Hormone management of trans women

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In the previous issue, the authors introduced some principles underlying the medical management of transgender people, before focusing on trans men. In this article they look at the hormonal management of men transitioning to a female gender.

As previously described for trans men, both practitioners and patients need to remember that the aim of hormone management is to mirror physical changes that occur through natural puberty. For females, these can be expected to take two to three years to complete.

Stepwise increasing dosages of oestrogen are used, until oestradiol levels match those of a young adult woman. Unlike the parallel situation with trans men, this monotherapy is usually not sufficient to adequately suppress the main form of assigned-gender sex hormone (testosterone in this case). Most trans women need additional therapy to achieve this. In the UK we usually recommend the use of a gonadotropin-releasing hormone (GnRH) analogue, usually the three-monthly form.

It could be argued that the ongoing management of trans women does not sit with this publication's focus on Men's Health, but there should be some relevant issues for those interested in general urology. It is also useful for all clinicians to know what may lie ahead as someone begins their physical transition from masculine to feminine.

Physical and mood changes

The various physical changes seen with oestrogen therapy, along with expected time frames, are summarised in Table 1.

One of the first changes usually noted, from around one to three months, is a lessening of spontaneous erections and libido. There is a variable response in erectile function with stimulation, generally declining more in older trans women. Reduced erections are often welcomed by this group, but some prefer to maintain function if possible, whether or not planning later genital reconstruction surgery. Standard erectile dysfunction treatments can be offered if required.

Another early change is seen in the skin and hair. The skin becomes softer and finer. Facial hair growth diminishes, maximally around four months. This hair loss is by no means complete, and other measures are typically required, commonly facial electrolysis or laser therapy. A number of sessions are usually available on the NHS. Use of eflornithine cream may be a helpful adjunct. For scalp hair, any male pattern baldness will slow and stabilise, but pre-existing loss will not be reversed. Minoxidil and finasteride can be used, but dramatic results should not be expected.

From around three to six months, changes in body composition will be seen. Muscle mass (and resultant strength) decreases, and body fat
increases. A more feminine body shape is acquired, with fat deposited around hips and buttocks. Average weight gain is around 4kg.\textsuperscript{5}

A crucial body shape change is of course breast development, again starting from around three months, with maximal growth taking two years or more.\textsuperscript{6} On average, patients can be advised to expect to achieve a B-cup bra size, or one cup size less than their mothers. The latter is a useful reminder that there is some genetic programming at work, just as for cis women. It has been shown that despite optimal hormone therapy 60% of trans women go on to seek breast augmentation surgery.\textsuperscript{7} As breast development is dependent on fat deposition, encouraging moderate weight gain in underweight trans women can help. Patients should be advised against early self-medicating with high doses of oestrogen, which can lead to rapid breast growth but premature termination at a mid-puberty stage, resulting in small conical-shaped breasts.\textsuperscript{2} Furthermore, spironolactone (used by some for anti-androgen effects) has been shown to increase the number requiring breast augmentation.\textsuperscript{8}

Testicular size will decrease, with noticeable change seen from three to six months, peaking around two to three years. Fertility declines, so sperm storage should be discussed, and local arrangements sought if required. While sperm counts decrease, complete azoospermia is not assured, meaning contraception may still be required.

Trans women should know that their voices will not change to a higher register with hormone therapy. In much the same way as more familiar hormone replacement therapy (HRT) can help improve mood in perimenopausal women, a positive effect has been reported with oestrogen therapy in trans women.\textsuperscript{9} Anecdotally, many report a calmer mood with their increased sense of femininity.

<table>
<thead>
<tr>
<th>Effect</th>
<th>Onset (months)</th>
<th>Maximum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decreased libido</td>
<td>1–3</td>
<td>3–6 months</td>
</tr>
<tr>
<td>Decreased spontaneous erections</td>
<td>1–3</td>
<td>3–6 months</td>
</tr>
<tr>
<td>Sexual dysfunction</td>
<td>Variable</td>
<td>Variable</td>
</tr>
<tr>
<td>Reduction in facial hair</td>
<td>1–3</td>
<td>3–6 months</td>
</tr>
<tr>
<td>Skin softening, decreased oiliness</td>
<td>3–6</td>
<td>Unknown</td>
</tr>
<tr>
<td>Decrease in muscle mass and strength</td>
<td>3–6</td>
<td>1–2 years</td>
</tr>
<tr>
<td>Redistribution of body fat</td>
<td>3–6</td>
<td>2–3 years</td>
</tr>
<tr>
<td>Breast growth</td>
<td>3–6</td>
<td>2–3 years</td>
</tr>
<tr>
<td>Decreased testicular size</td>
<td>3–6</td>
<td>2–3 years</td>
</tr>
<tr>
<td>Decreased sperm production</td>
<td>Unknown</td>
<td>&gt;3 years</td>
</tr>
<tr>
<td>Decreased terminal hair growth</td>
<td>6–12</td>
<td>&gt;3 years</td>
</tr>
<tr>
<td>Scalp hair</td>
<td>No regrowth</td>
<td>-</td>
</tr>
<tr>
<td>Voice changes</td>
<td>None</td>
<td>-</td>
</tr>
</tbody>
</table>

Table 1. Physical effects seen with hormone therapy in trans women, and expected timings\textsuperscript{3}

Potential adverse effects of therapy

Venous thromboembolism (VTE)

While still representing the major side-effect of oestrogen therapy, VTE rates have decreased considerably over recent years. This is due to the ongoing move away from the more pro-thrombotic oestrogens, ethinylestradiol and conjugated equine oestrogens.

Initially, it was shown that using estradiol patches halved the VTE risk, compared to oral ethinylestradiol, from 40-fold to 20-fold.\textsuperscript{10} It was thought that this reduction in risk could be attributed to the route of administration, but more recent evidence showing low VTE rates with oral estradiol suggests it may be the type of oestrogen that is important, rather than the route.\textsuperscript{8} Hence, the most common form of oestrogen therapy given to trans women in the UK is oral estradiol, though topical forms may sometimes still be favoured.

It is very likely that the same factors that further increase VTE risk in cis women on oestrogen therapy will play a role here. Evidence in these women reveals that smoking causes a doubling of risk, increasing to nine-fold with obesity.\textsuperscript{11}

Consequently, trans women in the clinic need to have stopped smoking before therapeutic doses of estradiol are given, and they are encouraged to keep weight under control.

Cardiovascular risk

A recent meta-analysis showed that, for trans women, the only significant change in the lipid profile seen with hormone therapy was a small rise in triglycerides (+0.38mmol/L), with no change in other parameters.\textsuperscript{12} This study found low rates of stroke (0.9%) and myocardial infarction (MI) (1.3%). For the latter figures, while reassuring, numbers were too low to draw significant conclusions, and largely driven by a centre where high-dose oestrogens were used.

Of note, a previous study that had shown some increased cardiovascular mortality in trans women found that this was only significant in the
subgroup that were currently using ethinylestradiol. Previous evidence has suggested that, compared to those assigned male at birth, MI rates are halved.

**Cancer**

Studies indicate that there is no increased breast cancer risk with oestrogen therapy in this population, demonstrating the same background risk as for cis men. While reassured by this low risk, we still advise older trans women to access the same breast screening programme in the same way as cis women.

Risk of prostate cancer in trans women, with suppressed testosterone levels, appears to be very low.

**Bone mineral density**

While there could be the potential to lower bone mineral density with testosterone suppression, it appears that replacing with oestrogen negates this problem. A recent meta-analysis actually found that lumbar bone mineral density increases a little in treated trans women.

**Hyperprolactinaemia**

Physiologically, high levels of oestrogen in pregnancy stimulate prolactin release. The same response has been seen in trans women. However, recent data suggest a low incidence of hyperprolactinaemia (around 2%). Symptomatic high levels and, indeed, prolactinomas are rarely seen when oestradiol levels are kept within the target range.

**Liver function**

High-dose oestrogen therapy is linked to liver dysfunction, but again this is rarely significant with careful and responsive monitoring of oestradiol levels and liver function. At most it will usually cause a mild and temporary increase in liver enzymes. In one series, no trans women had a significant problem.

**Other medications**

Progesterone is recommended by some gender clinics internationally, but rarely in the UK. Some trans women strongly believe that it should be added, to enhance breast development. A meta-analysis found no additional benefit for breast development when comparing progesterone plus oestrogen to oestrogen alone. We advise patients that oestrogen-only hormone therapy is the best and safest option, as progesterone is not produced during the breast development phase of physiological female puberty, and trans women do not have endometria to protect. At a cellular level, progesterone reverses oestrogen-induced cell proliferation and, more importantly, evidence in cis women has shown that adding progesterone to oestrogen therapy is associated with increased risk of cardiovascular disease and breast cancer.

As mentioned above, we favour GnRH analogues for testosterone suppression. These medications are extremely safe and in trans females the usual side-effects of hot flushes, tiredness, increased cardiovascular risk and reduced bone mineralisation do not occur as the person is taking oestrogen at the same time. Other forms of medication have been used

<table>
<thead>
<tr>
<th>Preparation</th>
<th>Formulation</th>
<th>Frequency</th>
<th>Target range, oestradiol</th>
<th>Monitoring method</th>
<th>Maximum dosage</th>
<th>How to adjust if needed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tablets</td>
<td>Estradiol valerate or (used less) estradiol hemihydrate</td>
<td>1 and 2mg tablets</td>
<td>Take once daily, in the morning</td>
<td>400-600 pmol/L</td>
<td>Bloods 4–6 hours after taking tablets</td>
<td>8–10mg daily</td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>Patches</td>
<td>50–200mcg / 24hour</td>
<td>Change patch/es twice a week</td>
<td>As above</td>
<td>Bloods at least 48 hours after patch application</td>
<td>200mcg twice weekly</td>
<td>Usually 50mcg adjustments, less if oestradiol only a little out of range</td>
</tr>
<tr>
<td>Topical gel</td>
<td>0.5–1mg sachets</td>
<td>Apply in the morning, to anywhere on body except breasts</td>
<td>As above</td>
<td>Bloods 4–6 hours after application (no gel on the arms)</td>
<td>5mg daily</td>
<td>Usually 1mg adjustments, less if oestradiol only a little out of range</td>
</tr>
<tr>
<td>Implants (rarely used)</td>
<td>50–100 mg</td>
<td>6–24 monthly</td>
<td>Trough value of 400–500 pmol/L</td>
<td>5 months after implant then repeated monthly until &lt;500pmol/L (to notify secondary care)</td>
<td>100mg</td>
<td>Secondary care oversight</td>
</tr>
</tbody>
</table>

Table 2. Forms of recommended estradiol therapy
with this intention. Cyproterone acetate was once favoured, but we do not recommend it. As well as a progesterone-like effect, it is associated with liver dysfunction and depression. Similarly, we do not support the use of spironolactone, which is more commonly used in the USA. As well as well-known effects on electrolytes, and on breast development as above, a recent study showed that only a minority of trans women on spironolactone achieved testosterone levels in the usual female range.

Post-operatively, some trans women experience reduced libido and sexual function and meet the diagnostic criteria for hypoactive sexual desire disorder. This can be treated with low-dose testosterone (as for menopausal cis women), once therapy is stabilised.

Oestrogen therapy regimes and monitoring

We recommend the use of oestradiol, in its various forms (most commonly oral). The aim is to achieve an oestradiol level equivalent to the upper follicular range of a young cis female (400-600pmol/L), increasing doses over 6–12 months until the correct level is achieved. Topical treatment may achieve adequate levels if not reached with 8–10mg of oral oestradiol. If testosterone is not suppressed (<3nmol/L) with oestradiol levels in range, then the GnRH analogue is added, until orchidectomy (if this occurs).

Post-operatively, some trans women experience reduced libido and sexual function and meet the diagnostic criteria for hypoactive sexual desire disorder. This can be treated with low-dose testosterone (as for menopausal cis women), once therapy is stabilised.

Table 2 shows the forms of oestradiol therapy recommended by the Gender Identity Clinic in London, with Box 1 outlining our advised monitoring strategies.

Conclusion

The effects of cross-gender hormone treatment in trans women and men are usually very reliable. Changes are largely reversible if hormones are stopped, with a return to function of the assigned gender over one to two years. However, some changes may be permanent, such as the development of facial hair in trans men or breast development in trans women. Thus, medications should not be commenced until thorough assessment is complete. Using this approach, the majority of trans people achieve safe, effective and fulfilling gender transition.

Declaration of interests: none declared.

References


Box 1. Monitoring: blood tests and actions to take

Blood tests that need to be requested (including safety blood tests, for monitoring):

- Oestradiol, testosterone, prolactin and LFTs. For timings, see above.
- When a preparation dose is changed, repeat blood tests need to be taken eight weeks later. Once hormone therapy is stabilised, bloods should be taken six-monthly for two years, then annually.

Cut-offs for action with the monitoring bloods:

As well as looking to keep the oestradiol level within range, as in Table 2, other blood results may occasionally need action:

1. Testosterone
   - If testicles are still present, medication is usually used to suppress testosterone, ie under 3nmol/L. If it rises, check compliance with this medication (usually a GnRH analogue). Seek advice if needed.

2. Prolactin
   - Small rises in prolactin are often seen with oestrogen therapy.
     - a) New rise of >750 mIU/L: repeat test
     - b) New rise of >1000 mIU/L: seek advice from local endocrinology department

3. Liver function tests
   - Values of greater than three times the upper limit of normal: seek advice.
Transgender health