

HORMONE REPLACEMENT THERAPY AND THE TRANSSEXUAL

Introduction

The most important component in hormonal replacement therapy (HRT) for male-to-female transsexuals (MtF TS) is oestrogen.

For the pre-op TS, the aim is feminisation while maintenance of health is the aim of the post-op TS. In practice, for pre-op TS, this means smoother skin, more feminine curves but top-most on the TS's list of priorities is breast development. For the post-op TS, hormone replacement is necessary because the body no longer produces adequate sex hormones (gonadal).

For the pre-op TS, Progesterones are added because of their anti-androgenic effect. They also have a direct effect on breast development.

There are no specially manufactured products for MtF TS. This means that she usually has to rely on medications manufactured for contraception or menopause.

Oral contraceptives¹

They usually contain a combination of an oestrogen and a progesterone. The progesterone is used to prevent pregnancy while the oestrogen is used to prevent bleeding from the uterus.

There are 4 types of OC's. They are classified according to the progesterone content.

1st generation OC's usually contain high doses of oestrogen combined with norethisterone, norethynodrel, lynestrenol or ethynodiol acetate.

2nd generation OC's usually contain a lower dose of oestrogen combined with norgestrel, levonorgestrel (Loette, Microgynon 30) or norgestriene. The oestrogen content was lowered because it was thought that the high oestrogen content in the 1st generation OC's were responsible for causing stroke and heart attacks.

3rd generation OC's usually contain a low doses of oestrogen combined with desogestrel (Marvelon, Mercilon), gestodene (Gynera, Meliane) or norgestimate. It was initially claimed that 3rd generation progesterones caused fewer complications.

The 4th type of OC's are unclassified. They contain an oestrogen in combination with cyproterone acetate (Diane 35, Estelle-35) or drospirenone (Yasmin).

Gerstmann² reported that OC's containing less than 0.05mg ethinyl oestradiol were associated with a lower risk of thrombosis.

Women on 3rd generation OC's are twice as likely to get thrombosis compared to those on 2nd generation OC's³.

Diane 35 was initially marketed as a contraceptive but was later withdrawn. It is now a drug given to women for treating acne, excessive hair growth and polycystic ovary syndrome. It has twice the risk of thrombosis compared to conventional OC's⁴. Diane 35 is very popular among TS's because many of them find the combination of two drugs in one pill to be convenient and effective.

Since OC's are taken by women during reproductive age, the studies mentioned above were on this group of women taking one tablet a day. TS's usually take higher doses.

Anti-androgens

Cyproterone acetate or Androcur is very popular with TS's. It is like a chemical castration. Diane 35 only contains 2mg of the drug but androcur contains 50mg to 100mg.

When men with terminal prostate cancer take androcur or if they have an orchidectomy alone, their breasts enlarge even without taking any oestrogen.

Androcur may damage the liver causing the person to have jaundice (the white part of the eye turns yellow).

Most men with prostate cancer, take androcur for 2 - 3 years, after which they die of their cancer. The long term (beyond 2 - 3 years) side-effects of taking 50mg - 100mg daily (as in androcur) or in smaller doses (as in Diane35 or Estelle 35) are not certain but there are TS's who have taken Diane 35 for longer periods than that with no apparent side-effects.

Cyproterone Acetate is usually useful for pre-op TS's, because their testes still produce testosterone. After Sex Reassignment Surgery, it is unnecessary because the testes are removed and testosterone production drops drastically.

There are newer anti-androgens available which are safer than androcur because they are non-steroidal anti-androgens.

One way to avoid the side-effects of cyproterone acetate is to take spironolactone (aldosterone) instead. It is a diuretic, a drug meant to make the person pass urine. It was initially meant for treatment of hypertension. It is a potassium-sparing diuretic and potassium is not lost when the person produces urine. With prolonged treatment, the level of potassium in the blood needs to be monitored because it may rise to dangerous levels causing the heart to beat irregularly. Potassium-rich foods e.g. Bananas need to be consumed with care.

Another popular progesterone with anti-androgen effects is medroxyprogesterone (Provera). The implications of adding this drug are discussed below.

HRT for menopause

The important component is oestrogen. Progesterone is added to prevent endometrial cancer in women who still have a uterus.

Provided there are no special risk factors, e.g. smoking, pre-menopausal women have a lower rate of heart attack than men or post-menopausal. Oestrogen improves a person's lipid profile. Previously, one of the reasons for giving HRT to post-menopausal women was to lower the heart-attack risk. But does HRT after menopause really lessen heart disease?

The WHI study⁵ finally answered this question. It showed that:

For post-menopausal women on oestrogens alone (0.625 premarin daily) (average 6.8 years follow-up):

1. No increased risk of heart attack (if you have no heart problems)
2. Risk of stroke = 0.44%, if not on HRT risk = 0.32%
3. Venous thrombosis = 0.21%, if not on HRT risk = 0.15%

4. Increased Risk of blood clots in lungs = insignificant
5. Only increase in benefit = fewer hip fracture

For post-menopausal women on premarin 0.625mg + provera 2.5mg daily, the relative risks are (measured in person-years) are⁶:

1. Breast cancer +8
2. CHD +7
3. Stroke +8
4. Pulmonary embolus +8
5. Hip fracture -5
6. Colorectal cancer -6

If a post-op transsexual is like a post-menopausal woman without a uterus, there is no reason for her to add a progesterone or anti-androgen to her HRT regimen. Oestrogen replacement alone is sufficient and safer.

Indeed, there are transsexuals in Singapore who have taken nothing but 2mg of oestradiol valerate (progynova) daily from the time they started HRT pre-op and continued doing so post-SRS.

Injectable contraceptives

Most injectable contraceptives were manufactured to be given once a month.

Unijab (Dihydroxyprogesterone Acetophenide 150 mg + Estradiol-3-Benzoate-17-Butyrate 10 mg) is the most popular injectable contraceptive among transsexuals in Singapore. It produces faster breast development than orally administered HRT.

There are few specific studies on unijab. An article in Italian by Selvaggi⁷ reported that it is safe. Unfortunately, the translated text is not available.

Deladroxate is another injectable contraceptive containing Dihydroxyprogesterone Acetophenide. It was withdrawn by the manufacturer after animal studies showed that this substance caused breast cancer in dogs and pituitary tumours in rats⁸. Human studies are not available.

There are three other injectable contraceptives that do not contain Dihydroxyprogesterone Acetophenide: Chinese Injectable No. 1 (250 mg 17alpha-hydroxyprogesterone caproate + 5 mg estradiol valerate), Cyclofem (25 mg medroxyprogesterone acetate + 5 mg estradiol cypionate) and Mesigyna (50 mg norethindrone enanthate + 5 mg estradiol valerate). They are supposedly safe.

The main side-effects of injectable contraceptives are vaginal bleeding and pregnancy, complications that will not occur in a TS.

Injection results in high levels of circulating oestrogen and this route of administration is prone to over dosage⁹.

When a complication happens, e.g. thrombosis, the first thing to do is to stop the cause, i.e. stop HRT. It is easy to stop taking tablets but it is impossible to remove the injected substance, hence the objection by some doctors to giving HRT via injections.

The transsexual's considerations

The reason for HRT in a post-SRS MTF is to maintain health and it appears that an oestrogen-only regimen makes sense.

The pre-op MTF aims to feminise and the doses prescribed for women are not enough to achieve this. The trend seems to be titrating the dose of HRT according to blood hormone levels. This usually results in a HRT regimen where the doses exceed that taken for contraception or menopause. With larger doses come greater risks.

Gooren⁹ reported that 50% of his TS patients were satisfied with their breast development with HRT. Will Asian TS's get the same "success rate" with the same doses of HRT as the Dutch? Asian women naturally have smaller breasts to begin with.

The annual risk of venous thrombosis in women taking OC's is between 2 per 10 000 and 3 per 10 000. This works out to between 0.02% to 0.03% incidence¹.

Gooren⁹ reported that TS's, on their regimen of HRT had a 2% - 6% risk of venous thrombosis. His regimen consisted of a daily dosage of: ethinyl oestradiol 0.050 to 0.1mg with either 50mg - 100mg cyproterone acetate or 5mg - 10mg medroxyprogesterone acetate.

This means that pre-op TS's on this regimen are 100 times more likely to get venous thrombosis compared to a woman on OC's.

Toorians¹⁰ noted that MTF taking ethinyl oestradiol had a significantly higher rate of thrombosis compared to those on transdermal oestradiol. He compared biochemical changes in the blood of MTF's who were on cyproterone acetate (CPA) only, and with CPA in combination with transdermal oestradiol, oral ethinyl oestradiol, or oral oestradiol.

The study showed that only those taking ethinyl oestradiol showed significant biochemical changes in the blood. This shows that the risk of clotting was caused by the chemical structure of ethinyl oestradiol. It could not have been caused by the "first-pass" effect on the liver, as is commonly assumed, because those taking oestradiol orally did not show the same changes.

When a TS is on ethinyl oestradiol, it is not accurate to use blood tests to adjust dosages. The blood test measures oestradiol levels not ethinyl oestradiol. Since ethinyl oestradiol (not oestradiol) is responsible for causing thrombosis, just because the blood oestradiol level is within normal range, it does not mean that the dosage of ethinyl oestradiol is safe.

Gooren⁹ and Van Kesteren¹¹ found that the rate of thrombosis among their TS patients dropped after they started using transdermal oestradiol (0.1mg 17-oestradiol, twice weekly) in TS's above 40 years of age and in those with a history of thrombosis.

Dittrich¹² reported equally good and safe results in TS's using oral oestradiol.

What would be interesting to know is whether sublingual oestradiol is as safe and as effective as transdermal administration.

Most TS complain that the feminising effects of oestradiol is not as good. However all three groups of researchers found that combined a oestradiol and anti-androgen regimen is safe and effective. A similar HRT regimen can be found at Anne Lawrence's¹³ website.

The transsexual who does not intend to have surgery

There are transsexuals who do not intend to have either SRS or breast implants but yet desire some physical feminisation. They almost always take large doses of oestrogens, progesterones and anti-androgens given simultaneously.

Typically, such TS's in Singapore will have unijab together with oral medication. The oral medication is usually a mixture of Andocur, Premarin and Diane 35. The dosages of the cocktail seems to vary from person-to-person. They may continue such a combination for quite a long period.

The problem of long term HRT, is shrinkage of the male genitals. Both scrotal and penile skin are used to construct the neo-vagina. The smaller the genitals, the less donor skin is available, which makes it difficult to create a neo-vagina of adequate depth.

Another related concern is that long term ingestion of anti-androgens, especially by TS's above 40 years of age, is the impaired ability to achieve orgasm post-SRS. There is no hard clinical data to support this. It is an suspicion that arose from transsexual's comparing their orgasmic ability.

The continued use of large doses of anti-androgens post-SRS is also suspected to cause a lack of orgasmic ability.

Historically, pre-op TS's were given big doses of oestrogens alone. Cyproterone acetate only came in to use later. The rationale behind co-administering anti-androgens is so that smaller doses of oestrogens need to be given, thus lowering the rate of thrombosis.

Conclusions

- 1.) It is safer for MTF to take oestradiol or oestradiol valerate than ethinyl oestradiol.
- 2.) Oestradiol/cyproterone acetate combination is a safe and effective HRT regimen for pre-op TS.
- 3.) Combined oestrogen and progesterone HRT is associated with more complications than an oestrogen-alone regimen

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