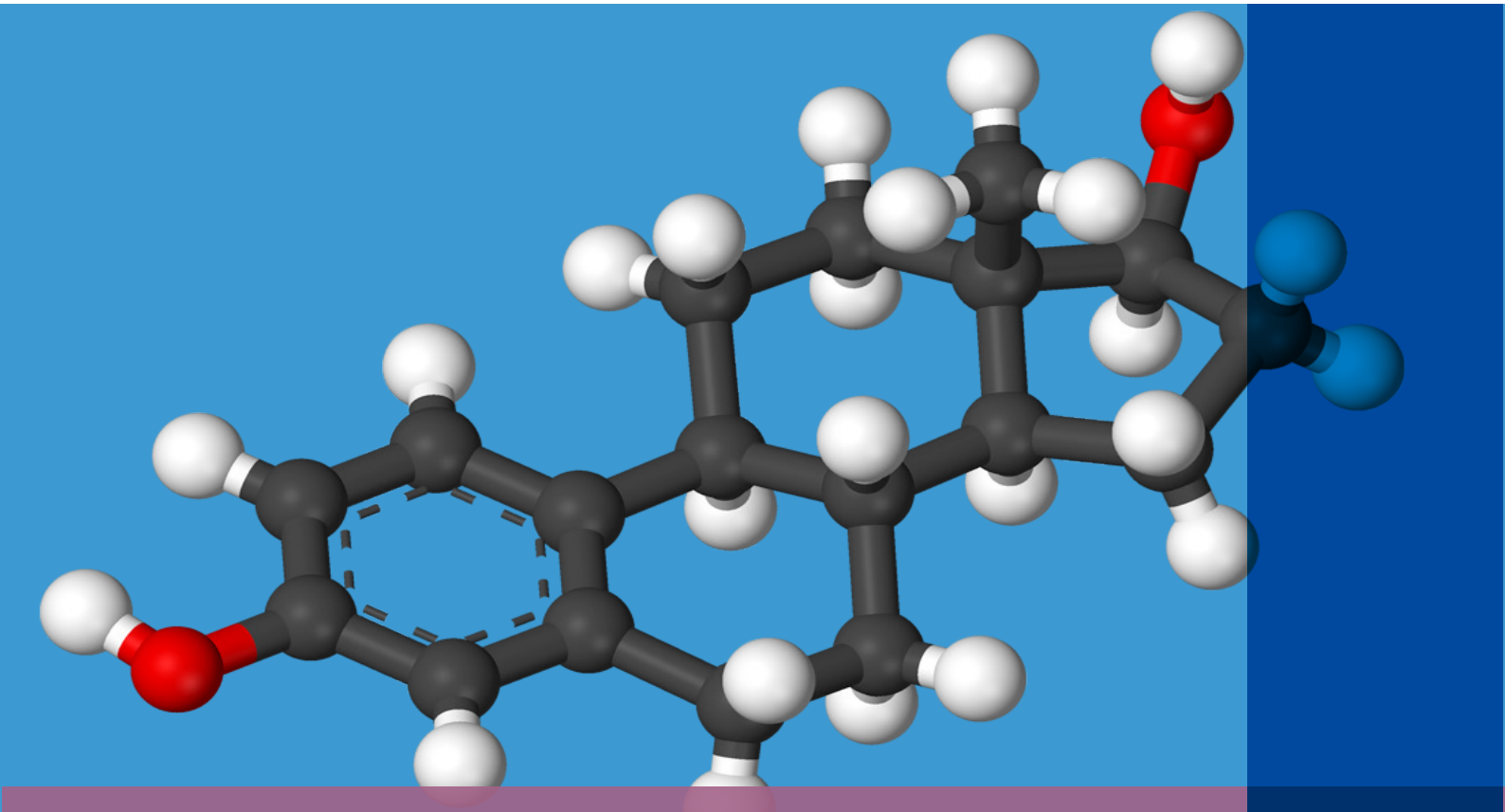
Gender Identity Clinic

NHS
The Tavistock and Portman
NHS Foundation Trust



Hormone treatment (feminine)

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Introduction

You have requested feminising hormone treatment, in order to help treat your gender dysphoria and to make your body more congruent with your gender identity. We will be recommending that your GP prescribe you the female hormone oestrogen. Oestrogen will result in your body developing a more female physical appearance. At the same time we will decrease your body's production of the male hormone testosterone, which will decrease your male physical appearance. Oestrogen treatment automatically stops you producing testosterone to a degree, but sometimes you will need to use a GnRH analogue drug as well; this stops production of the brain hormones that cause the testicles to produce testosterone.

Although hormone treatment is very effective and causes noticeable changes, you may also wish to undergo other procedures to further feminise some aspects of your body, such as electrolysis and genital reconstructive surgery.

Hormone treatment is generally very safe, but there are some side effects that you should be aware of and that will be explained to you at the time of prescribing. One of the most important side effects is an increased risk of blood clots, including blood clots in the legs (deep vein thrombosis or DVT) and the lungs (pulmonary embolus or PE). However, the good news is that the risk of this is not as high with modern forms of oestrogen (estradiol valerate and estradiol hemihydrate) as it is with older oestrogens (ethinylestradiol or conjugated equine oestrogens such as Premarin©).

If you ultimately decide to have genital reconstruction surgery this would involve removal of the testicles, and would mean that, even without testosterone suppression, your body would produce very little testosterone. Oestrogen treatment would need to be continued to prevent the complications of having no sex hormone production, such as osteoporosis (brittle bones) or early heart disease.

How hormone treatment fits with other aspects of your transition

At the Tavistock and Portman NHS Foundation Trust (Charing Cross) clinic you will be assessed by 1 or 2 clinicians, and sometimes more, before hormone treatment is recommended. This is in order to make sure that hormone treatment is the best way to manage your gender incongruence.

We follow an internationally agreed guideline known as Triadic Therapy, which consists of three successive stages; firstly, social gender role change (living in a female or transfeminine role, and formerly called the Real Life Experience); secondly, hormone treatment; and finally, gender related surgery.

This means that we normally ask you to change social gender role before hormone treatment is started; indeed, studies have shown that it is social gender role change, and not hormone treatment, that has the biggest effect on reducing psychological distress and making a person feel better about themselves. Once hormone treatment is started, we then normally want you to become established on this before any surgical interventions. We follow these three stages because as you progress through them there are progressively more significant and irreversible physical changes, which may make it harder to revert to your gender assigned at birth.

It is also important to say that not everybody wants or needs to go through all three stages. Some people change social gender role without having hormone treatment, and some people who have hormone treatment choose not to have any gender related surgery. A minority of people will also have gender related surgery without hormone treatment.

Our standard hormone regimen

The standard oestrogen used at our clinic is estradiol valerate, initiated at 2mg daily and increased in 2mg steps every 3 months as needed, up to a usual maximum of dose of 8mg daily (sometimes 10mg after discussion with the clinic). Estradiol valerate is the same as the oestrogen that the body naturally produces, which means we can measure it in your blood and change the dose until we get to the level seen in a young cisgender female (400-600pmol/l). Different people will reach this level on different doses. In many cases higher doses are required than for cisgender women undergoing hormone replacement therapy (HRT), as a different outcome is being sought, namely generation of a female puberty.

We know from our experience with treating cisgender females who have not gone through puberty naturally, that if too much oestrogen is given too quickly then breast development is abnormal, with the breasts being smaller, harder and more cone shaped. Natural puberty occurs slowly over 2 years, during which time oestrogen levels in the blood slowly rise. We aim to mirror this in our treatment, so that you achieve the best possible breast development.

Similarly, using excessive amounts of oestrogen also does not improve breast development and may even be counterproductive, as there is an enzyme present in the body that converts excess oestrogen back into testosterone.

Forms of oestrogen other than estradiol valerate can also be used, such as Sandrena© gel 0.5-5mg once a day, or patches (such as Estradot© or Evorel©) at doses of between 50μg and 200μg twice a week. Most people ask for tablets first as they find them more convenient, but these other medications also work well. Also, forms of oestrogen that are given through the skin are not, unlike tablets, processed by the liver. This is better for some people with conditions such as liver or bowel problems, or those who do not achieve high enough blood oestrogen levels on tablets (because their livers are metabolising the oestrogen too quickly).

As well as increasing your oestrogen, we also want to reduce the amount of testosterone your body produces, so that you are producing the same amount of testosterone as a cisgender woman. Sometimes this happens with oestrogen treatment on its own. However, if your blood testosterone is not adequately suppressed on estradiol valerate 4mg daily then a GnRH analogue may be added, such as goserelin (Zoladex©) 10.8mg, triptorelin (Decapeptyl©) 11.25mg or leuprorelin (Prostap©), which are given by injection every 12 weeks. GnRH analogues work by over-stimulating a gland under the brain called the pituitary gland, which normally causes the testicles to produce testosterone. When the pituitary is over-stimulated it eventually goes to sleep and so the production of testosterone will stop. However, for the first 2 weeks following the first injection more testosterone is produced, and this can cause an increase in erections and sexual thoughts. To prevent this, cyproterone acetate 50-100mg per day is normally given for the first 2 weeks. It is not needed with subsequent injections.

If you choose to have genital reconstruction surgery then up to 6 weeks beforehand your oestrogen treatment may need to be stopped, in order to reduce the risk of deep vein thrombosis, but this may be done differently in different surgical teams. If oestrogen is stopped, it is restarted about 2 weeks after surgery.

Effects of Hormone Treatment

Feminisation with oestrogen therapy takes about 2-3 years.

Hair

You will find that your skin texture becomes finer and that there is a reduction in the growth of your facial hair. This effect is maximal after 4 months of treatment. Oestrogen treatment itself rarely eradicates facial hair growth once a person has adult beard development. However, additional treatment such as electrolysis and laser can be accessed locally to further reduce the appearance of facial hair.

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

Breast growth

During female puberty breast growth is stimulated by oestrogen and takes 18 months to 2 years. Your oestrogen treatment mirrors this process. Breast development will begin about 2-3 months after the start of oestrogen, with the maximum effect seen after 2 years. In general the maximum breast development you can expect to achieve is one bra cup size less than your mother (the size difference being because breasts typically become larger after childbirth). However, there can be considerable variation, much as there can be between cisgender women within a family. Using a very high dose of oestrogen, that gives you a blood oestrogen level higher than the normal female range, does not result in additional breast development.

Breast development is dependent on the deposition of fat into the breast, so if you are thin then gaining some weight can increase your breast growth.

Despite hormone treatment many transgender women and transfeminine people progress to breast augmentation surgery, although unfortunately at the moment this is not funded 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, which gives 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

Sexual and genital effects

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

Fertility

Sperm production will decrease and eventually stop. If you would like the possibility of having biological children in the future, either with a partner or via a surrogate, then you will need to store your sperm before you start oestrogen. This can be arranged at a local fertility clinic that your GP can refer you to. There may be a charge for this as sperm storage is not always available on the NHS.

Importantly, despite the effects on fertility, you cannot rely on oestrogen treatment as a contraceptive. If your partner is assigned female at birth then you will need to take appropriate contraceptive measures.

Negative effects of hormone treatment

Oestrogen treatment is safe and effective, but several side effects of this treatment have been described in the transfeminine population. The most important of these are thromboembolic complications (blood clot formation such as deep venous thrombosis), liver function abnormalities and hyperprolactinaemia (increased prolactin level in the blood).

Thromboembolic disease (VTE)

The major side effect of oestrogen treatment is the formation of clots in the blood vessels, called venous thromboembolism (VTE). There has been a great reduction in how often this happens as we have improved the forms and doses of the hormones we use. In the original study in 1989 there was a 45-fold increased 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. 12% of women over 40 years old were found to develop a deep venous thrombosis (a DVT, which is a blood clot in the legs), whereas only 2.1% of women under 40 did.

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 becomes more sticky (Toorians et al., 2003). They found that if you give estradiol via a patch rather than ethinylestradiol by a tablet then the stickiness of the blood is reduced. 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 the 40-fold increased risk of DVT went down to a 20-fold increased risk. This gives a VTE rate of 2.6% in total. 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 estradiol, but not ethinylestradiol, have shown very good DVT rates of 0.6%. This study also showed that people using oestrogen preparations called conjugated equine oestrogens (such as Premarin©) were 8 times more likely to have a DVT that those taking estradiol tablets. This later study suggested that it is the type of oestrogen that is used, rather than the way it is given, which is important in determining the likelihood of developing a DVT. As a result, at our clinic as people age we do not routinely switch them from tablets to transdermal oestrogen. In the UK most of the large transgender health clinics now use a combination of estradiol with a GnRH analogue for feminisation (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 2-fold and in people who are obese and smoke by 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.

Breast cancer

The incidence of breast cancer with standard HRT in cisgender females is 3.2/1000 in women aged 50-59 and 4/1000 in women aged 60-69 (Beral et al., 2002). This is based on large population studies.

There are no similar studies involving transgender women and transfeminine people, but there have only been seven case reports of breast tumours occurring in transgender women taking oestrogen. This suggests that the incidence of breast cancer is the same as the background rate of breast cancer in cisgender males, and that oestrogen treatment does not increase breast cancer risk.

It is known that for cisgender women prolonged HRT use beyond 5 years after the menopause (about age 55) is associated with an increased risk of breast cancer. However, we also know that breast cancer risk remains the same as your birth gender which is 10 lower than a cis gendered female, suggesting that for transgender women and transfeminine people long term oestrogen treatment beyond age 55 is not harmful. Therefore we do not routinely stop or reduce oestrogen beyond age 55, but if you do want to you can discuss this.

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 the pituitary gland. Oestrogen, which is high in pregnancy, causes the pituitary to grow and release more 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 the pituitary gland. Over a long period of time this growth may become a lump in the 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 known cases of prolactinomas (benign lumps in the pituitary gland) in transgender women and none have needed withdrawal of oestrogen treatment. Furthermore, a more recent study suggested that with newer hormone regimens using estradiol and GnRH analogues the incidence of high prolactin levels was reduced to 2.3%.

Very high levels of oestrogen increase the chance of prolactin levels rising which is one of the reasons why we keep the estradiol level at the normal range for an adult cisgender female and not higher. (Interestingly one of the patients who developed a pituitary lump had been self-administering oestrogen in addition to her prescribed oestrogen treatment.)

If your prolactin level rises it can be treated by reducing your oestrogen dose, alongside a GnRH analogue to reduce your testosterone.

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 about 3% in transgender women and transfeminine people taking oestrogen treatment. For half of these women 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 taking oestrogen gallstones are more common.,

Osteoporosis (thin bones)

The amount of calcium in the bones is controlled by the sex-steroid hormones, oestrogen in a female and testosterone in a male. Cisgender males generally have thicker and stronger bones than cisgender females, so people have worried that if testosterone levels are reduced during a transgender woman’s treatment then their bones may become thinner. However, most studies in transgender women reassuringly show that oestrogen treatment can keep the bones strong even though the amount of testosterone in the blood stream is lower. One group that have shown a decrease in bone area and mineral content is transgender women who take less exercise, and so transgender women and transfeminine people 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 Vitamin D. Vitamin D is needed for absorbing calcium into the bones, so if a transgender woman has a low vitamin D she should have this replaced.

Other side effects

Oestrogen treatment is associated with some other side effects that appear in the literature as isolated case reports. It may increase the risk of cardiovascular (heart) disease but this does not appear to happen with the more modern types of oestrogen. Other side effects 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 hormone treatment at an early stage, so that the treatment can be altered to prevent ongoing unwanted effects.

Before starting hormone treatment	Bloods: LH FSH Testosterone Estradiol SHBG Prolactin LFTs Lipid profile Glucose Vitamin D PSA Other: Weight Blood Pressure
After initially starting hormone treatment - every 3-6 months After 2 years on a steady dose - every 12 months	Bloods: Testosterone Estradiol (if on estradiol valerate) LFTs Prolactin Other: Breast examination Weight Blood Pressure
If needed	Mammogram (follow national guidelines) Aortic aneurysm screening (follow national guidelines) DEXA bone scan, if >12 months without hormone treatment, family history of osteoporosis or a history of low impact fractures

Additional treatments

Progesterone is used by some centres, although not in the large European centre, and is widely purported by transgender websites to improve breast development.

However, progesterone has no role in breast development. It is not produced by a cisgender female until the later stage of puberty, when she starts ovulating, typically a full 18 months after her first period; by this time breast development is complete. A recent summary study (meta-analysis) looking at breast development in transgender females showed that using progesterone and oestrogen does not give better breast development than using oestrogen on its own.

The big HRT trials in cisgender females suggest that progesterone in combination with oestrogen may increase the incidence of breast cancer, heart attacks and strokes. These risks were not seen in the oestrogen-only arm of these trials, suggesting that progesterone is bad for both cardiovascular and breast health. Progestins can also lower mood and increase the risk of depression in susceptible people.

As progesterone has no role in breast development, and can in combination with oestrogen have serious side effects, its use in transgender women and transfeminine people is therefore questionable, and in UK practice it is almost never used.

Anti-androgen treatment, such as either cyproterone acetate or spironolactone, is used by some centres but generally not in the UK. Anti-androgens fight against the testosterone that is produced in the body. Finasteride, which stops testosterone becoming its more active form (dihydrotestosterone), is also sometimes 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 their 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 cyproterone acetate is associated with depression, and in transgender women depression is already commonly seen. 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 that can press on the underlying brain tissue.

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 it lowers blood pressure is by changing the way that salt is removed by the kidney. However, this can lead to high potassium levels in the blood stream (hyperkalaemia), which is dangerous for the heart, as well as to 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 additional important side effect in transgender women and transfeminine people is that it may reduce the effectiveness of oestrogen treatment, because those who have used spironolactone are more likely to need breast augmentation than those that do not.

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 and transfeminine people can decrease sexual function (Seal, 2016). The same spectrum of side effects occurs with the use of finasteride; both liver function disturbance and depression have been described as side effects of this drug, although depression and liver problems are not as prominent compared with cyproterone acetate.

Anti-androgens were necessary in the past, because many people could not achieve sufficiently low testosterone levels by using oestrogen on its own. But now, instead of a person making testosterone in their testicles and then taking anti-androgen medicines that stop the testosterone working, we can give medications to stop the testicles making testosterone in the first place. These are Gonadotrophin Releasing Hormone analogues (GnRH analogues). As we have already discussed, these work by over stimulating the cells in the pituitary gland that control the reproductive organs; the cells eventually “go to sleep” and stop working, which 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. Their use in the hormone treatment of transgender women and transfeminine people appears to be safe, with minimal side effects. Indeed, the usual side effects of hot flushes, tiredness and reduction in bone mineral content do not occur, because oestrogen is being taken to replace testosterone.

Long term safety

Current studies suggest that long-term treatment with oestrogen in transfeminine people is associated with a slight increase in the standard mortality ratio. The increase in death rates seems to be linked to an increase in the risk of suicide in vulnerable. And more recnt tudoes suggest this is much better now. This may reflect improvements in the availability and quality of care and an improvement in the status of transpeople in society leading

There does seem to be an increase in heart disease and strokes. This increase however appears to be due using Ethinyloestradiol (the oestrogen that is used in the contraceptive pill), but not other oestrogen types, and so we do not use this oestrgen type. This is also the reason why it is very important not to smoke when you are using oestrogen treatment .

Summary

Hormone treatment can be central to the management of gender dysphoria. It should be undertaken only in the context of an active multidisciplinary approach involving your gender specialist, your GP and the endocrinologist. The principle of treatment follows international guidelines.

For transgender women and transfeminine people the hormone regimen consists of oestrogen, such as estradiol valerate tablets, often in combination with testosterone suppression, such as goserelin (Zoladex©), triptorelin (Decapeptyl©) or leuprorelin (Prostap©) injections. This combination allows accurate measurement of plasma oestrogen and testosterone levels to guide treatment. If genital reconstruction surgery occurs then the testosterone suppression can be stopped.

Taking excessively high doses of oestrogen does not improve the feminisation achieved, and can even make the treatment less effective. There is also no evidence that progestins improve breast development, whilst they may increase the risk of heart disease, stroke and breast cancer; for these reasons their use is difficult to justify.

Hormone treatment is generally safe if properly prescribed and monitored, but there can be side effects. The most important side effect of oestrogen treatment is the risk of developing blood clots, usually as a deep venous thrombosis in the leg, which can happen for 2-3% of people. Other important risks are abnormal liver function and hyperprolactinaemia (increased blood prolactin levels).

There are some limitations as to what hormone treatment can achieve. Although breast development will occur over a 2-year period, many people do choose to have additional breast augmentation surgery, which is not currently funded on the NHS. Additional treatments are also

usually required for facial hair removal. However, overall the treatment is usually very successful. Good feminisation, including breast growth, fat redistribution and a reduction in body hair, is achieved in the majority of cases.