin as well. You may question why I called Estrone "weak." Many sources online claim it is the "most powerful estrogen," which isn't true. It may be the most DANGEROUS of the estrogens, however, because of its association with stimulating cancer cells in the breast. I don't know where those other folks got their info, but the medical resources I've consulted say Estradiol is the Queen of estrogens and Estrone and Estriol it's underlings.

The estrogen in most of the drugs that contain 17-beta-Estradiol is synthesized in a lab from plant extracts. Okay, so it's made in a lab but it comes from a natural source too. "Natural" or "Synthetic?" In this case "Natural" because the resultant molecule is bio-identical to that produced in the human body.

As for Ethinyl Estradiol (also called Estinyl Estradiol), it is a synthetic designed to be more powerful than endogenous estrogen with a very long half-life in the body (designed to make it very difficult for the liver to break it down). Incidence of thrombosis are primarily linked to this estrogen. Some women have suffered thrombosis on just 0.035mg/day, but some M2F transsexuals have survived up to 1mg/day. The danger is real enough that the .50mg pills are no longer even manufactured! I personally think the manufacturer's choice to market it under the name "Estinyl" was to purposely create confusion with Esterified Estrogens, or those created with an ester of 17-beta-estradiol (i.e., Estradiol Cypionate, or Estradiol Valerate). All of which are not nearly as dangerous as Estinyl/Ethinyl Estradiol.

THE GREAT SYNTHETIC UNKNOWN:

There is this class of compounds called "selective estrogen receptor modulators" (SERM). SERMs act like estrogen in the central nervous tissue, but not in other tissues susceptible to cancer-causing effects of estrogens. Well known SERMs would include Tamoxifen and Raloxifene. Both drugs are used in the treatment of female osteoporosis and breast cancer. A new compound, called STX has also been discovered to have SERM activity [[source](#)]

So what does this possibly mean for M2F transsexuals? Well, for those who are in the process of feminizing their bodies probably nothing. For those that have seen their maximum feminine development, are post-op, and are concerned about developing breast cancer from continued, long-term estrogen supplements - but who do not want to give up the psychological benefits of estrogens, SERMs may provide an alternative long-

term option for their HRT.

If you look under the drugs listed for F2M transsexuals you may notice that Tamoxifen is listed there as an estrogen BLOCKER, so you may be wondering why on Earth a M2F transsexual would ever consider taking it? SERMs are considered estrogen blockers because they occupy the hormone receptors in tissues but do not stimulate the cells in the same biochemical way. They DO, as mentioned above, act like estrogen in central nervous tissues - which are the tissues that benefit from the psychological effects of estrogens (which addresses things like memory loss and depression).

I frankly have never heard of a M2F transsexual using Tamoxifen or Raloxifene as part of her HRT regimen. Most likely because it seems counter-intuitive, given the drugs' reputation as a estrogen blockers. However, a closer look at the biochemistry involved shows that drugs like Tamoxifen still function as estrogen in select tissues but not in others. Once a M2F person has seen their maximum breast development estrogen supplements pose a cancer risk, especially since the drug will usually be taken for the rest of the individual's life. An alternative that still provides the psychological benefits of estrogen without presenting the cancer risk is a possibility that should not be overlooked by transwomen who are years past their final feminization results and post-operative (therefore not at risk of becoming androgen-dominant again, which could potentially reverse some of the feminization). Though optimal risk vs. benefit results would probably be achieved through a combination of Tamoxifen with estrogen, the exact amounts of each to assure the Tamoxifen didn't cancel out the estrogen is probably best left to a qualified Endocrinologist armed with more knowledge and lab results.

Any takers?

ESTRADIOL: THE "SUBLINGUAL SOLUTION?"

One reason many people don't like to take oral Estradiol formulations is because of the extra load they put on your liver. As mentioned previously, the amounts of estrogen in pills is actually quite high because a significant amount of the active hormones (~90%) will be destroyed in the process of digestion and the first pass through the liver before the drug ever reaches your bloodstream. Subsequently whatever your body couldn't use passes through the liver again to be broken down and excreted. The liver was only designed by nature to clean out small amounts of "leftover" hormones. The pills, though, overwhelm the liver's capacity to deal with the amount, thus allowing some of the active hormones to escape destruction in the liver and move into the bloodstream. Meanwhile your poor liver is working overtime, not to mention dealing with a hormone that is, itself, "liver toxic" and damaging to liver tissues. Okay, so what are you to do?

The most popular solution in the Transgender Community is to dissolve the estradiol pills either under the tongue (sublingually) or between the cheek and gum (usually while sleeping). The inside of the mouth is loaded with "mucous membranes" through which the hormone can easily pass into the bloodstream without first passing through the liver. Not only is there that benefit but there is also a great potential for higher yield from each pill because sublingual absorption is much more efficient than swallowing the pills. Instead of destroying ~90% of the hormones in the

pill, only ~20-30% may be destroyed, which can significantly increase serum estradiol levels and better stimulate the process of feminization.

It should be noted that, while many TS people take estradiol this way, this method of taking the drugs has never been studied to measure the actual effectiveness and it is not the recommended method of administration by the drug's manufacturer so if you do this, you do this at your own risk! Also be aware that some drugs are "coated" to prevent them so easily being destroyed by the stomach acids or to slow the dissolve time for "time release" action. For example the animal-friendly alternative to Permarin, the conjugated estrogen "Cenestin," has a "time release coating" that would make it less viable (perhaps completely unviable) for sublingual dissolving.

OTHER M2F HRT RESOURCES

See also the following references:

<http://www.trans-health.com> (off site link)

<http://www.gender-id.com> (off site link)

[Female Hormone Replacements](#) (off site link)

[Detailed Specific Drug Information](#) (this site)

[Transsexual HRT Study](#) (PDF file on this site)

[HRT Regimens by Dr. Anne Lawrence](#) (PDF file on this site)

[HRT Regimens by Dr. Thomas Waddell](#) (PDF file on this site)

Note: M2F specific information is on pages 6 - 10

I would also ignore their information under "Progesterone" as they are only referring to Medroxyprogesterone, not the real stuff.

[HRT Regimens by Dr. Jamie Feldman](#) (PDF file on this site)

Note: Refer to Table 3 on page 2

More info: [Minnesota Medical Association](#) (off site link)

[Hormonal Sex Reassignment by LJG Gooren](#) (off site link)

[Study: Percutaneous Absorption of Progesterone with Transdermal Estrogen](#) (PDF file on this site)

[A Review of Current Research on the Effects of Progesterone](#) (PDF file on this site)

*Footnote 1. **P-450 gene:** Cytochrome P450 (CYP450) is a family of genes involved in the metabolism of many compounds in the body. [source: [Roche Diagnostics Glossary](#)]*