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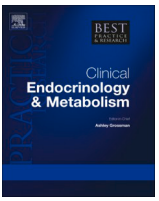

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# Gender-affirming hormone treatment modalities for transfemale & non-binary transfeminine individuals: A UK perspective

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Gender incongruence and the number of people seeking gender affirming hormone treatment has dramatically risen in the last two decades. In the UK, transgender women and non-binary transfeminine individuals are typically treated with simultaneous suppression of endogenous testosterone production through anti-androgens and exogenous oestradiol replacement. Oestrogen replacement comes in different forms and is primarily given as transdermal (gel or patch) or oral preparations in the UK. Decisions around preparation choice are based on a combination of individual preference and/or mitigating the chance of complications based on individual risk profiles. Time frames to achieve female physical changes are largely predictable and managing expectations of individuals prior to commencing treatment is highly important. Common complications include venous thromboembolism, liver dysfunction and effects on fertility, thus individuals should be thoroughly counselled prior to commencing treatment. This article provides an overview of the management and considerations of gender-affirming hormone treatment in transgender women and non-binary transfeminine individuals.


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## Introduction

Gender incongruence has historically been rare, yet in the past decade the number of individuals seeking gender-affirming hormone treatments has dramatically risen [1]. In the last 20 years there has been a more than fivefold increase in those with a recognised transgender identity, highest in those aged 16–29 years [2]. Despite this increase in demand, gender identify services have not increased proportionally [1]. Whilst true figures can be difficult to obtain, the 2021 census was the first to directly ask about the respondent's gender identity. 262,000 people responded that their gender identity and registered sex at birth differed. Of these, 0.1 % identified as a transwoman and 0.06 % as non-binary [3,4].

Unlike the endocrine treatment in transgender men, who are largely treated with testosterone monotherapy, transgender women (TW) and non-binary transfeminine (NB-TF) people typically require a reduction in endogenous testosterone production through androgen blockade as well as oestradiol replacement to adequately address both the physical and psychological aspects of the individual's gender incongruence. Goals of therapy therefore include the enhancement of feminising features (breast growth and feminine fat distribution) as well as a reduction in more masculine features (reduction in body hair and male-pattern hair loss). At present, within the UK, there are no nationally approved standardised guidelines for treating TW and NB-TF individuals, however, there are many commonly used practices both within NHS and private sector clinics.

This article will focus on the use of oestradiol treatment, androgen blockade and other less established treatment options used for gender-affirming hormonal therapy (GAHT) for TF and NB-TF people within in the UK including the desired effects, risks, side effects and long-term monitoring.

### *The role of oestrogen treatment in the management of transgender females and non-binary transfeminine individuals*

The three naturally occurring oestrogens are steroid hormones, all derived from cholesterol following a series of enzymatic reactions. They are predominantly produced in the ovaries and corpus luteum. 17β-Oestradiol (E2) is the most abundant and most potent during the pre-menopausal period. Oestrone (E1) is the most relevant after the menopause and Oestriol (E3), formed from E1, plays a larger role during pregnancy when it is produced in larger quantities by the placenta [5]. Synthesis of E2 within the internal theca of the ovary initially starts with acetyl-CoA and cholesterol. After a series of initial reactions, the androgen androstenedione is formed. From here, 17β-HSD facilitates conversion to testosterone. The cytochrome P450 enzyme, aromatase, is crucial in the final step of E2 synthesis from testosterone as well as E1 synthesis from androstenedione which can then form E2 (via 17β-HSD) [6].

Synthetic oestradiol comes in various forms including transdermal (patches), oral and injectable although the latter is not available on prescription in the UK but is commonly used in some other countries. Incremental dosing is often used until acceptable oestradiol levels are reached, typically aiming for levels comparable to those of a young adult woman [7]. In the UK, all exogenous oestradiol treatment in the management of TW or NB-TF is used off-license. Whilst there is an expectation that physical changes following initiation of oestradiol therapy and androgen blockade will commence within the first few months and progress for up to 3 years, high quality evidence about the specific timeline is limited.

#### *Facial and body hair*

One of the earliest changes seen following initiation of oestradiol therapy affects both body and facial hair. There are several changes seen including the softening of the skin and decreased oiliness based on the direct effect of exogenous oestradiol on the skin pilosebaceous unit [8]. The skin also tends to become finer. Further to this, oestradiol therapy leads to a reduction in facial hair growth which reaches its maximal effect around four months. However, this is often incomplete and if felt unacceptable to the individual options including both laser therapy, facial electrolysis or topical eflornithine cream. Whilst male-pattern scalp hair loss is another key focus for many individuals there is a variable impact from oestradiol therapy. In the vast majority, scalp hair loss will slow however pre-existing loss cannot be reversed by oestradiol initiation. This is often a challenging area of management and clear expectations

between the treating clinician and individual is crucial. Additional benefit may be gained from the used of finasteride, a 5α-reductase inhibitor. Terminal hair reduction elsewhere in the body can take longer, often only seen closer to 12 months following initiation of hormonal therapies but can continue beyond 3 years of treatment [9].

### *Libido, sexual function and mood*

Within the first three months of initiation of oestradiol therapy, a reduction of libido and spontaneous erections is usually seen. For many of this group, this is an important benefit of treatment. However, in those who wish to maintain function for sexual activity, standard treatment options for erectile dysfunction can be offered. Psychological benefit from gender-affirming hormone therapy has also been shown. Benefits have been demonstrated for self-esteem, body image and a greater sense of alignment between the individual's gender identity and physical appearance. Such positive effects on body image can then in turn have additional benefit for depression and anxiety [10]. Hormonal therapies alone have been shown to improve quality of life and psychological outcomes even without the additive impact from gender-reassignment surgery [11]. Anecdotally, some individuals associate GAHT with an increase in sense of femininity as well as a calmer mood, however more robust data would be required to draw more definitive conclusions.

### *Breast development*

Breast growth tends to commence within three to six months of beginning hormonal treatment and reach maximum effect around 2–3 years [12]. Careful management of expectations around breast development is once again recommended and there is a degree of impact from genetics in the likely final breast size. Fat distribution is also thought to have benefit and thus moderate weight gain is sometimes required to improve breast development [7] especially in patients with low-normal BMI. Despite optimisation of oestradiol therapy, as many as 70 % of individuals are reported to go on to have surgical procedures for breast augmentation [13]. In one study, no differences were observed based on the type of oestradiol treatment received [14]. In another study, duration of hormonal therapy and age of initiation of hormonal treatment were also not predictive of final breast size [15]. Testosterone suppression may also play a role given its impact on breast tissue proliferation demonstrated in vitro and animal studies, though in human studies data have been inconclusive [16–18]. Anecdotally the use of progestogens have been reported to help with breast development, however at present this practice is not currently widely accepted in the absence of conclusive evidence [9,12].

### *Testicular size and function*

Over time, in the presence of androgen blockade and oestradiol therapy, there will be testicular and prostrate atrophy. Within the first six months of commencing treatment, testicular size is expected to noticeably decrease and may continue for up to 2 years. However, many of the expected results of hormone therapy for transgender women and NB-TF are predicted from studies of male patients undergoing gonadotrophin-releasing hormone (GnRH) suppression in prostate cancer treatment. Variable and conflicting outcomes have been described in transgender people. Differing testicular weights and volumes have been reported by one study, depending upon the degree of germ cell depletion [19]. Testicular atrophy was more common in those aged > 40 years. Spermatogenesis is another key aspect and given the impact of oestradiol therapy on fertility, gamete storage should be considered and discussed prior to commencement. Impaired spermatogenesis to some extent was demonstrated in almost three quarter of the patients in one study [19]. With another study demonstrating that around 10 % of individuals had normal spermatogenesis despite a median duration of hormonal therapy of 4 years [20]. Thus, an important aspect of hormonal therapy in this cohort is the continued used of contraception.

*Body fat and muscle distribution*

Changes in body composition are another key aspect that many TW and NB-TF individuals seek from GAHT. Feminisation of the body is typically associated with a change in fat distribution and decrease in muscle mass. The onset of such changes is typically seen between three and six months after commencement of GAHT with maximal effects demonstrated by three years [9]. Evidence supports a decrease in insulin sensitivity following the introduction of oestradiol and an associated increase in visceral fat deposition [21]. Weight gain is often an area of concern for individuals before initiating GAHT, with one meta-analysis quoting around a mean gain of 2 kg in body weight (3 kg for body fat) in transgender women [22]. In addition to the described increase in body weight/fat, there is a corresponding loss of lean body mass and this is one postulated reason for the increase in cardiovascular morbidity seen in TW but not transgender men [23]. A significant increase in body mass index (BMI) was also demonstrated in a longitudinal study of TW, who entered the study prior to GAHT [24].

*Voice change*

Whilst often an important area of concern for individuals initiating GAHT, there is no evidence that either oestradiol treatment or androgen blockade result in any feminisation of the voice register.

*Pharmacological treatment options and considerations for transgender women and non-binary transfeminine individuals in the UK*

*Oestrogen replacement*

Currently within the UK there are 3 commonly used oestradiol preparations; transdermal gel, transdermal patch and oral oestradiol. Target range for transgender women is typically 300–600pmol/L, with specific targets for NB-TF potentially lower. Age, BMI and smoking history will often determine individualised oestradiol target levels. Typically, those with a normal body mass index (BMI), under 40 years old, non-smokers with no venous thromboembolism (VTE) history will have a target between 350–750pmol/l whereas those aged over 40 years, with an elevated BMI and smoking might aim for an oestradiol target of 200–400pmol/l. Exact targets should be managed on a case-by-case basis. Monitoring blood tests can be prone to assay interference and in such situations tandem mass-spectrometry can be used.

Oestradiol in gel form can be given either as a pumped dispenser delivering 0.75 mg per pump actuation or as oestradiol hemihydrate gel, typically dosed as 0.5–1 mg sachets, applied once in the morning anywhere on the body excluding the breasts [7]. The maximal dose is usually around 5 mg daily and can be incremented at 1 mg doses. From a monitoring perspective, bloods should be taken 4–6 h after application and on a day where arms have not been used. Different transdermal patches are available but are largely managed the same way and are often popular. Starting doses are usually 50- 100

**Table 1**
Estimated timings of initial effects and expected end of changes of oestradiol/androgen blockade[9].

| Effect of Oestradiol | Expected start of effect | Expected end of changes |
|---|---|---|
| Scalp hair loss | 1 –3 months | 1 –2 years |
| Reduction in libido | 1 –3 months | 1 –2 years |
| Fewer spontaneous erections | 1 –3 months | 3 –6 months |
| Reduction in haemoglobin | 2 –4 months | 2 –4 months |
| Difficulty in achieving an erection for use in sexual activity | Variable | Variable |
| Softer skin and reduced skin oiliness | 3 –6 months | 1 –2 years |
| Decrease muscle mass strength | 3 –6 months | 1 –2 years |
| Body fat redistribution | 3- 6 months | 2 –3 years |
| Breast growth | 3 –6 months | 2 –3 years |
| Testicular volume reduction | 3 –6 months | 2 –3 years |
| Reduced spermatogenesis | Variable | Variable |
| Reduction in body hair | 6 –12 months | Over 3 years |
| Voice change | No known effect | No known effect |

microgram/24 h patches applied twice per week [7]. Individuals are advised to apply the patch to clean and dry skin usually on the lower abdomen, upper thigh or buttocks. Individuals can swim, shower and bath as normal. The target range is the same as for gels and blood tests should be taken at 24–36 h after the patch was applied. The maximal dose is 400microgram/24 h patch with incremental adjustments of 25–100micrograms every few months until the target oestradiol range is achieved [7]. Oral oestradiol is again available in different forms. Doses usually commence as 1–2 mg tablets taken once daily. Doses are increased in 1–2 mg increments every few months with a maximal oral dose is of 8–10 mg daily. Target levels are individualised as previously discussed and monitoring bloods should be taken 4–6 h after taking the tablet [9].

Other oestrogen products including conjugated oestrogens are not routinely prescribed as GAHT due to the increased risk of venous thromboembolism (VTE) and breast cancer. In other parts of the world, injected oestradiol therapies are more widely used with the same goals of treatment to achieve the desired feminisation for TW and NB-TF. Despite efficacy in treatment, there have been some issues relating to fluctuations in oestradiol levels, including achieving supraphysiological oestradiol levels which far surpass the upper limit of reference ranges and have resulted in greater mood swings, hot flushes and anxiety as well as the associated increased cardiovascular risk profile [25].

There are several considerations when discussing the above options with individuals. Transdermal options are often considered the safest with regards to cardiovascular and VTE risk. In some areas, it is common practice to commence lower initial doses in older patients or those with pre-existing cardiovascular risk e.g. elevated BMI or current smokers. Transdermal preparations are often considered the first-line option in those who are over the age of 40 years, have co-existing risk factors for VTE such as previous VTE or raised BMI ($>35$ kg/m$^2$), or risk factors for cardiovascular disease such as smoking or presence of type 2 diabetes mellitus. If a transdermal preparation is not acceptable to an individual carrying some of the above risks, then lower starting doses and/or reduced maximal doses are usually preferred to reduce the risk profile. In those with known liver dysfunction, oral preparations are also generally avoided due to the increased first-pass metabolism of oral oestrogen by the liver [26]. Some individuals opt to take oestradiol tablets sub-lingually to avoid the liver first-pass effect, but there is no evidence that this is any safer than conventional oral dosing.

*Anti-androgen therapy*

In addition to oestradiol replacement, as briefly mentioned, the other component to the pharmacological management of TW and NB-TF is the suppression of endogenous testosterone production. Whilst there is some negative feedback through oestradiol treatment on the GnRH axis, alone it is often inadequate in achieving testosterone suppression [27,28]. Anti-androgen treatment is therefore commonly used alongside oestrogen replacement in the UK and is particularly effective for reducing facial and body hair growth. GnRH agonists are the mainstay of this aspect of treatment. Following GnRH administration there is an initial surge in the release of gonadotrophins (follicle-stimulating hormone, FSH and luteinising hormone, LH) from the pituitary, however, the continued stimulation by the exogenous GnRH agonist desensitises the pituitary gland and downregulates GnRH thus resulting in a state of hypogonadotropic hypogonadism [29]. These effects in turn reduce testosterone production from the testes. In UK practice, the GnRH agonists Leuprorelin or Triptorelin are more commonly used. These are typically administered as intramuscular injections every 10–12 weeks at a dose of 11.25 mg. GnRH agonists are cautioned in those with known diabetes due to the impact on capillary blood glucose. Additionally, as with many hormone blocking therapies, there may be a potential increase in risk of osteoporosis which will be discussed in further detail later.

Beyond GnRH agonists, other anti-androgens can be considered based on individual need, patient choice or where primary care are not able to support GnRH prescription and/or administration.

Steroidal androgen receptor antagonists are more widely used in the management of TW and NB-TF, including spironolactone and cyproterone. These work by competing with testosterone and other androgens for binding to androgen receptors. There is additional inhibition of testosterone synthesis through the blocking of key enzymes including 17α-hydroxylase and 17,20-lyase. This dual mechanism of action helps in reducing testosterone levels in the body, making it effective in contributing to the previously described feminising effects of GAHT [28]. Whilst there is some conflicting evidence around spironolactone, whereby spironolactone monotherapy has not been shown to decrease testosterone

levels in healthy men [30], there is evidence to support its use in the suppression of testosterone when used in conjunction with oestradiol in transgender women [31]. Starting doses of spironolactone are usually 100 mg daily in one or two doses. Doses can be gradually increased to a maximum of 200 mg per day. Due to the diuretic effects, blood pressure lowering is a common side effect and thus careful titration is required. Cyproterone, again given orally, is typically commenced at 12.5 mg alternate days, titrated up as required to a maximum dose of 25 mg daily, though this is rarely needed. Side effects are commonly reported including low mood, and there are concerns about the increased risk of meningiomas when used long-term [32] at doses above 25 mg per day. Thus cyproterone tends to only be considered in the short term as an alternative to spironolactone in patients awaiting orchiectomy.

Bicalutamide is a non-steroidal anti-androgen, that is used in the UK chiefly in the management of prostate cancer or hirsutism in women, however, concerns around liver toxicity typically preclude its use in this setting [28]. Despite these concerns about hepatotoxicity it is used in some other countries.

*Progesterone*

Progesterone is another steroid hormone that is produced primarily by the ovaries in pre-menopausal cisgender women [33]. As well as oestradiol, progesterone is thought to play a role in breast growth during puberty in cisgender female adolescents, though most growth occurs before they start to produce progesterone [34]. Whilst there is therefore a theoretical argument for using progesterone to augment breast growth in TW, there is only a small amount of anecdotal evidence to back this up.

These anecdotal reports in TW claim that for some people it may improve breast growth and support feminisation after an individual has had 18 months of oestrogen therapy as well as affording potential improvements in fat redistribution, libido, sleep and general well-being. However, evidence is lacking and it is not known if any of these reported benefits are transient or permanent [33,35].

Progestogens are used in post-menopausal cis women to protect the endometrium from the oestrogen used for hormone replacement therapy (HRT). In postmenopausal cisgender women, combined HRT (oestrogen and progestogen) is associated with increased risk of breast cancer and cardiovascular morbidity [36–38]. Meanwhile, oestrogen-only HRT is not associated with an increased risk of breast cancer in cis-women without a uterus. The cardiovascular risk is also less than that of combined HRT [36,38]. Micronised progesterone has also been showed to be safer than synthetic progestogens when used as part of HRT but would not necessarily completely remove risk[39]. There is no data indicating that the extent of these risks can be extrapolated from post-menopausal cisgender women to TW. There is no conclusive evidence that progesterone improves libido for post-menopausal cis women.

The progestogen component of combined HRT for some cisgender menopausal women causes significant side effects and/or progesterone intolerance [40]. Some progestogens can cause masculinising side-effects such as acne or increased body/facial hair as well as fluid retention and weight gain. Further to these physical effects, some evidence also suggests increased mood changes[40]. These side effects again appear to be more commonly associated with synthetic progestogens compared with micronised progesterone [40].

At the time of writing SoC 8 WPATH (World Professional Association for Transgender Health) and The Endocrine Society do not advocate routine use of progesterone, both citing a lack of robust and reliable data to support this [9,41]. However, a randomized controlled trial studying the impact of micronized progesterone on breast growth is currently underway [33].

*Monitoring considerations with oestradiol treatment and androgen blockade*

Whilst achieving target range oestradiol is an important aspect of monitoring, there are other aspects that must also be considered following initiation of GAHT in TW and NB-TF.

*Prolactin*

Physiologically, oestrogen leads to an increase in pituitary secretion of prolactin. Rises in prolactin are often seen in settings of high oestradiol such as pregnancy [42]. In the setting of GAHT, this is no different with up to 20 % of TW reported to see a rise in prolactin levels associated with pituitary gland enlargement[9,43]. Prolactin levels typically fall following a reduction or cessation of oestrogen treatment [44]. One systematic review aimed to assess the impact of anti-androgens alone on the risk of

hyperprolactinaemia in TW but there was insufficient evidence to support this [45], however other studies have suggested that cyproterone does augment the prolactin elevating effects of oestradiol [46]. The mentioned systematic review also failed to find conclusive evidence of a definitive increase in risk of prolactinomas in TW or NB-TF, after case reports published suggested a possible association [45]. Baseline and periodic monitoring of prolactin is typically recommended for those on oestrogen treatment. Practically, in individuals where the prolactin levels are persistently > 1000miu/L or in the presences of symptoms suggestive of an elevated prolactin e.g. galactorrhoea advice from local endocrinology teams should be sought [42].

*Liver function and serum electrolytes*

Whilst oestrogens given at physiological doses are rarely associated with liver dysfunction, higher doses resulting in supraphysiological oestradiol levels are more concerning for liver disease. The risk of liver disease is typically considered higher with oral oestrogens due to high concentrations following rapid absorption into the portal circulation and therefore liver function should be more closely monitored in individuals on oral preparations. Cyproterone acetate has also been linked to liver dysfunction and so individuals on this treatment should be monitored particularly closely [47]. Following baseline testing, liver function should be routinely checked and in situations where the liver enzyme alanine transaminase (ALT) rises above three times the upper limit of normal, further investigation and/or advice should be sought. Routine monitoring of renal function is not typically required for TW and NB-TF on GAHT, however in patients on spironolactone electrolytes (specifically potassium) should be checked at baseline and at least six monthly in the first year of treatment [9].

*Metabolic screening; lipids and diabetes*

Although evidence supports beneficial effects of oestrogen and anti-androgen treatments in TW and NB-TF, the overall metabolic risk is typically increased. Increases in triglyceride levels as well as subcutaneous and visceral fat support the need for monitoring of lipid profiles and commencement of primary prevention such as statin therapy in line with the non-transgender population where required [21]. Local guidance should also be followed in cases where triglycerides rise after initiation of oestrogens. Again, a baseline fasting lipid-profile should be performed and typically monitored annually thereafter. Those on oral oestrogens are again at the greatest risk of elevations in triglycerides and may therefore need closer monitoring [21,48]. As a result of the risk of worsening insulin resistance in TW or NB-TF treated with oestrogens, those with pre-existing diabetes or pre-diabetes should be closely monitored. There is an increased risk of hyperglycaemia and adjustments to the treatment of the individuals' diabetes may be warranted. Baseline HbA1c screening should be considered in all individuals with subsequent monitoring typically only required in those with confirmed diabetes or pre-diabetes [49].

Blood pressure is another important aspect of metabolic monitoring in TW and NB-TF individuals. There are variable effects depending on the combination of treatments. Those commenced on spironolactone often see a small reduction in systolic blood pressure due to its diuretic effects. In those on cyproterone acetate and oestrogen, evidence has shown a mean rise 14 mmHg over a 5-year follow-up time with nearly 5 % of the cohort developing new onset hypertension [50]. As a result, it is recommended that all individuals on GAHT should have blood pressure monitoring, with any elevation in blood pressure managed according to local guidance [9]. Rarely, changes to the anti-androgen or a reduction in oestrogen dosing may be warranted [51].

*Screening*

There is limited evidence for breast cancer risk specifically in TW and NB-TF on GAHT. Breast cancer risk is thought to be no higher in TW compared with cisgender women, thus the recommendation remains to ensure breast cancer screening is undertaken in line with the screening pathways for cisgender women [9]. In the UK this is routinely available to those aged 50–70 years. Additionally, if there is continued use of oestrogen beyond the age of 70, screening should continue until oestradiol treatment is stopped.

Prostate cancer risk is thought to be low in TW who have suppressed testosterone levels. Screening is therefore not routinely carried out in the UK but can be individualised according to the personal risk factors.

*Risks and adverse effects of oestradiol treatment in transgender women and NB-TF*

*Bone mineral density*

Hypogonadism in cisgender males is a risk factor for the development of osteoporosis and thus is an important consideration in the management of TW and NB-TF with anti-androgens. However, serum oestradiol has been shown to correlate with bone mineral density more closely than serum testosterone in older males [52]. The impact of oestrogen treatment in TW and NB-TF is therefore thought to be beneficial for bone health [9]. One meta-analysis demonstrated that GAHT in TW was associated with an increase in bone mineral density at the lumbar spine [53]. Specific data relating to fragility fractures in TW and NB-TF are lacking. There is no current consensus on whether clinicians should use sex assigned at birth in individuals undergoing GAHT in adulthood, when assessing osteoporosis using fracture risk tools such as FRAX. This is based on evidence that peak bone mass is achieved in early adulthood. Thus, fracture risk must be assessed on an individual basis. In terms of monitoring, baseline DXA scans should be considered in those who have pre-existing risk factors for osteoporosis and managed in accordance with local guidance [9].

*Liver*

Excess accumulation of oestrogens can result in impaired bile acid flow and intrahepatic cholestasis, with associated symptoms such as pruritis and jaundice [54]. Although most evidence for the development of gallstones stems from oestrogens used in contraception or hormone replacement therapy in cisgender women, there may also be a comparable association in TW or NB-TF on GAHT and this is another important consideration [55]. As mentioned above, cyproterone acetate has also been linked to potential liver toxicity albeit, typically transient mild rises in liver enzymes. Overt hepatotoxicity with cyproterone has been reported, although these data have largely come from studies of cisgender males where cyproterone has been used in the management of prostate cancer, so extrapolating from this population may not be reliable [47].

*VTE*

The increased risk of VTE associated with oestrogen replacement is one of the key considerations in commencing GAHT and individuals must be appropriately counselled. Type of oestradiol treatment is also an important aspect of individualised care and lowering risk. In the Dutch cohort study of TW, VTE risk was increased twenty-fold [56], though many individuals were prescribed ethinyloestradiol in this cohort. Conjugated and synthetic oestrogens carry the highest risk and thus, as described, are largely avoided in GAHT. In another study, in TW using oral oestrogen and GnRH agonist injections, VTE was found in 1 of the 60 individuals [57]. In a larger and more contemporary study of more than 1000 individuals, 10 cases of VTE were demonstrated [58]. In one UK clinic, VTE risk was 1.2 %, most frequently seen in those on conjugated oestrogen [15]. Whilst the use of trans-dermal oestrogen may as much as halve the risk, some evidence suggests it may be the type rather than preparation alone that determines risk [7,56]. It remains common practice in the UK to choose transdermal rather than oral oestrogens in those at highest risk of VTE i.e. previous VTE, BMI > 35 and smokers.

*Metabolic and cardiovascular risk*

Favourable changes in lipid profiles have been demonstrated in TW on GAHT, with an increase in high-density lipoprotein (HDL) levels and fall in low-density lipoprotein (LDL) levels compared with cisgender men [59]. These potential positive changes are thought to be balanced out by the previously described increase in blood pressure, triglyceride levels, weight gain, increased peripheral and visceral fat and insulin resistance [21]. One study reporting increased cardiovascular mortality in TW, was only significant in the subgroup prescribed ethinyloestradiol at the time of the study [60]. One large cohort of TW with a mean follow-up of 10 years demonstrated no significant increase in cardiovascular mortality

even in the context of almost one third of the cohort being smokers [56]. Low rates of both stroke and myocardial infarction in this cohort have also previously been published [59].

*Malignancy*

Case reports have highlighted the incidence of breast cancer in TW, yet the overall risk is thought to be low and importantly, no greater than the risk in cisgender women [61]. Evidence is limited, but one large scale study examined data from over 2000 TW, with 15 cases of breast cancer over a total person time of greater than 30,000 years [62]. This puts breast cancer risk in TW as greater than that in cisgender men (typically quoted around 0.1 %) but lower than the risk in cisgender women (roughly 14 % in the UK) [63]. Most tumours in this series were of ductal origin and both oestrogen and progesterone receptor positive.

Prostate cancer in the context of anti-androgen therapy and testosterone suppression is very rare. There is evidence to show that oestradiol treatment does not lead to prostate hypertrophy nor pre-malignant changes in TW [64]. Other studies have suggested that long-term oestradiol treatment can be associated with the development of benign prostatic hypertrophy in TW and rare reports have been published on prostate cancer in TW. Screening, for example through measuring prostate-specific antigen levels, is not routinely carried out in the UK but can be considered on a case-by-case basis.

*Fertility*

The effects of GAHT in this group on fertility are not completely understood and dedicated studies are required. As earlier described, spermatogenesis has been shown to be impaired to some extent in up to 75 % of TW [19]. However, another study demonstrated that nearly 10 % maintained normal spermatogenesis [20]. Given decreases in size of testicular volume by almost 25 % within the first three to six months, sperm storage should be discussed with individuals prior to commencing any oestrogen and/or anti-androgen therapies [19]. Following cessation of GAHT in TW, restoration of spermatogenesis and/or fertility has also not been studied. Equally, given the fact that complete azoospermia can be difficult to predict or guarantee, contraception should be recommended where needed.

*Risks of not treating*

Whilst complications of GAHT are important to consider and inform individuals about prior to commencing treatment, it is equally important to acknowledge the consequences of not starting GAHT. Evidence supports significant issues relating to psychosocial functioning amongst the transgender population[65]. It is estimated that almost one third of transgender people attempt suicide in their lifetime [66]. Social anxiety has also shown to be higher in transgender people as well as more negative experiences in relationships at least in part driven by stigma [67,68]. Although strong data specifically exploring the benefits of GAHT on psychosocial functioning in transgender women are still lacking, some data supports the reduction in both depression and psychological distress as well as improvements in well-being owing to the reduction in gender incongruence following GAHT [65,69,70].

## Conclusion

Combined GAHT with oestradiol replacement and androgen blockade is now common, established treatment in the management of TW and NB-TF in the UK. Whilst there are currently no nationally agreed guidelines, common practice is well established across NHS gender clinics in line with international recommendations. Preparation choice of oestradiol therapy may be determined by individual risk profiles as well as personal preference. Early discussion of time frames for physical changes and other aspects such as fertility, are important to manage individual expectation. Risk profiles of adverse effects are largely based on studies conducted in cisgender women using oestrogen in contraception and hormone replacement therapy or cisgender men on anti-androgens in prostate cancer. Dedicated studies in transgender women are much needed. Monitoring practices are in place to detect any potential side effects and address these proactively, thus commencing GAHT remains best provided in a multi-disciplinary setting in established gender clinics.

**Research agenda**

- Specific evidence of the impact of GAHT on psychosocial functioning in the transgender women population
- Randomised controlled trials exploring the role and safety of progesterone in the transgender women population

**Practice points**

- In the UK, transgender women and non-binary transfeminine individuals are usually treated with simultaneous oestradiol replacement and anti-androgens
- Commencing GAHT is best done in a multi-disciplinary setting in an established gender clinic but monitoring can be continued in a primary care setting under guidance from a specialist clinic.
- Oestrogen replacement comes in different forms and is primarily given as transdermal or oral preparations in the UK. This decision is made on an individual basis through a shared-decision making process after discussing specific risks versus benefit.

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