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Impact of Gender Affirming Hormone Therapy on Hematological Values of Transgender and Gender Diverse Patients

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Abstract

Purpose

It is recognized that sex hormones, including gender affirming hormone therapy (GAHT), affect the rate of erythropoiesis, demonstrated in complete blood count (CBC) measurements. While exogenous hormonal impact is understood, established reference ranges are based on sex assigned at birth, signifying endogenous hormone states. Leading organizations providing GAHT guidelines recommend using affirmed gender when assessing laboratory values. This study sought to further the understanding of the impact GAHT may have on hematological values through a statistical comparison of gendered adult laboratory values and population means.

Methods

A retrospective chart review of patients who received transgender healthcare at an urban university health system was performed. Electronic medical record documentation of transgender and gender diverse (TGD) patients on GAHT, meeting study criteria, allowed for categorical analysis of transmasculine and transfeminine cohort hematological laboratory values and comparison to adult cisgender la-

boratory derived population means.

Results

Criteria for analysis was met for 139 transmasculine and 57 transfeminine patients. Data identified statistically significant difference in transmasculine cohort red blood cell (RBC) means as well as hematocrit (Hct) means from those of both established cisgender male and cisgender female adult laboratory derived population mean values.

Conclusions

An advanced understanding of the impact of GAHT on common laboratory values is critical. Transmasculine RBC and Hct means existing between laboratory established adult cisgender male and cisgender female population means may impact the proper diagnosis and treatment of hematological based clinical conditions. Further research studies on hematological laboratory values of the TGD population may improve the equity and quality of care received.

Key Words: Transgender health, gender affirming care, hormonal replacement therapy, laboratory reference standards, complete blood count monitoring

Introduction

Transgender patients face numerous health disparities often as a result of stigma, discrimination, and poor access to health care.[1-10] As the recognized population of transgender and gender diverse (TGD) patients accessing gender-affirming hormone therapy (GAHT) increases, the need for research continues to ensure best care is received.

Clinicians may face unique challenges when treating TGD patients.[11-13] Clinician knowledge and experience in the care of gender minority patients is variable and unique physiology can result from gender-affirming medications, including hormone therapy, and surgeries.

It is recognized that the rate of erythropoiesis is affected by sex hormones. Complete blood count (CBC) measurements reflect this physiological phenomenon that is best explained by a presumed adaptation of the erythropoietin-renal circuit, as cisgender males have a relatively higher mean hemoglobin (Hgb) and hematocrit (Hct) when compared to cisgender females. Interestingly, the anthropological purpose of this physiological occurrence is not yet clear.[14] GAHT alters testosterone concentration, affecting CBC measurements of red blood cells (RBC), Hct and Hgb. These values will decrease in those on estrogen therapy and increase in those on testosterone therapy.[14-18]

While it is understood that exogenous hormones impact laboratory studies, such as the aforementioned hematological values, established reference ranges are based on sex assigned at birth, signifying endogenous hormone states. Leading organizations providing GAHT guidelines have recommended using affirmed gender when assessing laboratory values, as it is assumed to be the closest available reference that reflects the patient's physiology.[1-4]

Numerous studies have reported changes in CBC values of RBC, Hct and Hgb, as well as triglycer-

ide, liver enzymes, and prolactin levels associated with GAHT.[19-27] Current research has demonstrated that a steady states of changes in Hct and Hgb are noted by at least 12 months of stable GAHT, if not earlier.[16,17] Recent publications have established hematological reference intervals for transgender individuals on stable GAHT, bearing clinical relevance. These validated laboratory studies confirm recommendation that hematological parameters of transgender individuals on stable GAHT should be evaluated against hormonally congruent cisgender individuals' reference ranges.[17]

Recognizing these reference intervals (RI) greatly aid in interpretation of hematology laboratory values for transgender individuals. Particularly, RI assist clinicians in diagnose of conditions such as anemia, polycythemia, erythrocytosis, and thalassemia, in providing optimal care, and in laboratory resource stewardship.[14,18,28-32]

As 70% of clinical decisions are supported by laboratory values, identification of accurate reference ranges may lead to the prevention of over or under-diagnosing TGD patients for numerous conditions, improvement of equity, as well as impact quality of care.[16] This retrospective chart review sought to further the understanding of how GAHT may impact hematological values of TGD patients through statistical comparison with cisgender values.

Materials and Methods

A retrospective chart review of patients who received gender affirming medical care from the Department of Family Medicine at Oregon Health & Science University (OHSU), an urban university health system in Portland, Oregon was performed. This study was approved by the OHSU Institutional Review Board and a waiver of patient consent was granted.

Inclusion Criteria

Primary inclusion data included: TGD patients; active GAHT care received from June 1, 2014 - June 1, 2019 with laboratory confirmation of hormone level; twelve months or greater treatment on GAHT; adults of reproductive age range, as defined by the Centers for Disease Control and Prevention (CDC) as 15-44 years of age (definition at time of this study); recorded body mass index (BMI) withing the last twelve months; and non-smoker status.[33] Secondary exclusion criteria included prescribed medication or diagnosed health conditions known to alter the lab values of interest. (Figure 1) GAHT dosing guidelines of leading organizations determined the absolute maximum and minimum dosages included in the study.[1-4]

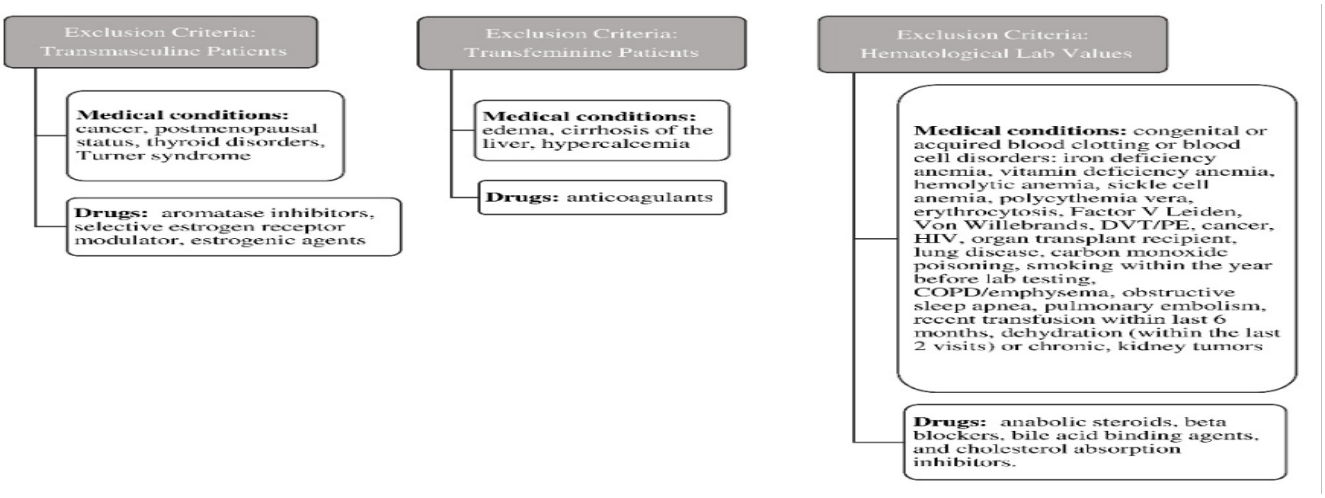


Figure 1: Secondary Exclusions Based on Medical Condition or Prescribed Medication

Secondary exclusion criteria of medical conditions and drugs are illustrated in the context of transmasculine patients, transfeminine patients, and hematological lab values.

Deep venous thrombosis (DVT); Pulmonary embolus (PE); Human immunodeficiency virus (HIV); Chronic obstructive pulmonary disease (COPD)

Cohort Data

Data retrieval was performed through the Oregon Clinical and Translational Research Institute using Cohort Discovery, a web-based tool allowing cohort count data for research purposes. Patients were identified utilizing electronic medical record (EMR) documentation of 1) transgender, nonbinary, or genderqueer identity via a structured sexual orientation and gender identity (SOGI) data field, 2) through sex and gender discordance, or 3) diagnosis of gender dysphoria or other similar diagnosis utilizing International Classification of Diseases (ICD) codes.[34]

The sample of TGD patients was classified as 1) transmasculine (any patient assigned female at birth and taking testosterone-based gender affirming hormone therapy) and 2) transfeminine (any patient assigned male at birth and taking estrogen-based gender affirming hormone therapy). This definition includes patients who identify as nonbinary and are on gender affirming hormone therapy.

Laboratory Analysis

The CBC values included in this study were the initial laboratory collection after at least twelve months of stable GAHT. These venipuncture samples were collected in lavender top ethylenediaminetetraacetic acid (EDTA) tubes with minimum of 1ml of whole blood and were analyzed at no more than 24 hours from time of collection per laboratory protocol. Two labs at OHSU, both accredited by the College of American Pathologists, process CBC samples collected in the outpatient setting. All university labs use Sysmex XN analyzers for CBC's and differentials and use RI derived from the Sysmex literature.

RBC (10^6 /µL), Hct (%), and Hgb (g/dl) are referenced by sex denoted as male and female, and pertinent to this study, adult age strata of 18-150 years. RI include the following: RBC cisgender male reference range of 4.5-6.0 10^6/µL; RBC cisgender female reference range of 4.0-5.2 10^6/µL; Hct cisgender male reference range of 41.0-53.0 %; Hct cisgender female reference range of 36.0-46.0%. Hgb cisgender male reference range of 13.5 -17.5 g/dl; and Hgb cisgender female reference range of 12.0-16.0 g/dl. Laboratory population mean (µ) included: RBC cisgender male value of 5.25 10^6/µL and cisgender female value of 4.6 10^6/µL; Hct cisgender male value of 47% and cisgender female value of 41 %; and Hgb cisgender male value of 15.1 g/dL and cisgender female value of 14.0 g/dL.

Data were analyzed using categorical analysis of transmasculine and transfeminine patients' mean laboratory values and compared against standard RI and population mean values using a single simple Z score.

Results

Initially 796 TGD patients were identified. After exclusion of 600 TGD patients, the sample includ-

ed 139 transmasculine patients for review for RBC, Hct and Hgb; 57 transfeminine patients for RBC and Hgb, and 56 transfeminine patients for Hct.(Figure 2) Transmasculine patient cohort average age was 27.85 years and average BMI 27.39, range of 18.23-46.78. Transfeminine patient cohort average age was 30.79 years, and average BMI 26.39, range 17.05-40.69. Hematological findings in regard to specific GAHT formulation, dose, route of administration including oral, topical, or injection, were not analyzed nor reported as categorical sample size did not achieve statistical significance.

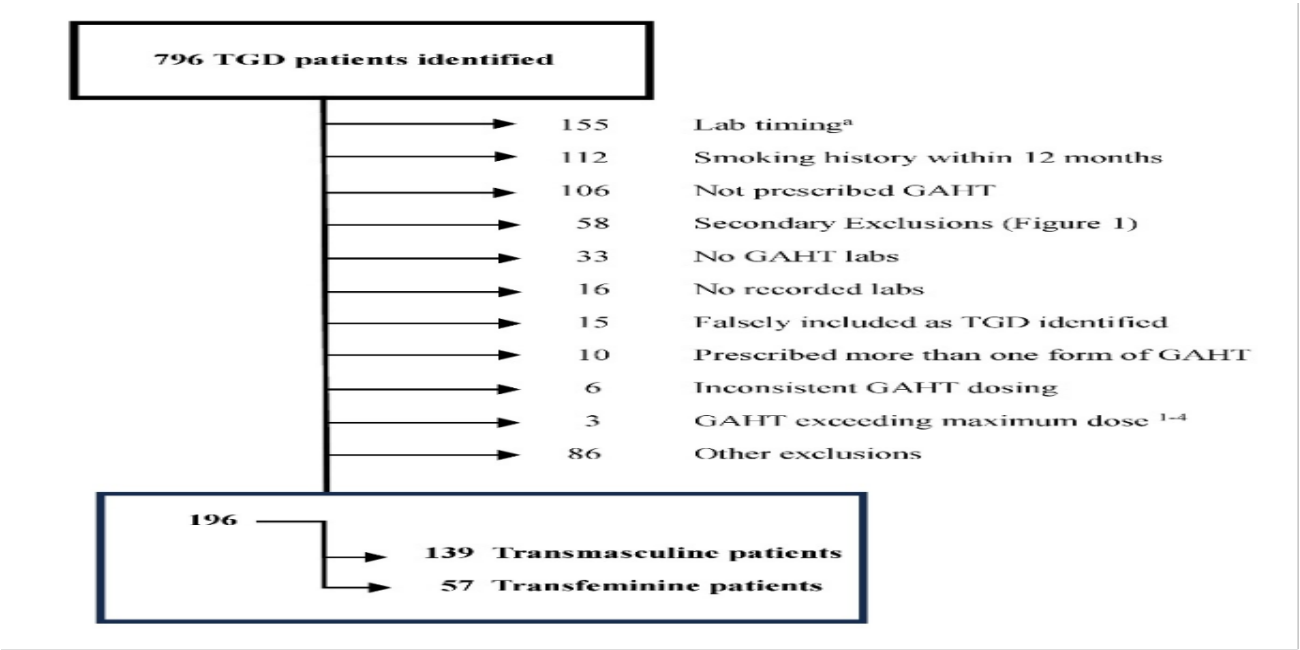


Figure 2: Transgender and Gender Diverse Patient Exclusion Criteria

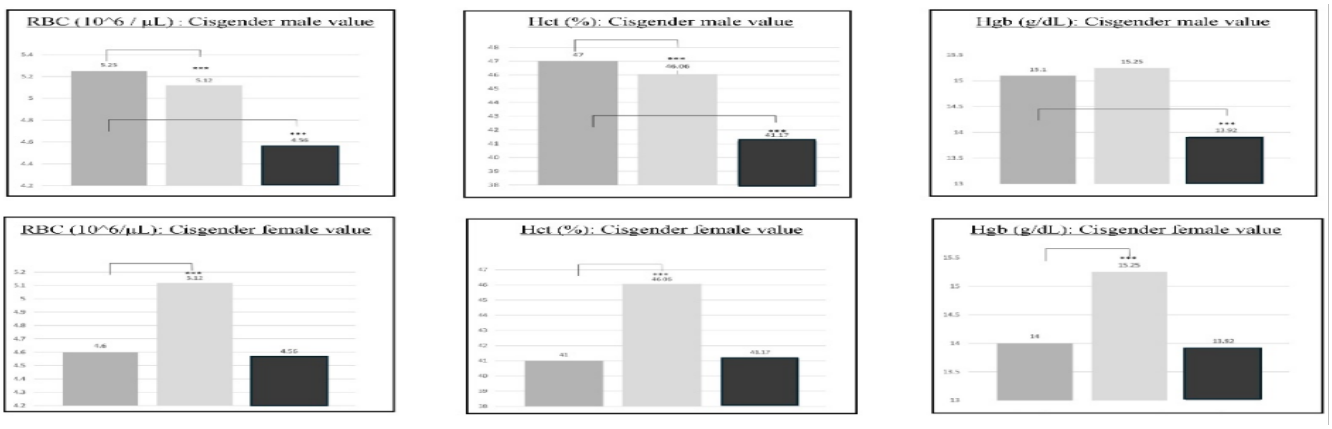
Study cohort as delineated by primary exclusion criteria.

[a] Hormonal labs were not collected within one week of lab value of interest.

Transgender and gender diverse (TGD); Gender affirming hormone therapy (GAHT)

Transfeminine cohort RBC mean of 4.56 10^6/µL correlates to cisgender female population mean value of 4.6 10^6/µL with p value >0.05**.** In contrast, transmasculine cohort RBC mean of 5.12 10^6/µL reveals a statistically significant difference from cisgender male population RBC mean value of 5.2510^6/µL with p-value <0.00001, as well as from cisgender female population RBC mean value of 4.6 10^6/µL with p-value of <0.0001.(Table 1, Figure 3)

Figure 3. Transgender vs Cisgender Red Blood Cell, Hematocrit, and Hemoglobin Values



Statistical significance from cisgender male and cisgender female red blood cell (RBC) and hematocrit (HCT) population mean is demonstrated in the transmasculine study cohort. Significance to cisgender female and cisgender male values are reported as: *** $p < .0005$

Red blood cell (RBC); Hematocrit (Hct); Hemoglobin (Hgb)

Table 1. Red Blood Cell Transgender vs. Cisgender Laboratory Values

RBC: Cisgender Male Lab Values				RBC: Cisgender Female Lab Values			
	Standard Reference Range (10^6/µL)	Transmasculine	Transfeminine		Standard Reference Range (10^6/µL)	Transmasculine	Transfeminine
Population Mean (µ)	5.25			Population Mean (µ)	4.6		
Population Variance (σ2)	0.140625			Population Variance (σ2)	0.09		
Standard Deviation	0.375			Standard Deviation	0.3		
Sample Mean		5.12	4.56	Sample Mean		5.12	4.56
Sample Size		139	57	Sample Size		139	57
Z Score		-4.08714	-13.8917	Z Score		20.4357	-1.0066
p-value		<.00001	<.00001	p-value		<.00001	0.3125

Transmasculine cohort red blood cell (RBC) mean revealed a statistically significant difference from cisgender male as well as cisgender female population mean value (p-values <0.0001). Transfeminine cohort RBC mean correlated to cisgender female lab value (p values >0.05).

Transfeminine cohort Hct mean of 41.17% correlates to cisgender female population mean value of 41% with p value >0.05. Again, in contrast, transmasculine cohort Hct mean of 46.06% reveals a statistically significant difference from cisgender male population mean Hct value of 47% with p-value 0.0022, as well as from cisgender female population mean Hct value of 41% with p-value of <0.0001. (Table 2, Figure 3)

Table 2. Hematocrit Transgender vs. Cisgender Laboratory Values

Hct: Cisgender Male Lab Values				Hct: Cisgender Female Lab Values			
	Standard Reference Range (%)	Transmasculine	Transfeminine		Standard Reference Range (%)	Transmasculine	Transfeminine
Population Mean (µ)	47			Population Mean (µ)	41		
Population Variance (σ2)	9			Population Variance (σ2)	6.25		
Standard Deviation	3			Standard Deviation	2.5		
Sample Mean		46.06	41.17	Sample Mean		46.06	41.17
Sample Size		139	56	Sample Size		139	56
Z Score		-3.69415	-14.54258	Z Score		23.86261	0.50887
p-value		0.00022	<.00001	p-value		<.00001	0.61006

Transmasculine cohort hematocrit (Hct) mean revealed statistically significant difference from cisgender male population mean (p value of <0.0005) as well as cisgender female value (p value of <0.0001). Transfeminine cohort Hct mean correlated to cisgender female value (p value >0.05).

Transfeminine cohort Hgb mean of 13.92 g/dL correlates to cisgender female population mean value of 14 g/dL with p-value >0.05**.** Similarly, transmasculine cohort Hgb mean of 15.25 g/dL also reveals congruence to cisgender male population mean value of 15.1 g/dL with p-value 0.07672.(Table 3, Figure 3)

Table 3. Hemoglobin Transgender vs. Cisgender Laboratory Values

Hgb: Cisgender Male Lab Values				Hgb: Cisgender Female Lab Values			
	Standard Reference Range (g/dL)	Transmasculine	Transfeminine		Standard Reference Range (g/dL)	Transmasculine	Transfeminine
Population Mean (μ)	15.1			Population Mean (μ)	14		
Population Variance (σ2)	1			Population Variance (σ2)	1		
Standard Deviation	1			Standard Deviation	1		
Sample Mean		15.25	13.92	Sample Mean		15.25	13.92
Sample Size		139	57	Sample Size		139	57
Z Score		1.76847	-8.9088	Z Score		14.73728	-0.60399
p-value		0.07672	<.00001	p-value		<.00001	0.5485

Transmasculine cohort hemoglobin (Hgb) mean correlated to cisgender male population mean value (p-value 0.07672). Transfeminine cohort Hgb mean correlated to cisgender female population mean value (p-value >0.05)**.**

Discussion

This retrospective chart review study sought to further the understanding of GAHT impact on hematological values of TGD patients through statistical comparison with cisgender values. Individuals receiving gender-affirming care at an urban university were identified utilizing EMR documentation through SOGI data field, sex and gender discordance, or diagnosis of gender dysphoria or similar diagnosis. The TGD cohort were between the ages of 18-44, non-smokers, on GAHT for at least twelve months, meeting dosing guidelines of leading organizations, and had available laboratory data of interest not altered by excluded medication therapy or health conditions. Transmasculine and transfeminine cohorts were determined by sex assigned at birth and treatment with testosterone or estrogen based GAHT.

From an identified pool of 796 TGD individuals, 139 transmasculine patients with average age of 27.85 and BMI of 27.39, and 57 transfeminine patients with average age of 30.79 years and BMI 26.39 met study criteria and had at least one laboratory value available for analysis. The majority of patients had multiple laboratory values recorded.

Per data analysis, the transfeminine cohort's hematological; RBC, Hct, and Hgb; values align with cisgender female adult laboratory population mean values. Specifically, transfeminine RBC mean of 4.56 10^6/μL, cisgender female reference range of 4.0-5.2 10^6/μL with population mean of 4.6 10^6/μL; Hct mean of 41.17%, cisgender female refer-

ence range of 36.0-46.0% with population mean of 41%; Hgb mean of 13.92 g/dl, cisgender female reference range of 12.0- 16.0 g/dl with population mean of 14 g/dl, revealed congruence. This finding echoes the current practice endorsed by leading organizations and recent research.[1-4,14,16] Likewise, transmasculine values for Hgb with mean of 15.25 g/dl, cisgender male reference range of 12.0-16.0 g/dl with population mean of 15 g/dl, align with the current established cisgender male adult laboratory population mean value and also support this practice.

In contrast, transmasculine cohort RBC mean value revealed statistically significant differences from both established cisgender male and cisgender female adult laboratory defined population mean values. The transmasculine cohort mean RBC of 5.12 10^6/µL, when compared to the cisgender male reference range 4.5-6.0 10^6/µL with population mean of 5.25^6/µL, and to the cisgender female reference range of 4.0-5.2 10^6/µL with population mean of 4.610^6/µL, was found to have p-value of <.00001, revealing incongruence to both cisgender male and cisgender female values. Transmasculine cohort Hct mean of 46.06% reveals a statistically significant difference from cisgender male population mean Hct value of 47%, as well as from cisgender female population mean Hct value of 41% with respective p-values of 0.00022 and <0.0001.

Transmasculine cohort RBC and Hct means were below the cisgender male and above the cisgender female defined adult laboratory population standard means. Implications of this finding bear clinical significance when considering hematological conditions of anemia and polycythemia, as both conditions are based on laboratory values including RBC, Hct, and Hgb. Transmasculine cohort RBC and Hct mean existing between laboratory established adult cisgender male and cisgender female population mean may impact the proper diagnosis and treatment of both conditions. Transmasculine patients may become anemic at higher values than the general cisgender female population and lower values than the general cisgender male population.

This study revealed additional clinical relevance in care of the TGD population. 16 patients had neither hormone nor hematological lab records (2%), suggesting differing provider care styles as well as potential patient facing barriers. While no conclusion can be reached upon this data, it does serve as a reminder to follow leading organizations gender affirming care guidelines when possible. As does the finding of 3 patients excluded for higher dosing than our absolute maximum dosages allowed in the study, based on current guidelines.[1-4]

It is well established that rates of smoking in the TGD community are higher than the national average as two nationally representative studies have shown smoking prevalence ranges from 27.2-35.5%.[20-22] The reported rate of tobacco smoking in the general population of the United States was 14.2% in 2019.[35-39] Data revealed that 112 (or 14%) of TGD patients on GAHT were current tobacco smokers or had a quit date within twelve months of laboratory value collection. Criteria of non-smoker status yielded a considerable number of individuals excluded from the study. The potential impact from this excluded cohort on analysis of hematological values is unknown.

Higher prevalence of tobacco use in the TGD community coincides with higher risk for tobacco related negative health outcomes. Additionally, tobacco smoking has been shown to affect hematological

values, specifically contributing to increases of Hct and Hgb.[39] Studies investigating these effects in the context of concurrent GAHT are limited. Definitively, ongoing studies of more robust data repositories are needed.

Limitations

TGD patients are a difficult-to-obtain subclass of the larger majority, making up only 0.59% of the population in Oregon.[40] For this reason, a prospective specimen collection was not performed. Rather, a retrospective chart review was conducted as this analysis is acceptable for in the guidelines when studying lab values for a subclass of the population that is difficult to obtain.[2]

Limited sample size, retrospective design study which compromised timing and nature of laboratory collections available for analysis, limited type, and depth of statistical analysis of study data, and single institutional practice norms may have affected the strength of this study. Moreover, initial search criteria may not have been sufficient to capture all patients who could have qualified for this study.[41] Cohort difference in average age and BMI also may have affected the summative clinical impact of this study.

Further study interpretation limitations include lack of study cohort pre-GAHT baseline hematological laboratory values nor a comparison of these values to those presented. Also, for purposes of the study, the categories of transmasculine and transfeminine were used – based on sex assigned at birth and type of GAHT. This definition includes individuals who identify as non-binary, genderqueer, or other, and are on GAHT. Future study of expanded cohorts reflecting individuals' identified gender hematological laboratory values could be conducted to reveal the full extent and impact of GAHT.

As GAHT hormonal formulations were variable in agent, dose, and route of administration, further categorization of cohorts, based on each combination of variables, was not performed for the purposes of this study as these multiple cohorts did not reach level of statistical significance. Inconsistent and variable GAHT use also was not parsed. Analysis of hematological laboratory value findings in regard to specific GAHT variable combinations may be considered for future studies.

Conclusion

GAHT alters testosterone concentration, affecting CBC measurements of RBC, Hct and Hgb. Leading organizations providing GAHT guidelines rely on testing of laboratory values to provide best care and avoid complications of treatment for the TGD community. Discordance with gendered hematological laboratory values, foundational to best practices, may contribute to transmasculine individuals' risk of health inequities. Ongoing research studies on hematological laboratory values of the TGD population are suggested. These studies may lead to the prevention of over or under-diagnosis of clinically significant medical conditions of TGD patients and improve the equity and quality of care.

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Authorship confirmation/contribution statement:
Amy L. Wiser, MD, IBCLC: Conceptualization (supporting), Writing — original draft (equal), Writing — review & editing (lead); Leanna M. Knight, MD: Conceptualization (lead), Investigation (lead), Data curation (lead), Formal analysis (lead), Writing — original draft (equal);
Danielle Satow, PA-C: Conceptualization (supporting), Investigation (supporting), Data curation (supporting), Formal analysis (supporting); Carl G. Streed Jr., MD, MPH: Writing — review &

editing (supporting); Frank G. Dowling, MD: Writing — review & editing (supporting); Eric M. Wiser, MD: Writing — review & editing (supporting), Funding acquisition (lead).

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Disclaimer:

The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health, American Heart Association, Doris Duke Charitable Foundation, or their employers.

Presentations:

Dr Knight, Mx Satow, Dr A Wiser presented the poster "Laboratory Value Intervals for Patients on Hormone Therapy who Identify as Transgender" at the 40th GLMA Annual Conference in San Francisco, California in October 2022. Dr Knight also presented the lecture "Caring for Patients Who Identify as Transgender: Lab Values and the Role of Patient Encounter Documentation in Enabling Research and Patient Care" at the University of Rochester School of Medicine Student Research Symposium in Rochester, New York in October 2019.

Abbreviations:

treating transgender and gender diverse (TGD)
gender-affirming hormone therapy (GAHT)
hemoglobin (Hgb)
hematocrit (Hct)
red blood cell count (RBC)
Oregon Health & Science University (OHSU)
electronic medical record (EMR)
structured sexual orientation and gender identity (SOGI)
International Classification of Diseases (ICD)

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