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Hematology reference intervals for transgender adults on stable hormone therapy

Dina N. Greene[a,*], Gabrielle Winston McPherson[a], Jessica Rongitsch[b], Katherine L. Imborek[c], Robert L. Schmidt[d], Robert M. Humble[e], Nicole Nisly[f], Nancy J. Dole[f], Susan K. Dane[g], Janice Frerichs[g], Matthew D. Krasowski[g]

[a] Department of Laboratory Medicine, University of Washington, Seattle, WA, United States
[b] Capitol Hill Medical, Seattle, WA, United States
[c] Department of Family Medicine, University of Iowa Hospitals and Clinics, Iowa City, IA, United States
[d] Department of Pathology, University of Utah, Salt Lake City, UT, United States
[e] Carver College of Medicine, University of Iowa Hospitals and Clinics, Iowa City, IA, United States
[f] Department of Internal Medicine, University of Iowa Hospitals and Clinics, Iowa, IA, United States
[g] Department of Pathology, University of Iowa Hospitals and Clinics, Iowa City, IA, United States

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ABSTRACT

Background: The complete blood count (CBC) is a cornerstone of patient care. Several of the normal values for the components of the CBC differ by sex and, therefore, male-specific and female-specific reference intervals are required to interpret these laboratory results. Transgender individuals are often prescribed hormone therapy to affirm their gender, with resulting serum hormone concentrations similar to those of cisgender individuals. Gender-specific reference intervals for transgender men and women have not been established for any laboratory measurements, including hematology. We established clinically relevant hematological reference intervals for transgender individuals receiving stable hormone therapy.

Methods: Healthy transgender individuals prescribed testosterone (n = 79) or estrogen (n = 93) for ≥12 months were recruited from internal medicine and primary care clinics that specialize in transgender medical care. Concentrations for hemoglobin, hematocrit, MCV, MCHC, and RDWCV, as well as counts for red cells, white cells, and platelets, were evaluated. Results were interpreted in reference to the overall distribution of values and relative to serum estradiol and total testosterone concentrations. Calculated reference intervals were compared to established cisgender reference intervals.

Results: Regardless of serum hormone concentration, individuals prescribed testosterone or estrogen had hematology parameters that were not clinically different from cisgender males and females, respectively.

Conclusion: The hematology parameters for transgender men and women receiving stable hormone therapy should be evaluated against the cisgender male and cisgender female reference ranges, respectively and does not require concurrent sex hormone analysis. Care providers can utilize this observation to aid in interpretation of hematology laboratory values for transgender people.

1. Introduction

Transgender people experience incongruence between their gender identity and birth sex [1]. Transgender women identify as female, but were assigned male at birth; transgender men identify as male, but were assigned female at birth. There are also people who were assigned either male or female at birth, but identify on a gender spectrum as something other than male or female (often called non-binary, genderqueer or third gender). A cisgender person is someone whose sex assigned at birth is congruent with their gender identity. Standards of care indicate that optimal psychosocial health is achieved by supporting a transgender person's gender and if gender affirming medical interventions are desired, hormone therapy is fundamental [2,3]. Hormone therapy for transgender women and some gender non-binary people includes estrogen administration, often combined with androgen suppressing agents such as spironolactone; hormone therapy for transgender men and some gender non-binary people includes testosterone administration. Hormone dose, formulation, and mode of

* Corresponding author.
E-mail address: dina.n.greene@kp.org (D.N. Greene).

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Table 1
Demographics of cohorts receiving estrogen and testosterone gender affirming hormone therapy.

	Testosterone cohort (transgender men)	Estrogen cohort (transgender women)
Cases (n)	79	93
Average age in years (range)	28.8 (19–55)	35.1 (18–69)
Mode of hormone administration	Injection (n = 73) Topical (n = 5) Topical and injection (n = 1)	Oral (n = 54) Injection (n = 30) Topical (n = 9)
Average hormone dose (SD)	Injection: 73 mg/week (13.5) Transdermal: 66.7 mg/d (28.9)	Oral: 5.3 mg/d (1.3) Injection: 7.4 mg/week (4.1) Transdermal: 0.4 mg/week (0)
Other gender affirming medications	Anastrozole (n = 1)	Spironolactone (n = 39) Progesterone (n = 12) Finasteride (n = 3)

Table 2
Serum total testosterone and estrogen concentrations of cohorts receiving estrogen and testosterone gender affirming hormone therapy. Cisgender adult reference intervals are sex, age, and/or reproductive phase specific, as follows. Testosterone: cisgender women ≤0.8 ng/ml; cisgender men ages 17–19 y: 2.5–10 ng/ml, ages 20–29 y: 2.2–7.8 ng/ml, ages 30–39 y: 2.0–7.3 ng/ml, ages 40–49 y: 1.8–6.8 ng/ml, ages 50–59 y: 1.7–6.3 ng/ml. Estrogen: cisgender women mid-follicular < 122 pg/ml, mid-luteal 49–291 pg/ml, peri-ovulatory 95–433 pg/ml, post-menopausal < 41 pg/ml; cisgender men < 48 pg/ml.

Analyte		Cohort	
		Testosterone (n = 79)	Estrogen (n = 93)
Testosterone (ng/ml)	Undetectable	1	24
	Median	4.6	0.4
	Range	0.3–10.5	0.3–5.9
	IQR	3.2–6.2	0.4–0.7
Estradiol (pg/ml)	Undetectable	32	2
	Median	51	207
	Range	31–353	32–1536
	IQR	37–63	114–265

administration differs based on patient and provider preferences as well as the goals of the patient, but desired physiological effects are usually achieved when the serum sex hormone concentration is similar to that of the affirmed gender [2].

Sex hormones influence the rate of erythropoiesis, leading to sex differences in several complete blood count (CBC) measurements [4]. These differences, in which males have relatively higher mean hemoglobin, hematocrit, and red cells compared to females, are evolutionarily conserved throughout mammals and are likely governed by modulation of the erythropoietin-renal circuit [4]. The physiological reasoning for this difference is not well understood, but the variation between sexes must be accounted for when clinically evaluating basic hematology parameters. Reporting of hematology results by the laboratory will include sex-specific reference intervals for hemoglobin, hematocrit, and red cell count [5,6].

Androgen therapies alter hemoglobin, hematocrit and red cell count, which has been demonstrated in a variety of contexts including cisgender men receiving testosterone for hypogonadism or undergoing androgen suppression for prostate cancer [7–9]. The role of estrogens in erythropoiesis is not well established, and is complicated by the loss of blood that occurs during menstruation and the effects that estrogen therapy has on the menstrual cycle [10,11]. The literature on the impact of estrogen is limited, but studies suggest that estrogens do not have a strong effect on erythropoiesis [12,13]. All gender affirming hormone therapies are designed to alter testosterone concentration, which can impact the concentration of hemoglobin, hematocrit, and red cells [5]. More specifically, these CBC measurements will decrease for transgender individuals receiving estrogen (and often additionally androgen suppressive therapies) and increase for those receiving testosterone. Retrospective analyses of transgender people who choose to transition with hormones have consistently demonstrated this hematological shift [14,15].

Reference intervals from a cohort of healthy transgender individuals have not been established [5]. Laboratory regulatory guidelines stress that reference intervals should be appropriate for the population being tested, particularly if there are known physiological differences relevant to the population. At present, no reference intervals are available to guide the interpretation of laboratory results for transgender people. This is, unfortunately, not surprising since transgender patients have historically been disenfranchised from the health-care system [1]

2. Methods

2.1. Patient recruitment, questionnaires, and sample collection

Study participants were prospectively recruited from lesbian, gay, bisexual, transgender, and queer (LGBTQ)-oriented primary care and internal medicine clinics in Seattle, Washington and Iowa City, Iowa between November 1, 2017 and July 1, 2018. Informed consent was obtained for venipuncture collection of whole blood (5 ml into a K2-EDTA tube; 5 ml into gold top serum separator tube). Basic demographic information, gender transition history, and hormonal therapy (dose/mode of administration/duration of therapy) were collected using a standardized questionnaire. Study numbers were used in place of participant names; no patient identifiers were retained.

Participants were at least 18 y, self-identified as transgender or “non-binary”, had been prescribed gender-affirming hormone therapy for at least one year, and consented to collection of relevant samples/information. The timing of CBC changes in response to therapy is not well established. We chose 1 year because multiple retrospective studies that have looked at changes in hemoglobin/hematocrit after initiation in hormones show that changes reach a steady-state at least by 12 months and possibly earlier [15–17]. Exclusion criteria included past history of diabetes, severe cardiovascular event (e.g., myocardial infarction or stroke), clotting or blood cell disorders (e.g., sickle cell anemia, deep venous thrombosis), HIV infection, obstructive sleep apnea, current pregnancy, active cigarette use, or current body mass index (BMI) > 30. The Western Institutional Review Board (IRB) approved the protocol for samples collected in Seattle. The University of Iowa IRB approved the protocol for samples collected in Iowa.

2.2. Sample analysis

Hematology parameters were analyzed within 8 h of blood collection using the Sysmex XN 9000 hematology instrument at either the University of Iowa or the University of Washington core laboratory. Both laboratories follow standard quality practices and are accredited through the College of American Pathologists. Measured analytes included hemoglobin(Hb), hematocrit(Hct), red cell count (RBC), Mean cell volume (MCV), Mean cell hemoglobin concentration (MCHC), Red cell distribution width – coefficient of variation (RDWCV), platelet count (PLT), and white cell count (WCC). Reference intervals for these

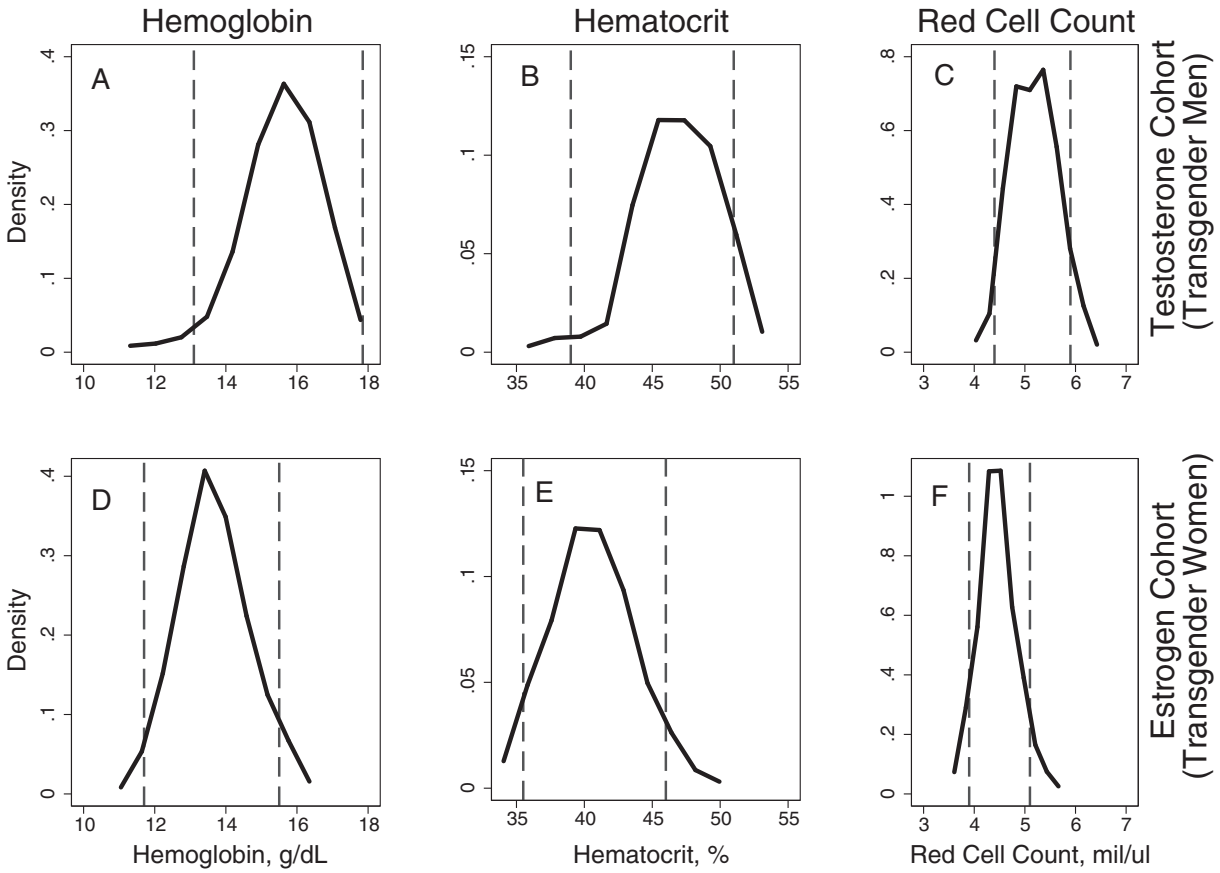

Fig. 1. Distribution of hemoglobin (panels A and D), hematocrit (panels B and E), and red cell count (panels C and F) in the testosterone and estrogen cohorts. The dashed lines indicate the reference intervals for cisgender individuals.

hematology parameters are listed in the supporting information.

Estradiol and total testosterone were measured either within 8 h of serum collection (Seattle cohort) or frozen immediately, stored at −80° and measured within 3 months of collection (Iowa City cohort) using the DxI 800 competitive immunoassays (Beckman Coulter, Brea, CA), which are linear from 30 to 4800 pg/ml and 0.3–16 ng/ml, respectively.

2.3. Statistical analysis

Statistical analyses were performed using Stata 14. Reference intervals for cisgender individuals were obtained by taking the average of the reference limits (2.5% and 97.5% centiles) used at the University of Washington and University of Iowa (supporting information). Distribution plots were created by kernel density estimation using the Epanechnikov kernel as implemented in the Stata 14 command, *kdensity*. Reference limits and confidence intervals for testosterone and estrogen cohorts (transgender individuals) were determined using bootstrapping with 1000 repetitions [18]. Differences in means were evaluated using *t*-tests. Results were considered significant when $p < .01$. If the cisgender reference limit fell outside of the 95% CI derived from transgender cohorts, reference change values (RCVs) were used to evaluate if the difference was clinically significant. An RCV is the percent difference required between two measurements to indicate clinical significance [17]. RCVs were calculated using the eq. $RCV = 2^{1/2} * Z * (CV_A^2 + CV_I^2)^{1/2}$ where Z = 2.35 and CV is the coefficient of variation for the analytical/instrumentation (A) and individual (I) [19]. The input CVs were previously published [20,21]. Results were considered clinically significant if the RCV was greater than the observed difference between the mean values of the reference intervals. A list of the calculated RCVs can be found in the supporting information.

3. Results

3.1. Study participants

A total of 172 transgender people participated in this study, 79 transgender men/non-binary individuals receiving testosterone (testosterone cohort) and 93 transgender women/non-binary individuals receiving estrogen (estrogen cohort, Table 1).

For the testosterone cohort, the average age was 28.8 y (range 19–55; SD 7.75) and the average number of years prescribed gender affirming hormones was 4.8 (range 1–20.5; SD 4.15). The majority (92.4%, n = 73) received intramuscular or subcutaneous testosterone. For the estrogen cohort, the mean age was 35.1 y (range 18–69; SD 11.7) and the mean number of years prescribed gender affirming hormones was 3.5 (range 1–26; SD 3.65). The majority (58.1%, n = 54) received estrogen orally, but many (32.2%, n = 30) were administered estradiol valerate intramuscularly or subcutaneously. Androgen suppressive medications (spironolactone or finasteride) were additionally used in 42 (45.2%) of the estrogen cohort. Further details are in Table 1.

3.2. Sex hormone concentrations

The median serum total testosterone concentration for those receiving testosterone was 4.6 ng/ml (Table 2). The estrogen concentrations in this cohort were undetectable (< 30 pg/ml) in 36.7% (n = 32) of the participants. For those with detectable estradiol (n = 51) the median concentration was 51 pg/ml.

The median estradiol concentration for those receiving estrogen was 207 pg/ml (Table 2). The total testosterone concentrations in the estrogen cohort were undetectable (< 0.3 ng/ml) in 24.7% (n = 24) of

Table 3
Comparison of reference intervals for cisgender and transgender individuals. Point estimates and confidence intervals for the 2.5% and 97.5% centiles were determined by bootstrapping. Values in red had reference limits for the cisgender cohorts that did not fall within the 95% CI of those derived from the transgender cohorts. RCV analysis showed that only the lower limit of RDWCV showed a statistical and potentially clinical difference.

Cohort	Parameter	Transgender Reference Intervals				Cisgender Reference Intervals	
		Lower 2.5%		Upper 97.5%		Mean	
		Mean	95% CI	Mean	95% CI	Lower	Upper
Testosterone	WBC (K/μl)	3.8	3.5 - 4.2	12.8	10.3 - 15.3	4	10.3
(Transgender Men)	RBC (M/μl)	4.3	4.1 - 4.6	6.0	5.8 - 6.3	4.5	5.9
	HB (g/dl)	12.8	11.3 - 14.3	17.4	17.2 - 17.6	13.1	17.9
	HCT (%)	39	35 - 43	51	50 - 52	39	51
	MCV (fL)	79	70 - 88	97	95 - 99	81.5	98.5
	MCHC (fL)	31.5	31.1 - 31.8	35.0	34.4 - 35.6	32.1	36.3
	PLT (K/μl)	181	166 - 196	415	365 - 465	150	400
	RDWCV (%)	11.9	11.7 - 12.1	15.2	13.3 - 17.1	10.3	14.5
Estrogen	WBC (K/μl)	4.4	3.6 - 5.2	12.8	11.0 - 14.5	4	10.3
(Transgender Women)	RBC (M/μl)	3.7	3.6 - 3.9	5.3	5.1 - 5.6	3.9	5.1
	HB (g/dl)	11.6	11.0 - 12.2	15.7	15.4 - 16.0	11.7	15.5
	HCT (%)	35.0	34.0 - 36.0	47.0	45.2 - 48.8	35.5	46
	MCV (fL)	83.4	82.3 - 84.4	98.6	95.9 - 101.4	81.5	98.5
	MCHC (fL)	31.5	31.1 - 31.9	35.9	35.2 - 36.6	32.1	36.3
	PLT (K/μl)	150	128 - 171	443	391 - 495	150	400
	RDWCV (%)	11.5	11.3 - 11.7	14.7	14.2 - 15.2	10.3	14.5

the participants. For those where testosterone was detectable (n = 69) the median concentration was 0.4 ng/ml.

3.3. Hematology differences between the testosterone and estrogen cohorts

The mean hemoglobin, hematocrit and red cell count was significantly higher in the testosterone cohort than in the estrogen cohort (Fig. 1 and supporting information, $p < .0005$). Significant differences were also seen in the mean concentration of WBC count (estrogen cohort $0.9 \times 10^3/mm^3$ higher relative to the testosterone cohort; $p = .002$) and MCHC (estrogen cohort 0.4 g/dl higher relative to the testosterone cohort; $p = .008$) between the estrogen and testosterone cohorts (supporting information). There was no difference detected between cohorts in the mean concentrations of MCV, platelet count, or RDWCV.

3.4. Hematology reference intervals in the testosterone and estrogen cohorts

For the hematology parameters that usually differ between cisgender men and women (hemoglobin, hematocrit, red cell count), the estrogen cohort had values similar to cisgender women and the testosterone cohort had values similar to cisgender men (Fig. 1 and Table 3). For example, a common reference interval used for hemoglobin in cisgender women is 11.5–15.5 mg/dl (supporting information). In the estrogen cohort the calculated reference interval was 11.6–15.7 mg/dl. Similarly, a hemoglobin reference interval commonly used for cisgender men is 13.0–18.0 mg/dl (supporting information). In the testosterone cohort the calculated reference interval was 12.8–17.4 mg/dl. For all other hematology measurements, the confidence intervals for the reference limits of the transgender population usually covered the point estimate for the cisgender population (Table 3). The exceptions were for hemoglobin, MCHC, platelet count, and RDWCV in the testosterone cohort and WBC, MCV, and RDWCV in the estrogen cohort. Comparison of the differences in these reference limits to the RCV for each measurement indicated that only the lower limit of RDWCV maintained clinical significance. All other reference limits differed by less than the RCV.

3.5. Sex hormone concentration and hemoglobin

The average hemoglobin concentration in the testosterone cohort was 2.0 g/dl higher than the estrogen cohort ($p < .0005$). The hemoglobin concentration increased with testosterone but the relationship was nonlinear and plateaued at concentrations of testosterone generally achieved at steady state (Figs. 2 and 3). The hemoglobin concentration was unrelated to the testosterone concentration in the testosterone cohort in which 90% of the testosterone values were between 2 and 6 ng/ml ($p = .42$), indicating that the majority of

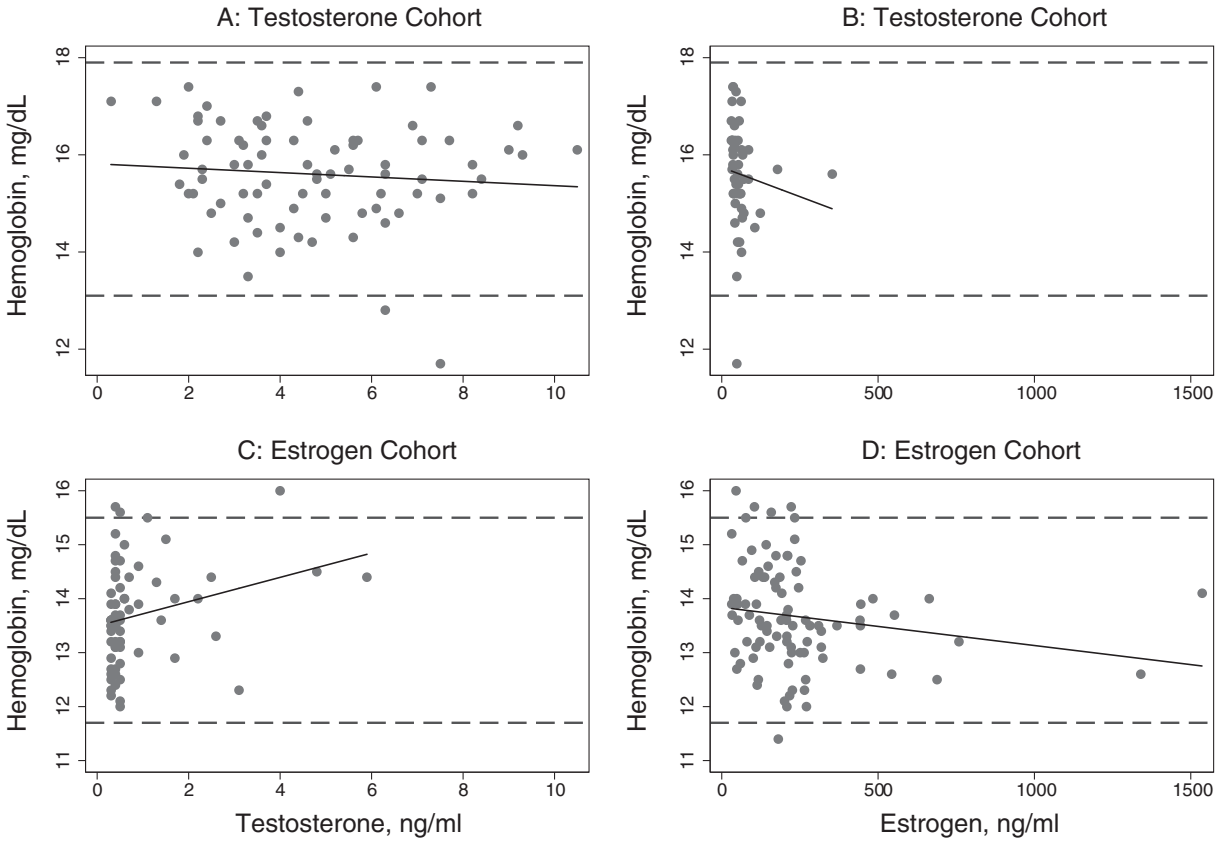

Fig. 2. Linear regression of hemoglobin concentration as a function of total testosterone (panels A and C) and estradiol (panels B and D) concentrations. Dashed lines indicate the hemoglobin reference intervals for cisgender individuals.

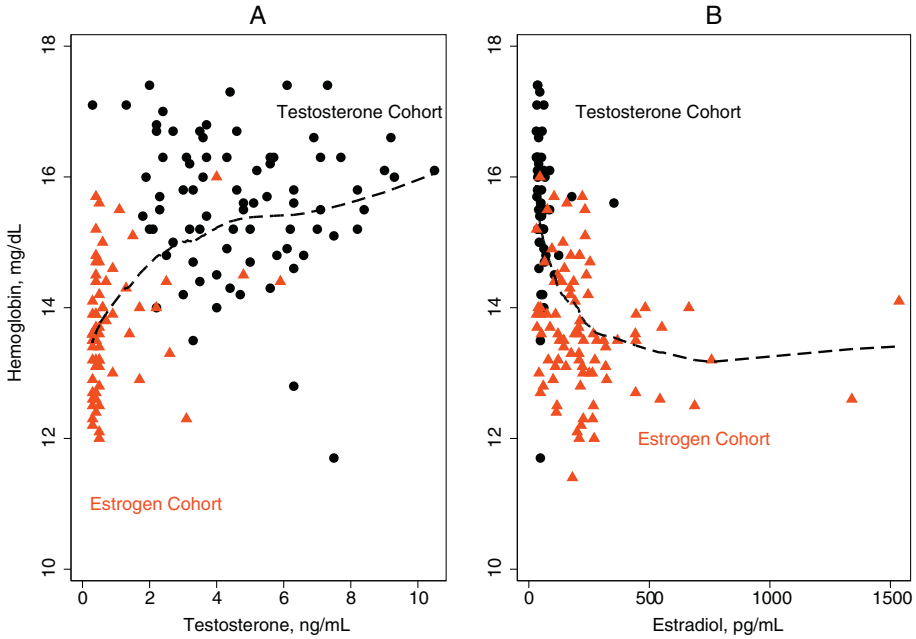

Fig. 3. Lowest smoothing regression of hemoglobin concentration as a function of total testosterone (panel A) and estradiol (panel B) concentrations within the cohorts. Hemoglobin concentration increases with total testosterone concentration, but the effect is nonlinear.

transgender men on stable hormone therapy have reached steady state and therefore minor fluxes in testosterone will not have a transient effect on erythropoiesis. In the estrogen cohort, 90% of the testosterone values were between 0.1 and 2.6 ng/ml and, within this cohort, there was a significant linear relationship between testosterone and hemoglobin (0.2 g/dl hemoglobin per ng/ml testosterone, p = .04).

4. Discussion

Here we present data from the first prospective study evaluating

hematology laboratory values in healthy transgender adults on stable hormone therapy. Our study provides hematological reference intervals, which were not previously available for this population. Our study shows that reference intervals derived from cisgender cohorts are applicable to transgender individuals as long as they are receiving stable hormone therapy. The main hematology parameters that are known to differ between cisgender men and women are hematocrit, hemoglobin, and red cell count. Our study confirms that these are the primary parameters that experience gender differences in transgender adults on stable hormone therapy. A difference was observed between transgender and cisgender ranges for RDWCV, however, the difference was unlikely to be clinically significant. This information will be useful to healthcare providers who care for transgender patients.

Previous data evaluating cisgender men and women has indicated that testosterone influences hematologic parameters [7–9,22,23]. Additionally, retrospective analysis of transgender populations has indicated that some hematology parameters will increase with testosterone and decrease with estrogen supplementation [14,15]. The data presented here support these observations, while also deriving ranges for what can be expected in normal, healthy individuals who administer sex-hormone therapy. Our calculations suggest equivalence within gender when evaluating hematology parameters. Meaning, regardless if a person is cisgender, transgender or non-binary, if their sex hormone profile is consistent with the standardized male or female concentrations, then the male or female hematology reference intervals are appropriate, respectively.

Hematology reference intervals are different between transgender men or non-binary people on masculinizing treatment and transgender women or non-binary people on feminizing treatment, but sex hormone concentration alone is not enough to predict hemoglobin concentration. Our data supports that hemoglobin concentration can be evaluated independent of the total testosterone concentration. For example, the transgender men in the lowest testosterone quartile in the present study still had hemoglobin concentrations within the standardized cisgender male reference interval. Similarly, some transgender women maintain somewhat elevated testosterone concentrations, but their hematology parameters still paralleled standardized cisgender female reference intervals. This is likely because of the fluctuations in hormone concentrations between doses, and also due to individual physiologic variability in response to hormones.

Currently, many electronic medical records (EMRs) have only a single field for gender [24]. This is traditionally the birth sex unless local laws and institutional policy allow the patient to officially change gender in the EMR. An EMR working group from the World Professional Association for Transgender Health has advocated that basic demographic variables of an EMR include gender identity (affirmed gender), preferred name, and pronoun preference by the patient [23]. As EMRs add functionality to document affirmed gender, the appropriate reference interval for hemoglobin, hematocrit, and red cell count should use affirmed gender rather than birth sex. One practical barrier is, however, is that the transgender population has historically faced discrimination and disenfranchisement from society and the health care system. Some transgender patients may therefore be reluctant to disclose gender identity.

For medical institutions currently using affirmed gender as the single field entry for sex/gender, these data indicate that the “correct” reference interval is already adopted for basic hematologic laboratory tests. In contrast, if the applied hematology reference intervals for the laboratory results of transgender people are specific to birth sex or a legal sex that does not align with the patient's hormonal milieu (as is currently the most common practice), three major consequences can occur. First, in transgender or non-binary people receiving testosterone treatment, hemoglobin, hematocrit or red cell counts within the standardized female reference interval, but below the lower end of the standardized male reference range may be erroneously interpreted as normal, when in fact anemia may be present. This can lead to delayed diagnosis, which may be especially problematic for progressive conditions such as gastrointestinal blood loss or vitamin B_{12} deficiency. Second, in transgender or non-binary people on feminizing hormone treatment (often including androgen suppression), providers may overdiagnose anemia in patients whose hematologic parameters move below the standardized male reference interval as a result of hormone therapy. Third, for individuals receiving masculinizing hormone treatment, providers may become concerned for polycythemia in patients whose hemoglobin or hematocrit exceeds the standardized female reference range. This may lead to a provider decreasing or discontinuing testosterone therapy, thereby ineffectively treating a patient's gender dysphoria because of an unwarranted fear of side effects. Additionally, the last two scenarios are problematic because they can potentially lead to unnecessary referrals and treatment, which is a stress on healthcare resources.

These data enable laboratory directors at any hospital to implement data-supported hematology reference intervals for transgender people. Ideally, laboratories should determine reference intervals for transgender patients; however, this will often be impractical. Our study shows that gender-specific reference intervals provide a very good approximation for CBC measurements. The detected differences are small and are unlikely to be clinically significant. Thus, current sex-specific reference intervals are “fit for use” and can be used to interpret hematology results for transgender people using their affirmed gender.

In addition, this study has the potential to motivate future studies with larger number of subjects that can help answer more subtle questions, such as impact of route of administration of hormones and the time course by which hematology parameters reach steady state during hormone therapy.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cca.2019.02.011.

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