Hematologic Concerns in Transgender Patients

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Abstract: Patients with gender dysphoria are increasingly seeking gender-affirming therapies, which can have adverse hematologic effects. For example, estrogen can increase the risk for arterial and venous thrombosis, whereas testosterone can cause erythrocytosis. This article reviews the hematologic issues associated with gender-affirming hormone therapies and discusses ways to lessen and monitor the risks. Common consult scenarios are also addressed.

Keywords
Estrogen, erythrocytosis, testosterone, transgender

Overview

Gender incongruence is dissonance between the gender assigned to an individual at birth and that individual's gender identity.[1] An estimated 1 million people in the United States identify as transgender, with a prevalence ranging from 0.5% to 8.4% of the population.[2] Gender incongruence can lead to gender dysphoria, which can manifest as (1) a strong dislike of one's current primary and secondary sex characteristics, (2) a strong desire to get rid of these characteristics, (3) a strong desire to have the primary and secondary sex characteristics of one's experienced gender, and (4) a strong desire to be treated/accepted as a person of one's experienced gender.[3] Gender dysphoria causes many people to seek gender-affirming hormone therapy and surgery to align their physical appearance with their gender identity. This approach has been shown to improve psychological outcomes.[1]

The consulting hematologist can be involved in gender-affirming therapy in several ways, with concerns ranging from the risk for arterial and venous thrombosis to the risk for erythrocytosis. This article reviews the thrombotic risks associated with hormonal therapy—both feminizing and masculinizing—in cisgender individuals (for whom data are more abundant) as well as in transgender individuals. Guidance for reducing the risks of therapy is discussed, as are issues of erythrocytosis and anemia. Finally, common consult questions are reviewed.

Estrogen

The cornerstone of gender-affirming hormone therapy for transgender women is estrogen (Table 1).[1,4] The feminizing effects of estrogen

Table 1. Feminizing Hormone Regimens

Oral estrogen
Oral 17β-estradiol, 2-6 mg per day Oral conjugated estrogens, 2.5-7.5 mg per day (less preferred)
Parenteral estrogen
Estradiol valerate, 5-30 mg IM every 1-2 weeks or Estradiol cypionate, 2-10 mg per week IM
Transdermal estrogen
Estradiol patch, 0.1-0.4 mg 2 times per week Estradiol gel, 1.5 mg 1-2 times per day
Antiandrogen
Spironolactone, 100-400 mg per day Cyproterone acetate, 50-100 mg per day (Europe) GnRH agonists

GnRH, gonadotropin-releasing hormone; IM, intramuscularly.

Sources: D'hoore L et al. *J Intern Med*. 2022;291(5):574-592[1]; Glintborg D et al. *Eur J Endocrinol*. 2021;185(2):R49-R63[4]; Gardner IH et al. *Curr Opin Endocrinol Diabetes Obes*. 2013;20(6):553-558.[54]

occur both directly and through negative feedback on the hypothalamic-pituitary-testicular hormonal axis, leading to a reduction in testosterone levels. Estrogen can be given orally, intramuscularly, or transdermally. The use of estrogen can result in the development of secondary sexual characteristics, causing breast growth and the redistribution of body fat. Estrogens are usually combined with antiandrogen therapy for a full suppression of secondary sex characteristics, such as body hair.[4] Typical antiandrogens are spironolactone, cyproterone acetate (outside the United States), and gonadotropin-releasing hormone (GnRH) agonists (Table 1). Hormone levels are routinely followed to ensure suppression of testosterone and avoid supraphysiologic levels of estrogen.

The prothrombotic effects of exogenous estrogen are well-known from studies in cisgender women.[5] Arterial thrombosis is more frequent, with the incidence of myocardial infarction increased 2-fold. The presence of other arterial risk factors adds dramatically to the risk. For example, smoking increases the risk for myocardial infarction 14-fold and obesity increases the risk 6-fold in the setting of estrogen therapy.[6,7] The low rates of stroke in young women are increased when combined hormonal contraception is used in the presence of well-established risk factors for stroke: smoking (2- to 4-fold increase), hypertension (7- to 8-fold increase), and adverse lipid profile (10- to 11-fold increase).[7,8] The absolute risk for any event is very small, however, given the low frequency of arterial thrombotic events in young women: approximately 1 or 2 in 10,000.

The increased risk for venous thrombosis has been recognized since the first days of estrogen-containing oral contraception. The current estimate is that oral contraception increases the risk for venous thrombosis on average 2- to 4-fold.[9] For young women, this increased risk represents an increase in the incidence of venous thrombosis of 2 per 10,000. Postmenopausal hormone replacement therapy also increases the risk for venous thrombosis approximately 2-fold, but only when it is administered orally.[9]

As with arterial thrombosis, many factors can augment the risk for venous thrombosis. Age is a major risk factor; as previously noted, the absolute increase in the incidence of venous thrombosis in women younger than 20 years using oral contraception is approximately 2 in 1000. Among women older than 50 years who are taking hormone replacement therapy, the odds ratio for thrombosis is 6.5.[9] Timing is also important; the risk is highest in the first 3 months of use, then decreases—but remains elevated—until 3 months after the patient has stopped using hormonal contraception or hormone replacement therapy. Obesity is another synergistic risk factor for thrombosis. In one study, the risk for venous thrombosis was increased by the use of estrogen-containing oral contraception, with an odds ratio of 4.2. The odds ratio rose to 24 in patients taking an estrogen-containing oral contraceptive who had a body mass index (BMI) higher than 30 kg/m^2.[10] In other studies, the odds ratio for thrombosis ranged from 2.7 to 4.6 for women whose BMI was higher than 30 kg/m^2 vs those whose BMI was 20 kg/m^2 or lower.[11,12] Obesity is becoming a more common risk factor as its incidence continues to increase.

The route of administration can affect the degree of risk, depending on the estrogen preparation used. Among women using estrogen-containing contraception, the increase in the risk for thrombosis is similar with all routes—oral, transdermal, and vaginal.[13] Among women using hormone replacement therapy, the rate of thrombosis is much lower with the transdermal route than with the oral route, and with the transdermal route, the risk appears not to be increased in users vs the risk in non-users.[9,14] The rate of thrombosis in women who use intrauterine devices that release levonorgestrel is not increased in comparison with the rate of thrombosis in non-users of combined hormonal contraception.[15,16]

The presence of a genetic thrombophilic state markedly increases the risk for thrombosis when estrogen is used. For example, the presence of a factor V Leiden mutation can increase the risk for venous thrombosis anywhere from 15- to 35-fold with the concomitant use of estrogen.[5,7,17] Again, the absolute risk for thrombosis is low, especially in younger patients. For this reason, screening for thrombophilia is not recommended before

Table 2. Retrospective Studies Evaluating the Incidence of Thrombosis in Transgender Women

Study	N	Venous Thrombosis	Arterial Thrombosis	Estrogen
Wierckx (2013)[55]	214	5.1%	3.2%	Various
Wierckx (2012)[56]	50	6%	6%	Various
De Cuypere (2005)[57]	23	0	4%	Various; 72% taking oral estradiol
Ott (2010)[58]	162	0	-	Transdermal estradiol
Wilson (2009)[59]	30	0	-	Oral conjugated equine estrogens, transdermal estradiol
Wierckx (2014)[60]	53	0	0	Age <40 years, 4 mg of oral estradiol valerate Age >40 years, transdermal estradiol
Van Kerteren (1997)[61]	816	5.5%	1%	Age <40 years, 4 mg of oral estradiol valerate Age >40 years, transdermal estradiol
Prior (1989)[62]	50	0	0	Oral conjugated estrogens
Dittrich (2005)[63]	60	1%	0	Oral estradiol valerate
Schlatterer (1998)[64]	46	0	0	Parenteral estrogen
Becerra Fernández (1999)[65]	31	0	0	Parenteral estradiol enanthate
Getahun (2018)[23]	2842	5.5/1000 patient-years	7.7/1000 patient-years	Oral estradiol "most common"
Nota (2019)[24]	2517	7.3/1000 patient-years	5.9/1000 patient-years	"Estrogen"

estrogen use unless other risk factors are present, such as a family history of thrombophilia.

Among cisgender women in whom thrombosis develops while they are on estrogen therapy, the risk for recurrence is low—approximately 1 per 100 patient-years if the estrogen is discontinued.[18] For women who must continue estrogen, added anticoagulation is protective against estrogen-induced thrombosis.[19] If estrogen is restarted without the "cover" of anticoagulation, however, the risk for recurrent thrombosis is high. For example, in one study of women who discontinued estrogen after estrogen-related thrombosis had developed, the recurrence rate was 27.3 per 1000 with any future use of estrogen.[20] During the time they actually were on estrogen, this recurrence rate rose to 55 per 1000. In women with non–estrogen-related thrombosis, the thrombosis rate rose from 16.2 per 1000 to 35 per 1000 with estrogen use. In the only randomized clinical trial, women with a history of thrombosis were randomly assigned to either hormone replacement therapy or placebo. This trial was stopped because of the high rate of thrombosis of 8.5% per year in the estrogen arm vs 1% per year in the placebo arm.[21]

The risk for arterial thrombosis with estrogen use appears to be greater in transgender women than in cisgender women.[22] Observational studies have tended to show an increased risk for arterial disease[4] (Table 2). In a large health maintenance organization (HMO) cohort study in which 2842 transgender women were matched with 48,775 cisgender women and 48,686 cisgender men, the risk for myocardial infarction was higher in transgender women than in cisgender women (hazard ratio, 1.80) but was not higher in transgender women than in cisgender men.[23] Another large cohort study, from Amsterdam, of 2517 transgender women with a total of 22,300 years of follow-up, also showed an increased rate of myocardial infarction in comparison with cisgender women (standardized incidence ratio of 2.64), but no difference in comparison with cisgender men.[24] These results from large cohort studies are consistent in showing an approximate doubling of the risk for myocardial infarction in comparison with cisgender women.

The transgender women in the Amsterdam cohort also had an increased risk for stroke in comparison with cisgender women (standardized incidence ratio, 2.42) and with cisgender men (standardized incidence ratio, 1.80).[24] In the HMO study as well, the risk for stroke in transgender women appeared to be higher than that in cisgender women (hazard ratio, 1.9), but not higher than that in cisgender men.[23] Again, both large studies showed a doubling of risk for transgender women vs cisgender women—this time risk for stroke. A recent study of mortality trends in transgender patients showed an increased risk for cardiovascular death of 2.6 in transgender women

in comparison with the general population.[25] However, this study did not account for the presence of additional cardiovascular risk factors, such as smoking and psychological stress, that might have accounted in part for the increased risk for death.

Studies have reliably shown an increased risk for venous thrombosis with feminizing therapy (Table 2). The large HMO cohort study previously discussed showed a 2-fold increase in the rate of venous thrombosis in transgender women in comparison with both cisgender men and cisgender women.[23] This risk—unlike that in cisgender women—increased with time.[23] For example, the difference in risk for venous thrombosis in transgender women vs cisgender men was 4.1 per 1000 persons at 2 years and was 16.7 per 1000 persons at 8 years. The Amsterdam study showed a higher standardized incidence ratio for venous thrombosis in transgender women than in cisgender women (5.5) and in transgender women than in cisgender men (4.55).[24] Several meta-analyses have confirmed the higher risk for thrombosis.[26,27] A 2021 meta-analysis of 18 studies including 11,542 transgender women showed an overall thrombosis rate of 2%, which increased with the duration of therapy.[27] As in cisgender women, the risk increased with age and obesity.

One major confounding factor in interpreting all these data on risk for thrombosis is that different forms of estrogen are now used for gender-affirming hormone therapy. Ethinyl estradiol (the estrogen used in the combined oral contraceptive pill) carries the highest risk for thrombosis and is no longer used in gender-affirming therapy. The most common formulation used at present is estradiol, with which the thrombosis rate appears to be lower. Even lower rates are seen with transdermal estradiol, which is recommended for patients older than 40 years.[4] Transdermal estradiol produces stable estradiol levels without the estrone metabolites that occur with oral estrogen.[4] It is thought that the lack of first-pass effect may account in part for the lower rates of thrombosis with this preparation. The thrombosis risk is also low with oral estradiol valerate. As a result, current thrombosis risks may be lower than those reported in older studies, in which ethinyl estradiol was the estrogen primarily used for feminization therapy. Because of this confounder, using data from cisgender women to assess risk in transgender women may not be reliable. One caveat is that many patients may be obtaining hormonal therapy without a prescription from a physician or other qualified health care professional. This practice may increase thrombosis risk, especially if ethinyl estradiol is used.[28]

The management of patients on estrogen therapy before gender-affirming surgery has been controversial. Some have suggested halting estrogen at any time from 1 to 6 weeks before the surgery, but no consensus has been reached either on how long estrogen should be held or on whether it should be held at all. However, given that it can take months for the prothrombotic effects of estrogen to decrease, in theory the time off medication may need to be months. Estrogen holding can result in undesirable effects of estrogen withdrawal. Symptoms of estrogen withdrawal, which can start in a few days, include depression, anxiety, and increased dysphoria.[29,30] In contrast, studies have shown that the risk for thrombosis with gender-affirming surgery is low, usually less than 1%.[31] For example, a large single-center chart review of 1517 transgender women who underwent gender-affirming surgery revealed a low rate of thrombosis (0.1%), with no difference seen between holding estrogen for 1 week or continuing estrogen through surgery.[32] A 2018 review of 12 studies on estrogen showed an inconsistent risk; most of the risk was with ethinyl estradiol, which is rarely used now.[29] A reasonable recommendation would be to continue estrogens through surgery and use standard thrombosis prophylaxis when indicated by various scoring systems, such as the Caprini score.

Table 3. Estrogen Risk Summary

Hematologic risks
Increase in arterial disease Increase in venous thrombosis
Risk amelioration
Avoidance of ethinyl estradiol Use of transdermal estrogen • Older patients • History of thrombosis • Thrombophilia Risk factor control • Smoking cessation • Monitoring of lipids and blood pressure

Table 4. Masculinizing Hormone Regimens

Parenteral testosterone
Testosterone enanthate or cypionate, 100-200 mg IM every 2 weeks or 50% weekly Testosterone undecanoate, 1000 mg every 12 weeks
Transdermal testosterone
Testosterone gel 1%, 2.5-10 g per day Testosterone patch, 2.5-7.5 mg per day
Oral testosterone
Testosterone undecanoate, 160-240 mg per day

IM, intramuscularly.

Source: Hembree WC et al. *J Clin Endocrinol Metab*. 2009;94(9):3132-3154.[66]

Estrogen Therapy Risk Reduction

Patients receiving estrogen for gender affirmation need to be advised of the small absolute risk for thrombosis, especially with the use of newer products (Table 3). Signs and symptoms of thrombosis should be reviewed. Patients who have an inherited thrombophilia should preferentially receive transdermal estradiol, which carries the lowest rate of thrombosis. Patients with a prior history of thrombosis who remain on anticoagulation can receive any estrogen product, as data show that anticoagulation is protective against new thrombosis. For patients who have a history of provoked or distal thrombosis and are currently off anticoagulation, transdermal products should be considered.

Given the increased risk for arterial disease, careful attention should be paid to reducing cardiac risk factors.[22,33] This would include monitoring lipids and blood pressure and the essential step of smoking cessation.

Testosterone

The goal of gender-affirming therapy for transgender men is to stop menses and induce masculinizing effects, such as the redistribution of body fat and growth of body hair[34] (Table 4). Serum testosterone levels are routinely monitored to ensure that they are within the physiologic range for cisgender men.

Unlike in the vast literature on estrogen, data concerning testosterone and thrombosis in cisgender men are sparse and less consistent. It does appear from more-recent studies that the use of testosterone is not prothrombotic, especially in patients who are hypogonadal.[35,36] No consistent risk for arterial disease has been found with testosterone, with some studies suggesting that its use may be protective in patients with pre-existing cardiac disease.[35]

A key issue is whether testosterone increases cardiovascular risks when used as gender-affirming therapy. Multiple reviews show no increased risk for ischemic heart disease in transgender men.[22,37] The HMO study looked at 853 transgender men and found no increased incidence of myocardial infarction or stroke with testosterone.[23] However, the Amsterdam study, which included 1358 transgender men, showed an increased risk for myocardial infarction in comparison with cisgender women, but not with cisgender men. In addition, the risk for stroke was not increased.[24] One study did point to adverse changes in cardiovascular risk factors such as lipid levels, with low-density lipoprotein (LDL) levels increased by 8 mg/dL.[22,38] In theory, this change would increase the risk for cardiovascular events by approximately 6% over 30 years in comparison with optimized risk factors.[38] To date, however, this theoretical increased risk for arterial disease has not been borne out.

An increased risk for venous thrombosis in transgender men has not been seen in multiple studies, including both the large HMO and Amsterdam studies.[23,24,37] Regarding surgery, a 2018 review showed no increase in thrombosis risk with testosterone during gender-affirming surgery.[29] Thus, patients receiving testosterone for gender-affirming therapy can be reassured that their risk for venous thrombosis is not increased.

Erythrocytosis Risk Reduction

Exogenous testosterone increases the hematocrit, mainly by making the red cell precursors more sensitive to erythropoietin. It can also increase iron absorption by decreasing serum levels of hepcidin, an iron absorption inhibitor.[39] Studies have shown that the hematocrit rises by 4% on average after the start of testosterone, with most of the increase occurring in the first 3 months (2.7%), but the red cell counts can continue to rise over years.[40-42] However, extreme erythrocytosis—in which the hematocrit is above 54%—was seen in only 0.5% of patients. When erythrocytosis develops, lowering or spacing out the dose may decrease the hematocrit.[43] Some experts recommend changing from testosterone esters to undecanoate, or using the transdermal route.[40,44] Guidelines recommend phlebotomy if the hematocrit is above 54%, although the true thrombotic risk with this form of secondary erythrocytosis is unknown.[40] Interestingly, the exact opposite occurs in transgender women who are starting estrogen, in whom the hematocrit falls by 4% on average.[41] One issue that is often seen in clinical practice is "pseudo-erythrocytosis," in which gender-inappropriate ranges for normal complete blood cell counts are used, so that the patient is incorrectly labeled as having erythrocytosis.[45]

Iron Deficiency Risk Reduction

Although not as well studied as erythrocytosis, another issue that often is seen clinically in transgender men is iron deficiency. The incidence of iron deficiency and iron deficiency anemia is very high in cisgender women because of obligate menstrual losses.[46] An additional cause of iron store depletion in transgender men is iron mobilization during testosterone therapy and increased red cell production when testosterone is started. Even in patients without anemia, low iron stores can cause fatigue (with a ferritin level <50 μg/L), impair exercise ability, etc. Transgender men should have their ferritin level checked before starting testosterone, and the level should be reassessed if symptoms consistent with iron deficiency occur, such as fatigue, pica, and restless legs.

Cardiovascular Risk Reduction

Given the concern about cardiovascular disease, attention

Table 5. Testosterone Risk Summary

Hematologic risk
Erythrocytosis Iron deficiency Adverse cardiovascular risk profile
Risk amelioration
Monitoring of red cell count Dose reduction or phlebotomy for hematocrit >54% Risk factor control • Smoking cessation • Monitoring lipids and blood pressure

needs to be paid to cardiovascular risk factors as closely in transgender men as in transgender women (Table 5). In addition, blood cell counts need to be routinely monitored, given the increased risk for the development of erythrocytosis over time.

Common Consultation Issues

Bleeding Disorders

Increasingly, hematologists are asked to see patients with bleeding disorders who are considering gender-affirming therapy. The changes in the hormonal milieu pose special challenges for patients undergoing gender-affirming surgery but also may have some advantages. Estrogens are well-known to increase levels of factor VIII, as well as those of von Willebrand factor.[47] Fewer data exist for testosterone, but it too may increase factor VIII levels. Therefore, gender-affirming hormone therapy may reduce bleeding, especially among patients taking estrogen.

Hemophilia occurs in approximately 1 in 10,000 men, with prophylactic factor administration in affected men the current standard of care to prevent disabling joint bleeds. Patients using estrogen as gender-affirming therapy who have mild factor VIII deficiency will benefit from the increase in their factor VIII levels. Regarding gender-affirming surgery, procedures such as phalloplasty and vaginoplasty carry a high risk for bleeding and the potential for devastating outcomes with hematoma formation. Therefore, factor VIII levels should be kept elevated for 2 weeks after surgery. Factor VIII levels should be kept elevated for 7 days after breast implant surgery.

Von Willebrand disease is the most common bleeding disorder and can be the source of some diagnostic confusion. Simplistically, in type 1 Von Willebrand disease, von Willebrand factor and factor VIII are normal but levels are low; in type 2, these factor are dysfunctional; and in type 3, no factors are present. As previously noted, estrogen increases the levels of von Willebrand factor and can reduce symptoms of bleeding in patients with mild type 1 disease and some with type 2 disease. However, for patients undergoing major surgical procedures, specific von Willebrand factor concentrates, such as antihemophilic factor/von Willebrand factor complex (Humate-P, CSL Behring) or recombinant von Willebrand factor, should be used. Again, as in patients with hemophilia undergoing complex procedures, one should aim for levels of approximately 50% for 2 weeks, with careful monitoring.

Cardiovascular Disease

When patients with a history of any type of arterial disease (coronary artery disease, stroke, or peripheral vascular disease) undergo any gender-affirming therapy, scrupulous attention needs to be paid to the control of vascular risk factors. Rates of smoking in transgender patients are high, and smoking cessation is a key part of preventing thrombotic complications of therapy.[48] Lipid levels need to be frequently monitored—especially for patients on testosterone—with a goal LDL level of less than 100 mg/dL. All patients with a history of any arterial vascular disease should be taking aspirin. Given that rates of obesity are also elevated in the transgender population, weight loss can also be helpful.[48]

Venous Disease

As previously discussed, estrogen therapy is often a source of concern in patients with a history of thrombosis because estrogen is a major risk factor for venous thrombotic disease. Patients taking estrogen should not be routinely screened for thrombophilia because 20,000 patients would need to be screened to prevent 1 death.[49] If the patient has a strong family history of thrombosis (ie, 2 first-degree relatives), then screening can be considered. A history of thrombosis without current anticoagulation is a contraindication to any route of estrogen administration except the transdermal route. For patients currently on anticoagulation, however, any route of estrogen administration can be used. Patients who are known carriers of thrombophilia, such as those with factor V Leiden mutations, should be offered only transdermal therapy. Those with antiphospholipid antibodies can receive any form of estrogen as long as they are at low risk, with no history of thrombosis or autoimmune disease, including mild or inactive lupus.[50]

Sickle Cell Disease

Increasingly, patients with sickle cell disease are undergoing gender-affirming therapy.[51] A theoretical concern regarding feminizing therapy is the thrombotic risk of estrogen. The data show that the use of estrogen-containing contraceptives is not risky in patients with sickle cell disease, but the preference should be for transdermal preparations. With testosterone, accounts

exist of increased vaso-occlusive episodes due to the rise in the hematocrit. However, when testosterone is used appropriately for hypogonadal patients with sickle cell disease, the risk for complications does not appear to be increased.[52] Patients with sickle cell disease who are considering gender-affirming therapy should be on maximal medical therapy, including hydroxyurea and—for selected patients—crizanlizumab (Adakveo, Novartis) or voxelotor (Oxbryta, Global Blood Therapeutics). Patients for whom even minor gender-affirming surgery is being considered should undergo transfusion to a hematocrit above 30%, as the TAPS study showed better surgical outcomes at this level even with simple procedures, such as tonsillectomy.[53] In this trial, the risk for serious complications, such as acute chest crisis, in patients who did not receive a transfusion was almost 4 times higher.

Summary

As the number of people seeking treatment for gender dysphoria increases, the need for gender-affirming hormonal and surgical therapy is expected to increase. Estrogens do raise the risk for thrombosis, but this risk will be outweighed by the benefits of therapy in most cases. For patients at risk for thrombotic complications, the use of transdermal estrogen is an option. Testosterone does not appear to carry an increased risk for thrombosis, but it can cause secondary erythrocytosis. With both hormonal therapies, conscientious attention needs to be paid to reducing cardiac risk factors, especially smoking cessation.

Disclosure

Dr DeLoughery has no relevant disclosures.

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