REVIEW ARTICLE

# Caring for Transgender Persons: Gender in Clinical Decisions, Tools, and Labs

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KEYWORDS

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ABSTRACT

Individuals who identify as transgender (TGD) who are taking gender-affirming hormone therapies (GAHT) may experience physiologic changes that impact the interpretation of laboratory results, diagnostic tools, and risk calculations. This review provides guidance for healthcare practitioners on navigating these challenges to ensure appropriate and safe patient care. Key considerations include interpreting standard laboratory results and vital signs, alongside recommendations for preventative cancer screening and cardiovascular risk assessments. Additionally, there are some key considerations when using the CHA2DS2-VASc score in TGD patients with atrial fibrillation, as well as when interpreting a QT/QTc interval. Hormone therapies may also influence a patient's risk of venous thromboembolism (VTE), necessitating vigilant monitoring and avoidance of supraphysiologic hormone levels. Renal function estimations in patients on GAHT require careful consideration, with alternative equations potentially offering more accurate assessments. Finally, pulmonary function testing poses challenges, highlighting the need for gender-affirming approaches in interpretation. Overall, this comprehensive review underscores the importance of individualized care and shared decision-making in TGD healthcare.

## BACKGROUND

A person who identifies as transgender (TGD) is someone whose sex assigned at birth (defined as one's chromosomal makeup and generally assigned based on external genitalia) is incongruent with the gender they identify with (defined by the societal characteristics of being a man or woman).[1] Patients experiencing psychologic stress due to this mismatch are said to be experiencing gender dysphoria.[1] TGD patients can transition and express their gender in a variety of means including social, legal, surgical, and medical via gender-affirming hormone therapies (GAHT). A TGD person may pursue all, none, or a combination of these therapy types. Transitions are often discussed in terms of patients going from male to female (MtF) or female to male (FtM), although patients who identify as nonbinary may also use these means to algin with their gender identity.[1] In terms of GAHT, there are various approaches to how these medications are titrated, all centered around the patient's satisfaction with secondary sex characteristics and safety.[1] Common medications used for this type of hormone replacement therapy (HRT) include estradiol and testosterone. Obtaining a detailed history of a patient's transition is crucial for providing appropriate care.

Laboratory tests, diagnostic tools, health screenings, and risk calculations differ based on one's sex assigned at birth. Surgical or medical transitioning can alter physiology, affecting the accuracy of these laboratory values, screenings, tools, or scores when the patient's sex assigned at birth is used. This review aims to review the use of such tools in patients on GAHT and discuss recommendations on when to use birth sex vs gender identity.

## INTERPRETATION OF STANDARD LABORATORY RESULTS AND VITAL SIGNS

Common laboratory tests may be affected by sex steroids or body size.[2] Accurate interpretation of these results, considering GAHT, is essential in providing accurate evidence-based care. Table 1 summarizes major changes in common laboratory values affected by GAHT. There is no significant impact on vital signs in TGD patients using GAHT.[3,4]

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TABLE 1: Common laboratory tests and effects of GAHT

| Laboratory Test | Persons on Masculinizing HRT | Persons on Feminizing HRT |
|---|---|---|
| **Hematology** | | |
| Hemoglobin, hematocrit, red blood cells (RBC) [3-5] | **Initial:** increase at initiation; stabilizing at 6 months<br>**Long term:** maintains for at least 5 years<br>**Typical levels:** same as cisgender males | **Initial:** decrease at initiation; stabilizing at 3 months<br>**Typical levels:** same as cisgender women |
| Platelets[3] | No change | **Initial:** increase from baseline; no absolute change |
| Mean corpuscular volume (MCV), white blood cells (WBC)[3,5] | No change | No change |
| **Basic Metabolic Panel** | | |
| Chloride[3] | **Long term:** decrease with use up to 3-5 years | No changes |
| Sodium[3] | No change | **Initial:** decrease at initiation; stabilizing at 3-12 months<br>**Long term:** maintains for at least 5 years |
| Glucose[3] | No change | **Initial:** increase at initiation for 6 months<br>**Long term:** returns to normal after 6 months |
| **Renal Function Tests** | | |
| Creatinine[3,4] | **Initial:** increase at initiation; stabilizing at 6 months | **Long term:** decrease at 12 months |
| Albumin[3] | No change | **Initial:** decrease at initiation<br>**Long term:** decrease continues for up to 5 years |
| **Liver Function Tests** | | |
| Alanine aminotransferase (ALT)[3,4,6] | **Initial:** increase beginning at 48 months<br>**Long term:** continued for at least 5 years | No changes |
| Alkaline phosphatase (ALP)[3,4,6] | No change | **Initial:** decrease at initiation<br>**Long term:** return to normal levels at 5 years |
| Aspartate aminotransferase (AST), total bilirubin[3,4,6] | No change | No change |
| **Lipid Panel** | | |
| Low-density lipoprotein (LDL)[3,4] | **Long term:** relative increase through 5 years | No changes |
| High-density lipoprotein (HDL)[3,4] | **Long term:** relative decrease through 24 months | **Long term:** relative increase through 5 years |
| Total cholesterol, triglycerides[3,4] | No change | No change |

For persons on GAHT, laboratory values that change with HRT use (Table 1) typically return to normal range around 10 weeks after discontinuing estradiol and 11 weeks after stopping testosterone therapy.[3]

## PREVENTATIVE SCREENING

When assessing an individual's need for adult preventative care, consider their use of GAHT and any gender-affirming surgeries.[7] Gender dysphoria does not affect cancer risk, but can decrease the likelihood of screening for birth sex organs due to both provider and patient factors.[7] Some patients might find screenings gender affirming, such as mammograms for patients on feminizing HRT, while patients on masculinizing HRT might experience physical and emotional discomfort during Pap smears.[10] When screening patients who have undergone gender affirmation, it is important to get a thorough organ inventory to assess their risks. Table 2 summarizes recommendations on which patients should receive gender-related preventative screenings.

### Cardiovascular Risk (Primary Prevention)

Current cardiovascular risk scores do not account for the impact of GAHT on patients. Cardiovascular risk assessment tools include the Framingham Risk Score, Reynolds Risk Score, SCORE (Systematic COronary Risk Evaluation), and QRISK/JBS, which all use gender or sex to stratify cardiovascular risk.[11]

GAHT may contribute to poor cardiovascular health in TGD people because of the potential cardiovascular effects of these treatments, such as an increased risk for venous thromboembolism (VTE) among TGD women taking estradiol.[12] Studies have identified a higher risk of CVD or stroke in TGD women on GAHT compared with cisgender counterparts.[10,13] However, these studies often do not quantify the individual's baseline cardiovascular risk before GAHT, nor differentiate the type, dose, or duration of GAHT utilized.

The American Heart Association (AHA) suggests coronary artery calcium (CAC) as a tool to classify cardiovascular risk in individuals with borderline or intermediate estimated 10-year risk, as part of shared decision-making.[11] CAC is recommended in adults ages 40 to 75 years with LDL 70 to 189 mg/dL and 5% to 19.9% 10-year atherosclerotic cardiovascular disease (ASCVD) risk, or those with <5% risk and a family history of premature ASCVD.[14] In a small cohort of TGD individuals (n = 47) on GAHT, the CAC score was similar to their cisgender age-matched counterparts.[15] Table 3 summarizes how the CAC score can inform statin use.

TABLE 2: Preventative health screening in transgender patients

| | Persons on Masculinizing HRT | Persons on Feminizing HRT |
|---|---|---|
| **Cancer** | | |
| Breast[7] | Without bilateral mastectomy: follow guidelines for cisgender females<br>With chest reconstructive surgery: yearly chest wall and axillary exams | GAHT 5-10 years: screening mammography every 2 years starting at age 50 years<br>No GAHT: no routine screening |
| Cervical[7,8] | Intact cervix: annual Pap smear over the age of 21 years<br>Consider pretreatment with vaginal estrogen to obtain adequate sample<br>Total hysterectomy, no history of precancerous cervical legions or cervical cancer: no screening needed | No screening needed |
| Colon[7] | Follow guidelines for cisgender patients | Follow guidelines for cisgender patients |
| Prostate[7] | No screening needed | Follow guidelines for cisgender males |
| Endometrial[7] | Follow guidelines for cisgender patients | Follow guidelines for cisgender patients |
| Ovarian[7] | Follow guidelines for cisgender patients | Follow guidelines for cisgender patients |
| **Osteoporosis Screening[9]** | | |
| | Recommended for patients who are not compliant with hormone therapy, or who develop risks for bone loss | Consider bone mineral density (BMD) testing at baseline.<br>Individuals at low risk: start screening at age 60 years |
| **Human Papillomavirus (HPV) Screening[8]** | | |
| | Follow guidelines for cisgender patients | No screening needed |
| **Abdominal Aortic Aneurysm (AAA) Screening** | | |
| | No formal recommendation | No formal recommendation |

TABLE 3: CAC score interpretation[14]

| Absolute CAC Score | 10-Year ASCVD Risk | Statin Benefit |
|---|---|---|
| ≥100 | >7.5% | Recommended |
| ≥300 | Higher than 7.5% | High intensity |
| ≥1000 | Need for aggressive LDL lowering | High intensity |

Although there is no consensus on how to utilize cardiovascular risk assessment tools in TGD patients, considering the type and duration of hormone therapy is important. Suggested strategies for quantifying risk with binary cohort equations include using sex assigned at birth, affirmed gender, or an average of both, though these may overestimate or underestimate actual risk. Alternatively, the CAC score may provide a more accurate cardiovascular risk assessment and inform therapy interventions better. Due to the lack of data in the TGD population, shared decision-making about potential cardiovascular risk and primary prevention is crucial.

## Atrial Fibrillation

The CHA2DS2-VASc risk score has the best evidence for predicting thromboembolic risk in people with atrial fibrillation requiring anticoagulation.[16] The sex category criteria apply one point to female sex as a risk factor, but do not account for estrogen use or TGD females on GAHT.

Nielsen et al. evaluated the impact of female sex as a risk modifier for stroke in atrial fibrillation and confirmed an excess risk among females. The risk was more pronounced in those with at least two nonsex-related risk factors.[17] The effect of female sex was notably higher stroke risk in individuals with a CHA2DS2-VASc score of 2, 4, or 5 compared to cisgender males.[17] While the study did not evaluate the impact of estrogen therapy on event risk, it suggests that hormone therapy in MtF patients may warrant consideration, especially in those with additional risk factors.

Decreasing testosterone levels have been linked with increased incidence of atrial fibrillation.[18] In cisgender males older than 55 years, there was a correlated increase in atrial fibrillation risk with each standard deviation decrease in testosterone levels.[18] Additionally, individuals who achieved therapeutic testosterone levels with replacement therapy had a lower risk of atrial fibrillation compared to those with subtherapeutic levels.

## QT/QTc

GAHT may influence QTc interval duration and risk for dysrhythmias, particularly if titrated to match levels in cisgender patients.[18] There is limited direct evidence to delineate appropriate changes in QTc changes in TGD patients on GAHT. Studies in cisgender patients on HRT have been used to inform the risks of QTc changes. The available studies also used different cutoffs for QTc prolongation.

The approach to hormone therapy in persons on feminizing hormones mirrors HRT in agonadal and menopausal cisgender females. Research in postmenopausal cisgender females taking HRT demonstrates that estrogen therapy is associated with QTc lengthening and progesterone limits the QTc prolongation.[18]

Effects of endogenous testosterone on repolarization are suspected to be responsible for the shorter QTc in cisgender males.[18] In hypogonadal cisgender males on testosterone HRT, normal testosterone levels reduce the QTc changes and risk of Torsade de Pointes ( TdP).[18]

In patients receiving GAHT, it is recommended to avoid supraphysiologic levels of hormones and monitor for QTc changes before and during GAHT. Also, one should consider the individual's overall risk for dysrhythmias and avoid QTc-prolonging medications, especially in patients with baseline QTc prolongation.

### VTE Risk

The use of exogenous hormones impacts the risk of VTE and is correlated to the patient's comorbidities, estrogen formulation (type and route), and duration of GAHT.[19,20]

Prediction and risk stratification tools for pulmonary embolism (PE) include the Pulmonary Embolism Rule-out Criteria (PERC), Wells Score for PE, revised Geneva score (RGS), Pulmonary Embolism Severity Index (PESI), simplified PESI (sPESI), and the Hestia criteria.[21] The Wells-PE and RGS do not consider sex, gender, or hormone use as risk factors. However, the PERC incorporates hormone use, assigning one risk point for use of oral contraceptives, HRT, or estrogen use in male or female patients, thus accounting for anyone on GAHT.

The PESI, sPESI, and Hestia criteria are used alongside clinical judgement to help identify patients suitable for outpatient treatment of PE.[21] The PESI assigns 10 points (out of a possible 125) to male gender, which may affect its accuracy in patients taking GAHT. In contrast, the sPESI and Hestia criteria do not rely on gender to inform the clinical decision, potentially making them more accurate for clinical decision.

### Nephrology

Literature on assessing renal function in TGD individuals is inconsistent or based upon small observational studies.[22] Although glomerular filtration rate (GFR) can be measured directly, it would be impractical for routine monitoring. Therefore, we utilize estimates of renal function based on surrogate biomarkers including serum creatinine and serum cystatin-C.

Creatinine clearance is dependent on gender and muscle mass, hence changes in serum creatinine. GAHT affects muscle mass, thereby impacting creatinine levels. Serum creatinine changes over time in patients on GAHT, with a significant increase at 6 months in individuals taking testosterone and a decrease at 12 months in those taking estrogen.[23]

Kidney Disease Improving Global Outcomes (KDIGO) recommends the use of the eGFRcr-cys equation to estimate a patient's GFR, which is an average of the eGFRcr and eGFRcys equations. However, both equations may be inaccurate in the TGD population.[22] An alternative for assessing renal function in TGD individuals is the KDIGO CKD EPI eGFRcys equation. Although gender is a variable in this equation, the results are less affected by gender.[22] Another alternative is the European Kidney Function Consortium (EKFC) cystatin equation, which does not differentiate results based on gender. It was found to be unbiased and more accurately reflects directly measured GFR compared to the KDIGO CKD EPI eGFRcys equation.[22,24]

Considering the limitations of the KDIGO CKD EPI equations, it is most appropriate to utilize the EKFCcys calculation to obtain the most accurate assessment of renal function for all patients, as this eliminates confounders relating to gender or muscle mass. Table 4 details which ideal body weight (IBW) equation and gender to use for patients on GAHT using the Cockcroft-Gault equation.[25]

TABLE 4: IBW and gender recommendations for the Cockcroft-Gault equation[25]

| | |
|---|---|
| Less than 6 months | IBW and gender: based on sex assigned at birth |
| At least 6 months | IBW and gender: based on gender identity |

## PULMONARY TESTING

Currently, the American Thoracic Society recommends identifying and respecting gender identity, but utilizing sex assigned at birth for the gender reference range during pulmonary function testing (PFT).[26,27] Altering the gender reference range when interpreting spirometry results can significantly alter the diagnosis of restrictive and obstructive lung disease, potentially leading to misdiagnosis and inappropriate treatment in TGD patients.[26]

PFT uses a cisgender algorithm for lung function estimation. Providers inconsistently apply female and male reference ranges for TGD patients when interpreting PFT. Using male predicted values for a female-sized body can result in pseudorestriction, while the opposite can mask true restriction.[28]

Lung function in patients who start GAHT earlier in puberty will likely align more closely to the lung function of their affirmed gender.[26] However, further research is needed to define the effects of prepubertal gender-affirming hormones on lung size in this population.[27]

Hormones play a role in the development of obstructive sleep apnea in cisgender individuals. Consideration should be given to repeating a sleep study in a patient who starts GAHT.[27]

Individuals who use chest wall binders report shortness of breath, chest pain, scarring, and rib fracture.[27] Up to 50% of binder users report respiratory complaints, yet only approximately 20% seek medical care.[2] Binder use may alter the outcomes of physiologic pulmonary testing.

## CONCLUSION

This review highlights the intricate landscape of caring for patients undergoing GAHT and emphasizes the need for further research across multiple domains. Nuanced guidelines that consider both sex assigned at birth and gender identity are essential in providing comprehensive recommendations. Continued investigation and innovation are crucial for advancing towards optimal care and support for this underserved population.

## LITERATURE SEARCH AND DATA SOURCES

Current disease state guidelines were utilized to identify commonly recommended scoring systems that included references to gender or hormone therapy. PubMed and Google Scholar were searched using these scoring systems and their associated disease states as primary search terms in addition to the terms gender, female, male, transgender, and hormones.

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