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Oestrogen and anti-androgen therapy for transgender women

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Abstract

Transgender women experience lifelong gender dysphoria due to a gender assignment at birth that is incongruent with their gender identity. They often seek hormone therapy, with or without surgery, to improve their gender dysphoria and to better align their physical and psychological features with a more feminine gender role. Some of the desired physical changes from oestrogen and anti-androgen therapy include decreased body and facial hair, decreased muscle mass, breast growth, and redistribution of fat. Overall the risks of treatment are low, but include thromboembolism, the risk of which depends on the dose and route of oestrogen administration. Other associated conditions commonly seen in transgender women include increased risks of depression and osteoporosis. The risk of hormone-sensitive cancer seems to be low in transgender women, with no increased risk of breast cancer compared with women and no increase in prostate cancer when compared with men. The evidence base for the care of transgender women is limited by the paucity of high-quality research, and long-term longitudinal studies are needed to inform future guidelines.

Introduction

Transgender and gender-non-conforming people often seek hormone therapy, with or without surgery, to change their physical appearance to match their reaffirmed gender, and to alleviate the stress and discomfort associated with living in the incongruent gender.¹ The uneasy feeling of living in an incongruent gender role is termed gender dysphoria.

Transgender women, also referred to as transwomen or male-to-female transsexuals, are born with male genitalia and are typically assigned a male gender at birth. Gender dysphoria often presents in childhood. However, children often cannot articulate their discomfort or do not have a supportive family environment to seek medical attention, and thus present to

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Declaration of interests

We declare no competing interests.

health-care providers with gender dysphoria later in adulthood. Gender dysphoria can also present in adulthood without a clear start in childhood.

The prevalence of gender dysphoria or non-conforming gender identity is a topic of ongoing investigation. The precise number of transgender women estimated in a given population depends on the definition used. One early study in the Netherlands defined all patients who were treated with hormones and underwent surgery as transgender,² and the investigators reported the prevalence of transgender women to be one in 11 900 people. A study from Ireland defined a transgender woman as a person assigned male gender at birth who is receiving oestrogen therapy,³ showing a similar prevalence of one in 10 154 people. Investigators of one of the largest cohort studies in the USA, which used US Veterans Health Administration data, reported a slightly higher prevalence of 3.29 in 10 000 people, based on codes in the ninth revision of the International Statistical Classification of Diseases used to charge for transgender services.⁴ Unfortunately, because of limitations of the study design, the researchers were unable to comment on whether these people were all transgender women; however, the veteran population tends to be predominantly men. In a 2016 systematic review of 29 studies,⁵ the prevalence of transgender women was roughly 5–20 per 100 000 when diagnostic codes or requests for medical treatment were used, or as high as 521 per 100 000 people if based on self-identification.

Hormonal therapy with gonadotropin-releasing hormone agonists can be started in early puberty (Tanner stage 2–3) to avoid the development of secondary sex characteristics in some individuals who have had appropriate mental health assessment, with the caveat that future fertility could be compromised. Oestrogen therapy follows treatment with gonadotropin-releasing hormone agonists in children, or can be combined with other testosterone-lowering drugs in adults. Several published guidelines exist to aid clinicians in the assessment, diagnosis, and medical treatment of adult transgender individuals. The World Professional Association for Transgender Health (WPATH) publishes comprehensive guidelines for health professionals that address all aspects of health care for gender-nonconforming people.¹ The Endocrine Society publishes clinical practice guidelines that address the initiation and monitoring of hormone therapy for transgender children and adults.⁶ Other guidelines exist, including a clinical practice guideline published by the Royal College of Psychiatrists in the UK.⁷

In this Review, we provide an overview of the published literature on oestrogen and anti-androgen therapy in adult transgender women (ie, after puberty). The focus will be on the established treatment regimens, reported potential adverse events, long-term care and monitoring, and areas of uncertainty in the care of transgender women.

Oestrogen and anti-androgen therapy

An important goal for transgender women is to live as a woman in society and to have—as far as possible—a body that appears female (ie, to undergo feminisation). Secondary sex characteristics are formed under the influence of sex hormones, so an important factor in the male-to-female transition is to change the balance between oestrogens and androgens (ie, cross-sex hormone treatment). Important physical features in feminisation are breast growth,

female body composition (ie, more adipose tissue on the hips and less in the abdominal region), and softer skin. Additionally, sex hormones affect the brain to change mood and have an effect on libido (figure).

Supplementation with oestrogens lowers testosterone concentrations because of negative feedback on the hypothalamic–pituitary–gonadal axis. With the initiation of oestrogen therapy alone, testosterone concentrations decrease into the low-normal range for a man (200–300 ng/dL [6.9–10.4 nmol/L]), but are still above the normal range for a woman (<75 ng/dL [<2.6 nmol/L]).⁸ Most patients will require the addition of an anti-androgen medication to further inhibit testosterone production or to block the androgen receptor. Anti-androgen treatments such as spironolactone (in doses up to 400 mg daily) and cyproterone (in doses up to 100 mg daily) are effective adjunctive therapies, given in addition to oestrogen to lower testosterone concentrations into the female range.^{9–12} Spironolactone is better known as an aldosterone antagonist, but it also has antagonistic effects on the androgen receptor and can act as an oestrogen receptor agonist.¹³ Spironolactone could induce hyperkalaemia, especially in patients with impaired renal function. Prior and colleagues⁸ showed that the addition of spironolactone to oestrogen therapy is often necessary to lower testosterone values to the female range. In this study, high-dose oestrogen plus medroxyprogesterone led to a mean testosterone concentration of 169 ng/dL (5.9 nmol/L; SD 193 ng/dL [6.7 nmol/L]), whereas adding spironolactone to this regimen led to a mean testosterone concentration of 87 ng/dL (3 nmol/L; SD 111 ng/dL [3.8 nmol/L]).

Several other drugs can be used to lower testosterone including cyproterone and gonadotropin-releasing hormone agonists such as goserelin. Results of studies by Toorians and colleagues¹⁰ and Gava and colleagues¹¹ showed that cyproterone, in combination with oestradiol, reduced testosterone to less than 30 ng/dL (1 nmol/L). However, there are no head-to-head studies that establish the superiority of one testosterone-lowering drug over another. Additionally, choices for one drug or another are primarily based on local regulations and reimbursement principles. Cyproterone seems to have a stronger anti-androgenic action than spiro nolactone,¹⁴ but depression is a potential side-effect.¹⁵ Cyproterone has anti-androgenic effects through antagonising the androgen receptor, but also has anti-gonadotropic effects. The gonadotropin-releasing hormone analogues such as leuprolide, histrelin, or goserelin work by reducing the secretion of luteinising hormone and follicle-stimulating hormone, which leads to decreased stimulation of testicular testosterone production. In 2016, the results of a small retrospective study showed similar anti-androgenic effects of both cyproterone and the gonadotropin-releasing hormone agonist leuprolide.¹¹ Gonadotropin-releasing hormone analogues have relatively few effects other than lowering gonadal hormone concentrations. Gonadotropin-releasing hormone agonists are commonly prescribed in adolescents with gender dysphoria as a puberty blocker, to block the onset of puberty, but they might be used also in adult patients who have adverse drug reactions to anti-androgen therapy with spironolactone or cyproterone. The occurrence of (multiple) meningiomas has been reported in association with longer-term use (ie, use over several years) of cyproterone at doses of 25 mg daily or higher.^{16–19} As a result, in the UK, gonadotropin-releasing hormone agonists are prescribed as the only androgen-lowering agents used in conjunction with oestrogens in the treatment of transgender women in National Health Service gender identity clinics.²⁰

Some patients request progesterone for enhanced breast growth. However, there have not been any well designed studies to assess the effectiveness of progesterone to improve breast development. Results of studies of progesterone combined with oestrogen in postmenopausal cis-gender women—ie, women who are not transgender—suggest that progesterone combined with oestrogen might be associated with an increased risk of cardiovascular disease.²¹ In fact, in a population-based study of premenopausal cis-gender women, taking oral contraceptives including progesterone with or without oestrogen was associated with increased risk of thromboembolism.²²

Finasteride has been used in transgender women as an anti-androgen.²³ This drug is a 5- α reductase inhibitor and might increase testosterone concentration by blocking synthesis of dihydrotestosterone from testosterone. However, this drug is not recommended as a first-line treatment because such drugs might lead to worsened depression.²⁴

Treatment regimens and guidelines

WPATH and the Endocrine Society have released evidence-based guidelines for the treatment of transgender women (table 1).^{1,6} Both guidelines suggest that cross-sex hormone treatment be initiated in adults with well documented gender dysphoria and who are able to provide informed consent for treatment.^{1,6} Furthermore, the guidelines recommend assessment of medical and mental health issues that can be exacerbated by hormone therapy before initiation of cross-sex hormone treatment.^{1,6}

The hormonal regimens used for transgender women are not standardised across the world (table 2), partly because of regional differences in the availability of oestrogen and testosterone-lowering preparations, as well as cost considerations and differences in practices between countries and centres.²⁵ For example, in some European countries (Belgium, Germany, Italy, Netherlands, and Norway) common regimens include oral oestradiol combined with cyproterone (50 mg daily).²⁶ In the UK, oral oestradiol is combined with gonadotropin-releasing hormone agonists.⁷ In the USA, all forms of oestradiol are available (parenteral, oral, and patches or gels) and are combined with spironolactone. Conjugated oestrogens and synthetic oestrogens such as ethinylestradiol are not recommended because physicians are unable to monitor their concentrations in the blood, and because of the potential of these drugs to increase the risk of thromboembolism compared with other oestrogens.²⁷ Because gonadotropin-releasing hormone agonists more effectively suppress endogenous sex steroids than other testosterone-lowering drugs, and could be associated with fewer short-term side-effects, the combination of oral oestradiol and gonadotropin-releasing hormone agonists might be regarded as the superior regimen; however, there are no published long-term studies apart from a small retrospective study in 40 patients, the results of which showed the equivalent effectiveness of cyproterone and leuprolide.¹¹ Furthermore, the use of gonadotropin-releasing hormone agonists is limited in many countries because of their cost, which is greater than 1000 per year per patient in Europe, with even higher prices in the USA.

Concentrations of oestradiol and testosterone should be monitored every 3–6 months in the first 2 years of therapy, then annually to ensure that they are in the physiological range for a

woman, and especially to ensure that oestradiol concentrations do not exceed peak levels (<400 pg/mL [13.9 nmol/L]) seen in women.⁶ The precise concentration of oestradiol that results in adequate feminisation with the lowest risk of complications is not known.²⁸ For transgender women taking spironolactone, it is advisable to measure serum potassium concentrations every 3–4 months in the first 2 years, then annually, since the potassium concentrations could increase during spironolactone therapy.⁶ After gonadectomy, testosterone concentrations drop to nearly zero—only a small amount is still produced by the adrenal glands—and thus, after surgery, anti-androgens can be discontinued. Serum testosterone can be measured within a month after surgery to confirm that testosterone concentrations are low (ie, <50 pg/mL [1.7 nmol/L]) and that testosterone-lowering medications are not needed. It is important to keep the dose of oestrogen at a level that not only maintains sex characteristics and relieves gender dysphoria, but is also adequate to prevent osteoporosis, hot flashes, and mood disorders.²⁹

We recommend that hormones be prescribed under medical supervision to allow monitoring of hormone levels and screening for potential adverse events. However, many transgender women have inadequate access to health-care providers who have experience with transgender medicine.³⁰ Other barriers to care include the financial costs of medical care, discrimination against transgender patients, and other socioeconomic and cultural barriers.³¹ As a result, up to 50% of transgender women might self-medicate with hormones before seeking the advice of a physician.^{15,32,33} Transgender women who self-prescribe often have a poor understanding of potential side-effects and safe doses of oestrogens, and can report inadequate breast growth.⁴⁰ Although less is known about transgender women who self-medicate with cross-hormone therapy, oestrogen and anti-androgen treatment taken under medical supervision seems to be associated with few adverse events.⁴²

Expected time course and physical changes

The Endocrine Society guidelines for endocrine treatment of transsexual people presents an overview of the feminising physical effects of cross-sex hormone treatment in transgender women, most of which start within a few months and progress for 2–3 years.⁶ However, there is a shortage of high-quality evidence about the precise time course and effect-modifiers of these feminising effects, which is partly because these changes cannot be easily measured. Clinically, the most compelling effects of cross-sex hormone treatment are softening of the skin, mood changes, a decrease in libido and erections, fat redistribution at the hips, and growth of breast tissue. Results of studies that focused on bodyweight and composition indicate an increase in bodyweight of 1–3 kg per year, with an increase in fat mass (2–4 kg) and a decrease in lean body mass (2–4 kg) after 1 year of cross-sex hormone treatment.^{9,12,36} The fat mass increases are apparent as both visceral and subcutaneous fat depots.^{37,38}

An important issue for many transgender women is breast development. But despite its importance, only a few low-quality studies have been done to investigate the effect of cross-sex hormone therapy on this outcome.³⁹ Breast development starts within 2–3 months after initiation of combined oestrogen and anti-androgen treatment, and takes up to 2 years to complete. In a longitudinal study by Meyer and colleagues,³⁴ breast hemi-circumference

increased by 14 cm after 3 years of oestrogen therapy. The response to oestrogen can vary from individual to individual. Up to two-thirds of transgender women are unsatisfied with their breast development and apply for breast augmentation surgery.⁴⁰ No evidence exists that the addition of progesterone improves breast development.³⁹ Cross-sex hormone treatment has also been reported to lead to softening of the skin and feminine hair growth, but systematic studies have not been done.^{35,41}

Comorbidities and pitfalls

Overview

Although cross-sex hormone treatment is now regarded as fairly safe when taken under medical supervision, several associated comorbid conditions can occur with hormone therapy.⁴² Since oestrogen and testosterone-lowering drugs are often taken in combination and the specific drugs used vary by country and region, it can be difficult to attribute comorbid conditions specifically to oestrogen or testosterone-lowering drugs.

Thromboembolic disease

Oestrogen use is associated with an increased risk of venous thrombosis, as has been reported in many studies of oral contraceptives and postmenopausal hormonal replacement in women.⁴³ The risk of venous thrombosis in the general population of non-transgender women and men who are not taking oestrogen ranges from one to two events annually per 1000 individuals; incidence increases with age.⁴⁴ Bell and colleagues⁴⁵ reported the remaining lifetime risk of thromboembolism to be 8.1% (95% CI 7.1–8.7) in a cohort of non-transgender, middle-aged adults (aged 45–64 years) living in the USA. Oestrogen is believed to be the key component in the causation of venous thrombosis, which might be modified by the route of administration of oestrogen or whether it is taken with progestogens.⁴⁶

The lifetime risk of venous thrombosis in transgender women has been reported to range between 1% and 5%. However, many of the studies were small and very short in follow-up time.⁴⁷ Furthermore, many venous thrombotic events are likely to be under-reported. Data from early studies in transgender women in the Netherlands suggested a high lifetime prevalence (about 5% over a mean of 10 years of follow-up) of thromboembolic disease.⁴⁸ However, subsequent studies indicate that the risk of thromboembolic disease is much lower, and that the cause of the increased risk of thromboembolic disease in the earlier cohort was due to the use of ethinylestradiol.⁴⁹ Indeed, reports from several European centres have suggested that the lifetime risk of thromboembolism is very low (about 1%).^{9,50,51} In one study from Belgium, the investigators reported that three of 50 transgender women had a thromboembolic event.⁵² In a retrospective chart review of 165 transgender women, the prevalence of thromboembolism was 1.2%, and was more frequent with the use of conjugated oestrogens, compared with other oestrogen preparations.⁴⁰

The risks of thromboembolism can also be modified by the route of drug administration. A meta-analysis and systematic review of oestrogen replacement therapies in cis-gender women showed that oral oestrogen, but not transdermal oestrogens, increased the risk of

venous thromboembolism.⁵³ A transgender clinic in Amsterdam, Netherlands, noted a 50% reduction in risk of venous thromboembolism after recommending that all trans-gender women older than 40 years change from oral to transdermal oestrogen.⁴⁸ Additionally, Ott and colleagues⁵⁰ identified no cases of venous thromboembolism 162 transgender women treated with transdermal oestrogen and followed up for a mean of 5 years, lending support to the belief that transdermal preparations could be less thrombogenic than oral oestrogen.

Although the lifetime risk of thromboembolic disease seems to be low in patients followed up in multispecialty gender clinics, providers should inform patients about the potential risk of thromboembolic disease due to oestrogen treatment, and which factors modify this risk. Modifiers in transgender women include the oestrogen preparation used (ethinylestradiol or conjugated oestrogens *vs* 17- β oestradiol), dosing method (oral *vs* transdermal), age (older than 50 years is associated with increased risk), obesity (body-mass index >27),⁵⁴ and postoperative state (with prophylaxis for deep venous thrombosis *vs* without).²⁷ We believe that transgender women who continue to smoke should be switched to transdermal oestrogens, although there are few data to suggest that this reduces risk of thromboembolism.

Osteoporosis

Cross-sex hormone treatment with oestrogens should be protective of bone density, since oestrogens are the major sex steroid hormone that prevents bone loss in both men and women.⁵⁵ Low bone density is common after gonadectomy if oestrogen is not prescribed at adequate doses to prevent oestrogen concentrations from dropping into a menopausal range.⁵⁶ Some study findings suggest that low bone density can be present initially in transgender women. Up to 16% of transgender women have T-scores less than -2.5 at the hip or spine bones at initial presentation, indicating that osteoporosis might occur even before initiation of oestrogen treatment, and can be present in transgender women in their 20s or 30s.^{57,58} The cause of low bone density in transgender women before the initiation of cross-sex hormone treatment is unclear. Potential causative factors might include poor nutrition and vitamin D status, and low levels of physical activity and exercise.⁴⁸ Although there are no established guidelines about when bone mineral density testing should be done, it might be prudent to check an initial screening dual energy x-ray absorptiometry after age 40 years if risk factors are present, or if there is a personal history of fracture. Despite reports of low bone density occurring in transgender women, there are very few reports of fragility fractures occurring in transgender women.⁵⁹

Liver disease

Liver disease was a concern in initial cohort studies, wherein abnormal liver function tests were reported to occur in up to 15% of transgender women.⁶⁰ However, it was subsequently determined that the cause of the abnormal findings was not the use of oestrogen; rather the liver function abnormalities identified were secondary to alcohol misuse or viral hepatitis.⁴⁸ In a longitudinal cohort study of transgender women in Europe, roughly 5% of study participants had transient increases in liver enzyme concentrations to greater than twice the normal range, but values returned to the normal range after 12 months.³⁶ Another study conducted in the USA found that measurements of aspartate aminotransferase and alanine

aminotransferase in transgender women did not differ from either the male or female reference range.⁶¹ These data suggest that oestradiol might not be hepatotoxic, as previously believed on the basis of data from earlier cohort studies.⁶⁰ The alterations in liver function tests reported in earlier studies might have been due to the older age of the early Dutch cohort compared with recent cohorts, differences in alcohol intake, and the formulation of oestrogen treatment used. The risk of oestrogen therapy with respect to liver function remains an area of uncertainty, and the Endocrine Society guidelines recommend periodic measurement of liver function tests.

Lipid abnormalities

Treatment of postmenopausal women with oestrogen, with or without progesterone, has been associated with an increase in triglycerides and HDL cholesterol and a decrease in total and LDL cholesterol.^{62,63} In premenopausal women, oral contraceptive pills containing oestrogen and progesterone also seem to be associated with increased total cholesterol, triglyceride, and HDL cholesterol concentrations.⁶⁴ Results of one of the largest studies examining the effect of oestrogen (given as conjugated equine oestrogen, 0.625 mg daily) and progesterone compared with placebo, in postmenopausal women, showed increases in HDL cholesterol and triglycerides, and decreases in LDL and total cholesterol.⁶²

Specific to transgender women, data from several longitudinal cohort studies^{15,38,65} suggest that oestrogen (with or without progesterone) increases triglyceride concentrations. In a meta-analysis of 23 studies including 3231 transgender women, Maraka and colleagues⁶⁶ reported that oral oestrogen increased serum triglyceride concentrations by about 30 mg/dL (0.34 nmol/L) after 24 months from initiation of oestrogen therapy, with no changes in other lipid parameters, including HDL and LDL cholesterol. However, the oestrogen regimens included in this meta-analysis included different anti-androgen preparations including cyproterone, gonadotropin-releasing hormone agonists, and spironolactone, making it difficult to attribute the changes in lipids caused by oestrogen treatment alone. Only 14 of 1073 transgender women were reported to have had a myocardial infarction in this meta-analysis. It is difficult to interpret whether this represents an increased risk of myocardial infarction without a control group of transgender women who are not being treated with oestrogen therapy. Furthermore, most individuals studied in this meta-analysis were prescribed the more prothrombogenic oestrogen, ethinylestradiol, which is no longer used.

Mental health and depression

The prevalence of psychiatric and mood disturbances is high among transgender people.⁶⁷ Several reports suggest that cross-sex hormone treatment improves quality of life and depressive mood symptoms.^{68–71} In a systematic review and meta-analysis of 28 studies including more than 1800 transgender people (with about 1100 transgender women), hormone treatment, with or without surgery, improved gender dysphoria and quality of life in 80% (95% CI 72–88; 16 studies; $I^2=78\%$) of patients.⁷² However, suicide rates remain high in transgender people after hormone therapy, with or without gender reaffirming surgery.^{73–76} Blossnich and colleagues⁷³ reported that the crude rate of suicide among transgender military veterans was 82 per 100 000 person-years, which is higher than the rates in non-transgender veterans and the US population, but similar to suicide rates seen in

veterans with depression, schizophrenia, and substance misuse.^{77,78} It is important that clinicians screen for signs of depression and suicidal ideation at each visit, and to refer patients for counselling and psychiatric treatment when needed.

Breast cancer

Several reports have suggested an increased risk of breast cancer in transgender women.⁷⁹ In one of the largest cohorts of transgender women and transgender men, the overall prevalence of breast cancer was 20.0 per 100 000 patient-years of cross-sex hormone treatment.⁸⁰ For transgender women specifically, the standardised incidence ratio was 0.7 (95% CI 0.03–5.57) compared with natal women, but 33.3 (21.89–45.17) compared with biological men.⁸¹ There are no clear guidelines for when mammogram screening for breast cancer should start. In the absence of any evidence, in our opinion, it could be reasonable to start mammogram screening in transgender women at the same age recommended for cis-gender women, or earlier if known risk factors are present, such as a family history of breast cancer.⁸¹

Prostate cancer

Since castration—either surgical or medical—is the primary treatment in prostate cancer, it might be expected that the incidence of prostate cancer is low in transgender women. Indeed, reports of prostate cancer have been limited to a few case reports.⁸² In a review of more than 1000 transgender women followed up by the Amsterdam clinic, only one case of prostate cancer was discovered.⁸³ On the basis of the low overall prevalence of prostate cancer, these authors suggest screening for prostate cancer only after age 50 years.

Special considerations

Gender-reaffirming surgery

Cross-sex hormone treatment affects secondary sex characteristics of transgender women, making them more feminine in appearance; however, it has little effect on the primary sex organs except to cause some testicular atrophy.⁶ Therefore, many transgender women will seek gender reaffirming surgeries to remove the testes and to create a neovagina.⁸⁴ Breast development under cross-sex hormone treatment can often be unsatisfactory and thus many transgender women might choose to have breast augmentation surgery.⁸⁵ In transgender women who initiate cross-sex hormone treatment after puberty, secondary male sex characteristics might require surgery such as chondrolaryngoplasty (the so-called tracheal shave) for a prominent larynx or facial feminisation for frontal bossing.^{86,87} Laryngoplasty can also be done to change the pitch of the voice.⁸⁸ Before laryngoplasty, transgender women can benefit from undergoing voice assessment, conditioning, and therapy by a voice and communication professional.⁸⁹

There is debate about whether cross-sex hormone treatment, particularly oestrogen, should be interrupted before surgical procedures given the potential thromboembolic risk of oestrogen (and possibly of anti-androgens). Many centres advise transgender women to cease oestrogen use at least 2–4 weeks before any major surgery and do not re-initiate oestrogen treatment until the postoperative patient is fully ambulatory.²⁵ It is important that transgender women undergo postoperative prophylaxis for deep vein thrombosis.²⁵

Furthermore, transgender women should reduce the risk of postoperative deep vein thrombosis before surgery by modifying lifestyle factors as bodyweight, smoking, and drug misuse, which can affect the outcome of surgery and the risk of complications.⁹⁰ This recommendation is especially true for plastic surgery procedures in which microcirculation is involved.

Fertility

Cross-sex hormone treatment in transgender women reduces sperm quantity and quality, and eventually results in irreversible infertility, even after cross-sex hormone treatment is stopped.⁹¹ The time course, doses of oestrogen and testosterone-lowering drugs, and risk factors that lead to irreversible infertility are not known. Many transgender women desire the opportunity to have their own biological children in the future, and seek cryopreservation of their sperm.⁹² Results of a case series of 29 transgender women showed a high rate of abnormalities in sperm characteristics, even before the initiation of oestrogen therapy, including oligo-azoospermia (27%, eight of 29), teratozoospermia (31%, nine of 29), and asthenozoospermia (31%, nine of 29).⁹³ Why sperm characteristics are altered in transgender women even before initiation of hormone therapy is not clear. Because cross-sex hormone treatment can reduce sperm number and quality, it is important to discuss fertility issues before the start of hormonal treatment.^{1,94} Transgender women should be offered sperm banking before the initiation of cross-sex hormone treatment, since it is more difficult to retrieve sperm after cross-sex hormone treatment has been initiated.¹ There are no published longitudinal data for the effect of hormone therapy on sperm quality and the time course over which sperm quality is permanently altered. Physicians should also remind transgender women that cross-sex hormone treatment is not an effective contraceptive.

Ageing

Concentrations of sex hormones vary with age. Whereas sex hormone concentrations increase during puberty in both sexes, there is a difference between men and women in the decline of circulating sex hormones. In men, there is a gradual decline of circulating testosterone, whereas in women there is a sudden decrease in circulating oestrogen after menopause. There is compelling evidence in cis-women that an earlier start of menopause is associated with an increased risk of osteoporosis and cardiovascular disease, whereas a later start is associated with an increased risk of uterine and breast cancer.⁹⁵ Results of the Women's Health Initiative study^{21,96,97} showed that hormone replacement therapy (oestrogen plus progestogen [medroxyprogesterone]) increased the incidence of breast cancer, coronary heart disease, and ischaemic stroke. The increased risk of breast cancer and coronary heart disease was not seen in women receiving oestrogen alone, without progestogens.⁹⁸

Data from transgender women at older ages (>50 years) are completely absent, and it is difficult to attempt to apply the existing evidence from natal women to transgender women because of physiological differences; for example, transgender women do not have a uterus, and breast cancer might have a different histopathology. So, although there are no compelling data about whether or not to stop oestrogen treatment in transgender women at age 50 years, the Women's Health Initiative study provides evidence that full oestrogen

replacement in late menopause might not be safe. In our opinion, it seems prudent to discuss with the patient the possibility of gradually tapering their oestrogen dose at an advanced age, as is done in some transgender health clinics (eg, in the Netherlands).²⁹ This topic is an important area of uncertainty that should be addressed in future research.

Conclusions

Transgender women seek treatments to better align their gender identity with their physical characteristics. Endocrine treatment remains a key component of care for transgender women. Although no randomised trials are available, hormonal and surgical treatment has been shown in several cohort studies to lead to a clear improvement in psychological wellbeing and quality of life. Health-care providers should understand that there is a wide spectrum of gender non-conforming conditions and that hormonal therapy is only one aspect of medical care. Health professionals should be aware of the WPATH standards of care and the Endocrine Society guidelines, both of which provide guidance on how to initiate and monitor hormone treatment. The recommendations are based on the currently available published evidence; however, most of the available evidence comes from low-quality studies. It might be difficult to conduct randomised controlled studies with sufficient power to answer specific questions related to transgender women. Results of large cohort studies have shown that, generally, when oestrogens are taken under medical supervision, the risks of adverse events are low.⁴² The establishment of large, long-term cohort studies from different regions of the world, where different hormone regimens are used in clinical practice, will help advance our understanding and determine whether hormone therapy is associated with any long-term health risks.⁹⁹ For now, key treatment goals are to avoid supraphysiological dosing of oestrogen and to reduce modifiable risks associated with oestrogen therapy.

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Search strategy and selection criteria

We searched PubMed using the keywords: “transgender”, “transsexual”, “trans*” AND “estrogen” OR “anti-androgen” OR “GnRH”, up to June 1, 2016. We also reviewed the guidelines published by the World Professional Association for Transgender Health, the Endocrine Society, and the Royal College of Psychiatrists, and consulted relevant references from these publications. We only included articles published in English. We largely focused on publications from the past 5 years, but we also cite some older studies, as well as a few key review articles that cover particular topics in detail.

Figure.
Effects of oestrogen and anti-androgen therapy in transgender women

Table 1Recommendations from the Endocrine Society's clinical practice guidelines⁶

	Quality of evidence
Before hormone therapy	
Confirm the diagnostic criteria of gender identity disorder or transsexualism and the eligibility and readiness criteria	Moderate
Evaluate and address medical conditions that can be exacerbated by hormone depletion and cross-sex hormone treatment	Moderate
During hormone therapy	
Maintain cross-sex hormone levels in the normal physiological range for the desired gender	Low
Review the onset and time course of physical changes induced by cross-sex hormone treatment	Low
Perform regular clinical and laboratory monitoring every 3 months during the first year and then once or twice yearly	Low
Monitor prolactin levels	Low
Screen for prostate cancer	Very low
Perform bone mineral density test if risk factors are present	Moderate
Screen for breast cancer by guidelines recommended for women	Low
Evaluate transsexual people treated with hormones for cardiovascular risk factors	Low
Before surgery	
Consider genital sex reassignment surgery only after both the physician responsible for endocrine transition therapy and the mental health professional find surgery advisable	Very low
Genital sex reassignment surgery recommended only after completion of at least 1 year of consistent and compliant hormone treatment	Very low
The physician responsible for endocrine treatment should medically clear transsexual individuals for sex reassignment surgery and collaborate with the surgeon regarding hormone use during and after surgery	Very low

Table 2

Oestrogen and anti-androgen preparations for transgender women

	Route	Dose	Advantages	Disadvantages
Oestrogens				
Oestradiol	Oral	1–6 mg daily	Inexpensive Oestradiol levels can be monitored	Might be associated with increased risk of thromboembolism in older patients (age >40 years)
Conjugated oestrogens	Oral	1.25–5 mg daily	Inexpensive	Might be associated with increased risk of thromboembolism in older patients (age >40 years) Oestradiol levels cannot be monitored
Oestradiol valerate or oestradiol cypionate	Intramuscular	10–20 mg intramuscularly every 1–2 weeks	Avoids liver first-pass effect Does not depend on intestinal absorption	Requires intramuscular injections, which can cause pain for some Can result in supraphysiological levels of oestradiol if not properly given
Oestrogen patch or gel	Topical	Varies depending on preparation	Least associated with risk of thromboembolism Avoids liver first-pass effect	Expensive Patches can be difficult to adhere to the skin Patches can cause skin irritation Risk of skin-to-skin transference of oestradiol to others
Anti-androgens				
Spironolactone	Oral	50–400 mg in divided doses twice a day	Inexpensive	Requires monitoring of potassium Has diuretic and antihypertensive effect
Cyproterone	Oral	50–100 mg daily	Inexpensive	Hepatotoxic at high doses Can suppress the hypothalamic–pituitary–adrenal axis Can cause depression Not widely available in the USA
Gonadotropin-releasing hormone agonists	Intramuscular or subcutaneous implant	Varies depending on preparation	Suppression of entire pituitary gonadal axis Few side-effects	Expensive Not widely available in some countries Limited long-term safety data

Some formulations are not available in certain countries.