

Information About Hormonal Treatment for Trans women©

**Leighton J Seal PhD FRCP
Consultant Endocrinologist,
Gender Identity Clinic,
(Charing Cross)
West London Mental Health NHS Trust
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Introduction

As part of treatment for gender dysphoria we will be prescribing you hormonal treatment (oestrogen). The aim of this treatment is to allow your body to develop the physical appearances of a cis gendered female by using oestrogen. At the same time we will decrease your production of male hormones (testosterone), which will decrease your male physical appearance using either oestrogen alone or more often using a GNRH analogue drug which will stop production of the hormones from the brain that control the testicles which will then stop making testosterone. The hormonal treatment is very effective, you can expect the changes in your body to be noticeable but it will be necessary to undergo other procedures to change certain features of your body (e.g. electrolysis, breast augmentation, genital reconstructive surgery (removal of the male genitals with or without formation of a vagina)) to get complete feminisation.

Although a very safe treatment there are some side effects with the oestrogen (female hormone) that you should be aware of and these will be explained. The good news is that transgendered people treated with oestrogen have much reduced risks of side effects such as deep venous thrombosis (DVT) or heart disease using modern oestrogen types (oestradiol valerate and oestradiol hemihydrate) compared with older oestrogen types (ethinylestradiol of conjugated equine oestrogens (CEE, Premarin®))

At the West London Mental Health NHS Trust (Charing Cross) clinic you will be seen and assessed by 1 or 2 clinicians before hormonal treatment is recommended to make sure that hormonal treatment is the best way to manage your gender incongruence. We also ask that you change gender role before hormonal therapy is started in all but the most exceptional of cases, so that in cases where a person chooses to remain in their female gender role there are

no permanent changes in their body that may need an operation to correct and they have not been exposed to the effects of hormone treatment.

Initiation of Hormone Therapy

The way that we organise hormone treatment is based on internationally agreed guidelines. This is known as Triadic Therapy, which consists of three critical elements; social gender role change (live in a female role) formerly called Real Life Experience; hormonal therapy of the desired gender and finally gender related surgery. We follow this strategy to protect you as you advance through a sequence of treatment that has progressively more irreversible effects on your body with more and more significant physical alterations should you choose to revert to your assigned birth gender.

It is important for you to realise that hormone treatment is a part of the holistic treatment plan and not the end point. For the vast majority of transgendered people social gender role change and establishing themselves in their experienced social gender role is their goal and studies show that it is this and not hormone treatment that has the biggest effect on reducing psychological distress and making a person feel better about themselves.

The aim of Hormone Treatment

The aim of treatment is to suppress the production of the sex hormones of your assigned male gender (testosterone) and to give the hormones of the experienced female gender (oestradiol) in order to produce the secondary sexual characteristics (way the body looks) of your experienced female gender. Following genital surgery (which includes removal of the testicles), hormone treatment needs to be continued to prevent the complications of not having sex hormone production such as osteoporosis (brittle bones) or early heart disease.

Hormonal Treatments

Our Standard Regimen

The standard hormonal regimen used at our clinic is the initiation of oestradiol valerate 2mg increasing to a maximum of 10mg per day. This is a natural oestrogen which means we can measure it in your blood and change the dose until we get to the level seen in a young cis gendered female. Dose increases are made after 3 months of therapy. We know from our experience with treating cis gendered females that have not gone through puberty naturally, that if too much oestrogen is given too quickly then breast development is not normal and you they end up with small cone shaped breasts not a natural female contour. Natural puberty occurs over 2 years and we aim to mimic this in our treatment so that you achieve the best breast development that you can .

Using excessive amounts of oestrogen does not improve breast development, indeed there is an enzyme present in the body that converts excess oestrogen back into testosterone and so this may be counterproductive.

Other forms of oestrogen can also be used such as a Gel preparation (Sandrena©) or patches (Estradot© or Evoreol©). These avoid the medicine passing through the liver but have to be applied to the skin instead. Most people ask for tablets first as they find it more convenient but these medicines are also good medications. We sometimes specifically recommend these alternative forms of oestrogen if your blood female hormone levels (oestradiol) remains too low when we use tablet oestrogen therapy.

A GnRH analogue such as Goserelin (Zoladex) 10.8mg/3months or Decapeptyl 11.25mg/3 months is added to your treatment if your testosterone is too high when you are on 4 mg of oestradiol valerate to suppress testosterone production. This medicine works by over activating the gland under the brain (the pituitary) which controls the testicles. When this

gland is over stimulated it goes to sleep and so the production of testosterone will stop. Because of the way this medicine works for the first 2 weeks following the first injection you may notice an increase in erections and sexual thoughts. To prevent this cyproterone acetate 50-100mg per day is usually given for the first 2 weeks, unless there is a specific reason why we can't use this medicine; it is not needed with subsequent injections. Cis gendered females produce testosterone and the aim of treatment is to get your testosterone level to that of a genetic female (<3nmol/l).

Oestrogen treatment alone may be enough to control your testosterone production. If your blood testosterone is not suppressed on 4mg o.d. then a GNRH analogue may be added.

Very rarely other forms of oestrogen may be used and this would be discussed with you by your gender specialist.

Six weeks prior to genital reconstruction surgery your oestrogen therapy will be stopped to reduce the incidence of perioperative deep venous thrombosis (DVT) and it is recommenced 2 weeks postoperatively. If you were on a GNRH analogue (Zoladex Triptorelin or Decapeptyl) before surgery you should continue with the same dose of oestrogen that you had before your operation. If you were not on a GNRH analogue before surgery you will need a lower dose, typically 1/3 – 1/2 of the dose you were taking before surgery.

The aim of treatment after your operation is to prevent osteoporosis (brittle bones), increase general well being and have a healthy heart. Standard hormone replacement dose can be used although in many case higher levels such as twice the normal amount are administered which reflects the generally larger body size of a transwomen. The replacement is monitored on clinical parameters and oestrogen monitoring with the aim of achieving a plasma oestrogen level in the upper follicular phase (350-600 pmol/l). Goserelin (Zoladex) is stopped after your operation.

Alternative therapies include oestrogen patches at either 50 or 100µg twice per week, oestrogen gel 0.5-4mg once a day. Oestrogen valerate has the advantage of allowing plasma oestradiol levels to guide therapy aiming for a plasma oestradiol of 400-600pmol/l.

Effects of hormone replacement

Facial Hair

The beneficial effects of oestrogen in transwomen are production of female characteristics. You will find that your skin texture becomes finer and there is a reduction in the growth of your facial hair. This effect is maximal after 4 months of treatment. Oestrogen therapy itself only rarely reduces facial hair growth adequately to provide a female facial appearance once a person has adult beard development. You will need local treatment such as electrolysis, waxing, shaving, sugaring or laser therapy to reduce the appearance of facial hair and help your female presentation.

Male pattern hair loss also slows and may stop as your testosterone levels fall however regrowth of hair once it is lost does not occur.

Breast Growth

During normal puberty breast growth needs oestrogen and takes 18 months to 2 years. Your oestrogen therapy mimics this process. Breast development will begin about 2-3 months after the start of treatment and the maximum effect of oestrogen on breast development is not seen until 2 years of oestrogen therapy. Doses of oestrogen in the order of oestrogen valerate 6mg are adequate for this to occur. Using higher doses of oestrogen does not have any additional benefit in inducing breast development. In general the maximum breast development a patient can expect to achieve is a cup size less than your mother.

Breast development is dependant on the deposition of fat into the breast and if you are thin gaining some weight can increase your breast growth.

Despite hormonal treatment 60% of transwomen progress to breast augmentation surgery, although unfortunately at the moment this is not provided as part of the NHS gender pathway by NHS England.

Body fat distribution

The proportion of fat in your body will increase. This is seen mainly around the hips and buttocks to give a more rounded form to the body. There is an average 4kg (9lb) weight gain.

This is accompanied by a decrease in muscle bulk and upper body muscle strength. The increase in subcutaneous fat will decrease muscle definition promoting a more female body outline

Genital Effects

Oestrogen treatment will decrease your sex drive and erections. The testicles will become smaller and softer.

Sperm production will decrease and eventually stop. If you would like to have children in the future with a female partner or surrogate then you will need to store your sperm before you start oestrogen. This will have to be arranged at a local infertility clinic. There may be a charge for this as sperm storage is not always available on the NHS. You cannot however rely on oestrogen to be a contraceptive and if you have a female bodied partner you will need to take appropriate contraceptive measures.

Negative Effects of Oestrogen Therapy

Oestrogen therapy is safe and effective, but several side effects of this treatment have been described in the transfemale population the most important of these are thromboembolic

complications (deep venous thrombosis), breast cancer risk, liver function abnormalities and hyperprolactinaemia (increased prolactin level in the blood).

The effects of Oestrogen Therapy on Blood Clotting

The major side effect of oestrogen treatment is the formation of clots in the blood vessels, this is called venous thromboembolism (VTE). There has been a great improvement in how often this happens as we have found out more about the types and doses of the hormones we use. In the original study in 1989 there was a 45-fold increase risk of VTE when using ethinylestradiol (the type of oestrogen in the contraceptive pill) and cyproterone acetate (Androcur). This rate was very high and there was a clear age related effect. Women over 40 years old were found to have a deep venous thrombosis (DVT) (clot in the legs) at a rate of 12% and those under 40 only 2.1%. When people started to look into why oestrogen increased the risk of clots they found that oestrogen treatment changes the chemicals in the blood so that the blood is more sticky (Toorians et al., 2003). They found that if you give oestradiol via a patch rather than ethinylestradiol by a tablet the stickiness of the blood is much less. People assumed from this study that it was that way you gave the oestrogen that was important in reducing VTE risk and so the clinic where the author of this paper is based began a policy of using transdermal (through the skin such as patches or gels) oestrogen after the age of 45 years. Since then incidence of DVT in their clinic population was reduced from a 40-fold to a 20-fold increased risk. This gives a VTE rate of 2.6%;. Most clots happened in the first two years of treatment but there was an ongoing risk of 0.4% per year (teren et al., 1997). Newer studies at our clinic using more modern oestrogen tablets containing oestradiol, but not ethinylestradiol have shown very good DVT rates at 0.6% for those treated with oral oestradiol. This study also showed that people using oestrogen preparation called conjugated equine estrogens (CEE,

Premarin[®]) were 8 times more likely to have a DVT than those taking oestradiol tablets. This later study would suggest that it is the type of oestrogen that is used, rather than the way it is given which is important in deciding just how likely it is that oestrogen treatment can lead to a DVT in transgender women. In the UK most of the large transgender health clinics now use a combination of oestradiol with a GnRH analogue for feminisation in transgender women (Ahmad et al., 2013). Lifestyle factors can also influence the risk of VTE in someone taking oestrogen. We know from studies in cisgender women taking the contraceptive pill that the incidence of VTE is increased in smokers by approximately two-fold and in obesity this risk increases to 9-fold. In the UK the treatment protocol used by the majority of transgender health clinics relies on people stopping smoking before high doses of oestrogen are given, in order to minimise the risk of VTE in the transgender women they treat.

Breast Cancer

The incidence of breast cancer with standard HRT in genetic females are 3.2/1000 aged 50-59 and 4/1000 aged 60-69 (Beral Lancet 2002). This is based on large population based studies. We know from big trials the inclusion of progesterone in the HRT administered increases this risk. There are no similar studies available in the transwomen. *There have only been seven case reports of breast tumours occurring in transgender women suggesting that the risk of breast cancer secondary to feminising hormone therapy is very low. It appears that the incidence of breast cancer is the same as the background rate of breast cancer in cisgender males. This evidence would suggest that oestrogen therapy does not increase breast cancer risk in transgender women.*

Progesterone is not involved in normal pubertal breast development, it has not been shown to help breast development, and that there is evidence they may increase breast cancer risk in

cisgender females. Some units do use progestins routinely as part of their hormonal regimen but there have been no studies looking at the effects of progestins on cancer risks in transgender women. Their use for the feminisation of transgender women has to be seriously questioned as these medicines do not improve breast development and may lead to an increase in the complications of HRT

Hyperprolactinaemia (Raised prolactin in the blood)

Prolactin is the hormone that is made during pregnancy to make the breast produce milk. It is made in a small gland called the pituitary gland, which sits below the brain near the back of the eyes. Oestrogen, which is high in pregnancy, causes the pituitary to grow and release the prolactin. After pregnancy the oestrogen level decreases and the gland goes back to normal. Your oestrogen treatment, especially if you are on very high levels of oestrogen, can cause a similar growth in this gland. Over a long period of time this growth may become a lump in this gland. If it does happen these lumps are almost always benign (not cancerous) but will need treatment as they can press on the nerves coming from your eyes and affect your vision. High prolactin levels occur in about 10-14% of patients but there have only been 2 cases of prolactinomas (lumps in the pituitary gland) in transwomen and none have needed withdrawal of oestrogen treatment. *A more recent study suggested that with newer hormone regimens using oestradiol and GnRH analogues the incidence of high prolactin levels was 2.3% Very high levels of oestrogen increases the chance of prolactin levels rising which is one of the reasons why we keep the oestradiol level at the normal range for an adult cisgender female and not higher .*

If your prolactin level rises it can be treated by reducing your oestrogen dose and the using Zoladex to reduce your testosterone. Interestingly one of the patients who developed a

pituitary lump had been self-administered oestrogen in addition to her prescribed oestrogen therapy showing how risky self-medication can be.

Abnormal Liver Function.

The liver is the organ in the body that removes toxins from the blood stream. It also destroys many chemicals such as hormones after they have finished working. As this organ is so important we measure the levels of the chemicals it makes (liver function tests) in your blood to make sure it remains healthy while you are on oestrogen treatment. The risk of abnormal liver function tests is approximately 3% in transwomen. In half of these the abnormalities persist for more than three months. However the increases are mild and as long as blood levels are watched closely will cause no harm. It is only very rarely that the liver function tests become very abnormal and then we have to stop oestrogen treatment.

In women on the oral contraceptive pill gall stones are more common but this has not been seen in trans people.

Osteoporosis (Thin Bones)

The amount of calcium in the bones is controlled by the sex-steroid hormones, oestradiol in a female and testosterone in a male. Cisgender males generally have thicker and stronger bones than cisgender females. People have worried that if testosterone levels are reduced during a transgender woman's treatment that their bones may get thin. Most studies in transgender women reassuringly show that oestrogen therapy can keep the bones strong even though the amount of testosterone in the blood stream is lower. One group however have shown a decrease in bone area and mineral content in transgender women was associated with a lower amount of exercise performance in these individuals, and so transgender women should be encouraged to maintain a good exercise programme to have healthy bones. It has also been shown recently that many transgender people are low in the hormone Vitamin D . This

hormone is one of the hormones that are important in getting calcium into the body and then into the bones. If a transgender woman has a low vitamin D she should have this replaced.

Other Side Effects

Oestrogen therapy is associated with other minor side effects that appear in the literature as isolated case reports. These are often minor and include dry hair and brittle nails, believed to be due to a decrease in oil production from the skin

Safety Monitoring

The safety monitoring for this ongoing treatment is outlined in the table. This monitoring is designed to detect the major side effects of hormonal therapy at an early stage so that the treatment can be altered and prevent ongoing unwanted effects of the treatment.

The side effects of oestrogen do appear to be related to the length of time that you take them. It is known that prolonged HRT use beyond 5 years after the menopause (about age 55) is associated with an increased risk of breast cancer. This fact applies to genetic females and although this is the best evidence available on the long term effects of oestrogen therapy we do know that the lifespan for transsexual people is normal suggesting that long term oestrogen therapy beyond 55 is not harmful.

	<i>Transwomen</i>		
Initial Visit	LH FSH Testosterone Oestradiol SHBG Prolactin Dihydrotestosterone	Weight Blood Pressure Lipid profile Glucose Vitamin D	Every 12 Months Testosterone After 2 years on Oestradiol Steady dose Prolactin LFTs Blood Pressure Weight
Every 3-6 Months	Testosterone levels until stable Oestradiol blood level (if on oestrogen valerate) LFT Prolactin Breast examination Blood Pressure Weight		
If Needed (Follow national Guidelines)	DEXA Scan (Gaps of >12 in hormone therapy, family history of osteoporosis. Low impact fracture) Mammograms Over 40: Consider Transdermal Oestrogen (Current evidence suggests this is not necessary) Over 55: Discuss stopping HRT (if a woman is worried about using HRT in the long term)		

Additional Treatments

Progesterone is used by some centres and is widely purported by self-help trans websites to improve breast development. In the large European centres progestins are not used. Progesterone is not made by a girl during puberty. She does not make that until the ovary starts producing eggs and by that time breast development is completed. Indeed progesterone reverses the cell growth that oestrogen causes. A recent summary study (meta-analysis) looking at breast development in transgender women showed that using progesterone and oestrogen does not give better breast development than using oestrogen on its own. As we discussed earlier the big HRT trials in cisgender females suggest that progesterone in combination with oestrogen may increase the incidence of breast cancer but it also increases the risk of heart attacks and strokes. These risks were not seen in the oestrogen-only arm of these trials, suggesting that progesterone is not good for both cardiovascular and breast health. The use of progesterone in transgender women is therefore questionable and in UK practice is almost never used. Anti-androgen therapy, as either cyproterone acetate or Spironolactone, are used by some centres but generally not in the UK. Antiandrogens fight against the testosterone that is produced in the body. Finasteride, which stops testosterone becoming its more active form (dihydrotestosterone) is used.

Cyproterone acetate is a progesterone derivative and is metabolised in the liver. It blocks the action of testosterone by stopping the hormone from binding to the cells of the body. It also decreases the production of the hormones that come from the pituitary gland and normally increase the production of testosterone. Its use is associated with abnormal liver function and a person must have regular monitoring of the liver function if they are taking this medicine. As it is a progestin it may be associated with the effects seen with progesterone use that we have just discussed. More importantly in transgender women depression is commonly seen (up to

60% of people) and the use of cyproterone is associated with depression. There have also been reports of the development of a type of tumour called a meningioma when people use high dose of cyproterone acetate. This is a tumour of the lining of the skull and can press on the underlying brain tissue.

Finasteride is a medicine that stops testosterone being converted to a more potent form (dihydrotestosterone) by the enzyme 5 alpha reductase. Finasteride inhibits this enzyme. Finasteride decreases the amount of hair on the body and slows the growth of facial hair. It can also stabilise the loss of scalp hair caused by high testosterone levels and at the dose used in transgender women can decrease sexual function (Seal, 2016). The same spectrum of side effects occur with the use of finasteride; both depression and liver function disturbance have been described as side effects of this drug. Although depression is not as prominent compared with cyproterone acetate in transgender women.

Spironolactone is a drug that is used to lower blood pressure but it also blocks the effect of testosterone on the cells of the body. It also binds to the oestrogen receptor and acts like a weak oestrogen in the body. The way that lowers blood pressure is by changing the way that salt is removed by the kidney. However, it can lead to high potassium levels in the blood stream (hyperkalaemia) as well as kidney damage (renal failure). It can also cause liver problems. Worryingly there have been reports of Spironolactone use being associated with bleeding from the gut. An important side effect in transgender women is that it may reduce the effectiveness of hormone therapy because transgender women who have used spironolactone are more likely to need breast augmentation than those that do not.

Anti-androgens were necessary in the past, because many people did not reduce their testosterone levels when using oestrogen on its own. Now instead of a person making testosterone and taking medicines that stop it working, we can give a medicine to stop the

testicles making testosterone in the first place. They are called *Gonadotrophin Releasing Hormone analogues* (GnRH analogues). This medicine works by over stimulating the cells in the pituitary gland that control the reproductive organs. When these cells are over simulated they “go to sleep” and stop working. This stops the testicles producing testosterone and sperm. There has been extensive experience in using these drugs both in the treatment of prostate cancer and infertility, and they have an excellent side-effect profile. The use in the hormonal treatment of transgender women appears safe with minimal side effects. The usual side effects of hot flushes and tiredness do not happen because transgender women are taking oestrogen to replace their testosterone, the reduction in bone mineral content does not happen because of the oestrogen treatment too .

Summary

Hormonal treatment is essential in the treatment of transwomen. It can produce permanent changes in the way your body looks and so it should only be given when your psychiatrist or psychologist feels it is the best treatment for you. Rushing into hormone treatment does not improve the result of feminisation and indeed can make the treatment less effective.

Hormone treatment is safe but there are side effects, especially the risk of blood clots and these must be minimised by stopping smoking and maintaining a normal body weight.

Hormonal treatment is intrinsic to the management of gender dysphoria. It should be undertaken only in the context of an active multidisciplinary approach involving both the mental health professional and the endocrinologist. The principal of treatment follows international guidelines and should not be initiated without approval from a mental health practitioner with a special interest in gender dysphoria.

For transwomen the hormone regimen usually consists of oestrogen as oestrogen valerate in combination with testosterone suppression, usually as goserelin. This combination allows

measurement of plasma oestrogen and testosterone levels to guide therapy. Alternative approaches include the use of the synthetic oestrogen ethinyl oestradiol and anti-androgens such as cyproterone acetate, spironolactone and finasteride.

The major side effect of oestrogen therapy is the development of blood clots usually as deep venous thrombosis with a rate of 2-3%. Other important risks are breast cancer, liver enzyme derangement and hyperprolactinaemia (increased blood prolactin levels).

Treatment is very successful with good feminisation in the majority of cases. Many patients, however, do require breast augmentation. Breast development occurs over 2 years of hormone therapy and treatment - beyond this will not produce further breast development.

There is no evidence that progestins improve breast development in transwomen. They may increase the risk of heart disease and stroke and promote breast cancer development. For these reasons their use is difficult to justify.

Following genital reconstruction surgery oestrogen doses can be reduced to levels used for high dose standard HRT but more usually higher doses are required. If oestrogen valerate is used plasma monitoring can be used to get the oestradiol level to the upper follicular range.

Oestrogen treatment may increase the risk of cardiovascular (heart) disease but this does not appear to happen with the more modern types of oestrogen, It also does not increase the incidence of any conditions that one might predict would be more common in hormonally treated patients such as breast cancer in transwomen with the exception of thromboembolism in oestrogen treated patients.