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Association of Surgical Risk With Exogenous Hormone Use in Transgender Patients
A Systematic Review

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IMPORTANCE A growing number of transgender patients are receiving gender-affirming hormone treatments. It is unclear whether the evidence supports the current practice of routinely discontinuing these hormones prior to surgery.

OBJECTIVE To determine how medications used in cross-sex hormone treatment (CSHT) affect perioperative risk.

EVIDENCE REVIEW A series of searches were carried out in PubMed and Excerpta Medica Database to identify articles using each of the terms *testosterone*, *estrogen*, *estradiol*, *oral contraceptive*, *spironolactone*, *cyproterone acetate*, *finasteride*, *dutasteride*, *leuprolide*, *goserelin*, and *histrelin*, in combination with the terms *surgery*, *perioperative*, *thrombosis*, *thromboembolism*, and *operative*. The search was not restricted to perioperative outcomes in transgender populations because many surgeons routinely discontinue hormone use prior to surgery in this population, which makes it impossible to study how hormones affect outcomes. Additional sources were also identified from the texts of reviewed articles. Articles were excluded if they were animal studies or case reports, did not explicitly discuss surgical outcomes, or were restricted to removal of hormonally sensitive tissues.

FINDINGS Eighteen articles addressing perioperative outcomes were identified by this systematic review, including 1 on CSHT, 12 on estrogens and progesterones, 1 on testosterone, and 4 on spironolactone and antiandrogens. Data were limited, but use of exogenous testosterone was not found to be associated with an increased risk of venous thromboembolism or other complications during surgery. Moderate evidence suggests that spironolactone is not associated with negative surgical outcomes. The data linking estrogen use and thrombosis is inconsistent in the perioperative period and does not address the types of estrogens most often used for CSHT.

CONCLUSIONS AND RELEVANCE Current evidence does not support routine discontinuation of all CSHT prior to surgery, particularly given the lack of information on risks associated with resuming these medications after they have been stopped. Evidence suggests there is no need to discontinue either testosterone or spironolactone, although their association with perioperative outcome quality has not been studied in depth. Most of the evidence that supports discontinuation of estrogen prior to surgery is based on oral estrogen regimens that are not typically used in transgender patients, and even with those formulations, there are conflicting reports on perioperative risk. Further research is needed to determine the safety of continuing hormone treatment and elucidate risks of short-term discontinuation.

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Studies estimate that there are likely to be more than 1 million transgender and gender-dysphoric individuals living in the United States alone.[1] Individuals with gender dysphoria experience intense discomfort owing to identifying as a gender that is different than how they are perceived by society and/or a gender different than that commonly associated with their physiological sex. Many individuals with gender dysphoria undergo medical and/or surgical treatments to address various sources of somatic discomfort (ie, dysphoria). In most but not all cases, the initial medical treatment involves the use of cross-sex hormone therapy (CSHT) and/or medications that block the effects of endogenous hormones (Table 1).[2,4]

Transgender and gender-dysphoric individuals need the same range of surgical care as the majority cisgender population (defined as those whose gender identity is aligned with their assigned sex at birth), and the medications used for CSHT have the potential to affect perioperative risk. In addition, transgender and gender-dysphoric individuals often seek out gender-affirming surgical procedures to help them align their appearance with their gender identity; these procedures can provide significant psychological benefit.[5] Such gender-affirming surgeries usually but not always take place after a patient has started CSHT. This is both reflective of patient choice and required by the World Professional Association of Transgender Health standards of care.[4] As such, the perioperative risk of ongoing CSHT must be taken into consideration.

There is very limited research on perioperative morbidity associated with CSHT in transgender individuals, although the overall morbidity and mortality is considered to be minimal.[6-8] The primary CSHT health concern relevant to surgical care is the potentially elevated risk of VTE from estrogen use in transgender women, and the subsequent risk of pulmonary embolism, myocardial infarction, and stroke.[6,9,10] Outside of the perioperative period, the proportion of the CSHT-treated transfeminine population experiencing varied thromboembolic events varies significantly across studies, ranging from approximately 0% to 6%.[6,9-12]

Increased rates of CSHT-associated thrombosis and cardiovascular mortality have not been observed in transgender men outside the context of surgery.[6,8,9,12] There have been reports[6,13] of unfavorable lipid profile changes with the use of CSHT in transgender men, but these changes remain within the normal range and may reflect a sexually dimorphic redistribution of fat from subcutaneous to visceral locations.

Because of well-publicized associations between oral contraceptive pills, hormone therapy, and venous thromboembolism (VTE), many surgeons routinely recommend that transgender patients discontinue CSHT for a month or longer before a scheduled operation.[9,14] However, stopping CSHT can increase dysphoria; this is particularly true for transgender women, who may fear and/or experience some revirilization in addition to unpleasant physiological symptoms, such as hot flashes and mood disruption.[3,15,16] As such, it is important to assess the ways ongoing use of hormones and associated medications may affect surgical risks and outcomes. Only then can policies be formulated to balance any potential surgical risks associated with hormone treatment with the emotional and other risks associated with discontinuing it.[2,3]

Previously published reviews of the literature through 2000 all state that the evidence is inconclusive on whether it is appropriate to discontinue oral contraceptives or hormone therapy prior to a scheduled surgery and generally acknowledge that other considerations may play a role in decision making.[17-19] Since 2000, results of studies examining the safety of more modern estrogens formulations in the perioperative period remain inconsistent. This systematic review summarizes current data on surgical risk associated with medications commonly used for CSHT, identifies areas for future research, and provides evidence-based recommendations for CSHT management in transgender patients seeking surgical care.

Key Points

Question Is it necessary for transgender patients to discontinue exogenous hormone use before surgical procedures?

Findings There has been insufficient research on how cross-sex hormone therapy affects surgical outcomes. Limited evidence suggests that exogenous testosterone is not associated with complications in the perioperative period, and spironolactone has not been associated with poor surgical outcomes; although oral estrogens have been associated with an increased risk of thrombosis, evidence is inconclusive about whether it is necessary to stop the use of commonly prescribed transdermal estrogens before surgery.

Meaning There is insufficient evidence to support routine discontinuation of exogenous hormones in transgender patients seeking surgery.

Table 1. Common Hormone Regimens Used in Transgender Adolescents and Adults[2,3]

Population	Gonadotropin-Releasing Hormone Agonists or Anti-Androgens	Steroid Hormones
Transgender adolescents[a]	Parenteral leuprolide acetate, parenteral goserelin, or a subcutaneous histrelin implant	NA
Transgender men	NA	Transdermal testosterone gel, cream, or patch; subcutaneous or intramuscular testosterone (eg, testosterone enanthate, cypionate, or undecanoate)
Transgender women	Spironolactone,[b] cypterone acetate,[b,c] finasteride,[d] and dutasteride[d]	Oral 17β estradiol; transdermal 17β estradiol patch or gel; parenteral estradiol valerate or cypionate

Abbreviation: NA, not applicable.

[a] Data collected prior to initiating cross-sex hormone treatment. Once an adolescent has initiated such treatment, they are prescribed the same medications that are used for transgender adults.

[b] This medication would not be used if an orchiectomy has been performed.

[c] Not available in the United States.

Methods

Observational and interventional studies on how the hormones (eg, estrogen, testosterone) and hormone agonists (eg, spironolactone, antiandrogens) used in CSHT affect surgical outcomes were eligible for inclusion. Studies were identified via electronic database searches and by review of previous literature addressing this topic. The search strategy was discussed by all authors and was implementing using each of the terms *testosterone*, *estrogen*, *estradiol*, *oral contraceptive*, *spironolactone*, *cyproterone acetate*,

finasteride, *dutasteride*, *leuprolide*, *goserelin*, and *histrelin* in combination with each of the additional terms *surgery*, *perioperative*, *thrombosis*, *thromboembolism*, and *operative*. These searches were applied to PubMed and the Excerpta Medica Database (Embase) from inception through April 2018. The search was not restricted to perioperative outcomes in transgender populations because many surgeons routinely discontinue hormone use prior to surgery in this population, which makes it impossible to study how hormones affect outcomes.

Owing to the extraordinarily high number of articles identified by the original search (n = 12 689 through PubMed and 3210 through Embase), first titles and then abstracts were screened by a single author (E.R.B.). Additional articles were also sought from the text of studies found through these searches, but no articles were identified through this method. Remaining articles were then screened for full review and data abstraction by 2 authors (E.R.B. and O.G.).

A data abstraction table was created to standardize the protocol for review. The following data were extracted from each article included in the systematic review: citation, date, type of study (eg, case-control, cohort, randomized clinical trial), whether the authors stated the study had been reviewed by an institutional review board, the question(s) asked by the study, methods, limitations, level of evidence,[20] size of study population, description of study population, type of hormones examined, type of surgery, examined outcomes, and study conclusions. Owing to heterogeneity in the included studies in both design and outcome measures, it was not possible to define a consistent summary measure to review. Study quality was assessed using the Grading of Recommendations Assessment, Development and Evaluation criteria[21] by 2 authors (O.G. and E.R.B.), and any differences in assessment were resolved through review by the third author (A.H.T.) and follow-up discussion. Studies were excluded from the systematic review for the following reasons: (1) the study design was a case report or case series (owing to concerns about the inability to assess risk from isolated reported events), (2) the study population was not human, (3) the study examined the behavior of hormonally responsive tissue (ie, using gonadotropin-releasing hormone agonists to shrink prostate tissue prior to surgery), or (4) the study did not report specifically on surgical outcomes.

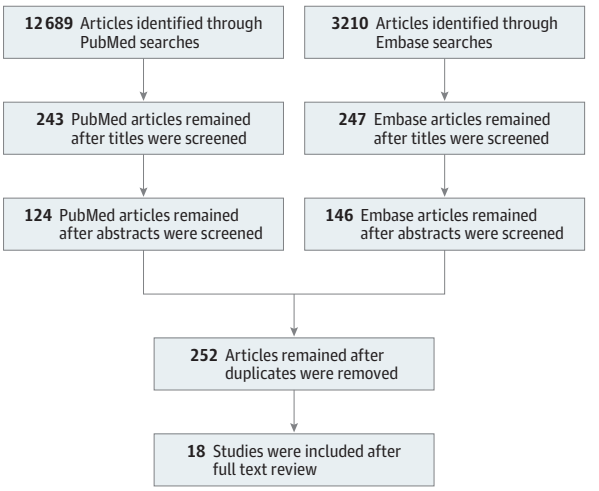
Results

A total of 18 articles discussing the impact of drugs used in CSHT on perioperative risk were included in the final systematic review (**Figure**). One article studied CSHT,[22] 12 estrogens and progesterones,[23-34] 1 testosterone,[35] and 4 spironolactone and antiestrogens.[36-39] One of the articles was a placebo-controlled randomized clinical trial,[38] 11 were cohort studies,[22,25-29,34-37,39] and 6 were case-control studies[23,24,30-33] (**Table 2**).

Perioperative Morbidity Associated With CSHT in Transgender Individuals

One prospective cohort study[22] of 88 transgender men who were taking testosterone did find that these individuals were more likely to experience hematoma after chest surgery than 12 individuals who were not taking testosterone at the time of surgery, but the difference was not statistically significant (Table 2). No studies were identified that examined perioperative morbidity in transgender patients associated with any of the other medications used in CSHT or the hormones used in puberty blockers for transgender youth.

Figure. Systematic Review Process



Perioperative Morbidity and Mortality Associated With Testosterone Therapy in Cisgender Men

One large prospective cohort study[35] examined the effects of exogenous testosterone use on postoperative morbidity and mortality. The study of more than 5000 cisgender men undergoing noncardiac surgery found no increased risk of postoperative mortality, thrombosis, or cardiovascular events for patients receiving preoperative testosterone (n = 947) compared with control participants (n = 4598; Table 2).

Perioperative Morbidity and Mortality Associated With Estrogen Use in Cisgender Women

A dozen studies[23-34] have attempted to examine whether use of oral contraceptives and or hormone therapy increase the risk of thrombosis after surgery, and results have been mixed. In this review, we found that 3 studies from the 1970s including a total of 437 women found that use of oral contraceptive pills significantly increased the risk of VTE after various surgeries,[23-25] and similar results were seen in 2 studies from 1980[26,27] that included a total of 452 women who were taking hormone therapy. A 1970 study[23] found that postsurgical VTE occurred in 12 of 30 oral contraceptive users (40%) and 9 of 60 matched control participants (15%; relative risk, 3.9; $P = .01$). A 1972 study[24] found that posttraumatic, postoperative, or postinfective VTE occurred in 21 of 60 oral contraceptive users (35%) and 10 of 60 matched control participants (16.7%; relative risk, 2.7; $P = .01$-$.02$). A 1976 study[25] identified 4 clinical cases of VTE and 2 cases of subclinical VTE in 31 women taking oral contraceptives and no cases of VTE in 19 control participants ($P < .05$). A 1980 study[26] looking at postmenopausal women undergoing surgery for uterine prolapse found fibrin deposits in 6 of 11 women (54%) taking low-dose estradiol, 4 of 8 women (50%) taking high-dose estradiol, and 18 of 157 women (11%) taking no treatment ($P < .001$). Another 1980

Table 2. Studies Evaluating the Association of Drugs Used in Cross-Sex Hormone Treatment With Perioperative Outcomes

Source	Design	Level of Evidence[20]/ Quality[21]	IRB Review	Population	Control or Comparison Population	Hormones Studied	Outcome	Type of Surgery	Relevant Results	Recommendations
Transgender patients										
Berry et al,[22] 2012	Retrospective cohort	3/Low	No	88 Transgender men aged 18-44 y taking testosterone at the time of surgery	12 Transgender men aged 18-44 y not taking testosterone at the time of surgery	Testosterone	Various	Chest reconstruction	11 Complications in the cohort, including 6 hematoma; all hematoma were in patients using testosterone, but the difference in overall complications was not significant.	Testosterone supplementation does not predispose patients to complications.
Estrogens and progestogens in cisgender women										
Vessey et al,[23] 1970	Case-control	4/Very low	No	30 Married women	60 Married women matched on parity, age within 5 y, year of admission for similar surgery	Oral contraceptives	Postoperative VTE (<1 mo after surgery)	Various	12 of 30 Active participants (40%) and 9 of 60 control participants (15%) used oral contraceptives (P = .01). The relative risk of VTE among oral contraception users was 3.8.	Suggested stopping oral contraceptives 4 wk before surgery but noted surgeons should balance risks of continuing with risk of pregnancy.
Greene et al,[24] 1972	Case-control	4/Very low	No	113 Women with thromboembolism, 60 included in final analysis	184 Control participants, matched on race, marital status, age within 10 y, date of discharge within 1 y, predisposition to thromboembolism, 60 included in final analysis	Oral contraceptives	Posttraumatic, postoperative, and postinfection VTE	Various	21 of 60 Active participants (35%) and 10 of 60 control participants (16.7%) used oral contraceptives in the month prior to hospitalization. In matched pairs, relative risk was 6.5 (P = .01). Overall, the relative risk was 2.7 (P = .01-.02).	Authors noted that black women were excluded owing to nonresponse rates; results may also have been confounded by weight differences. Concurred with recommendations of Vessey et al.[23]
Sagar et al,[25] 1976	Prospective cohort	4/Low	No	31 Women taking oral contraceptives	19 Women taking no oral contraceptives	Oral contraceptives containing 30-50 g. of estrogen	DVT, detected by fibrinogen uptake	Emergency abdominal	Identified 6 cases of DVT, 4 subclinical, in active patients and no cases in control participants (P < .05).	Stated that there is no general agreement on policies for dealing with oral contraceptive use in the perioperative period but suggested these patients should be considered suitable for heparin thromboprophylaxis.
Astedt et al,[26] 1980	Prospective cohort	3/Low	No	19 Women older than 50 y treated with 2 different estradiol options	157 Women older than 50 y taking no treatment	11 Active-arm women taking 50-µg oral ethinyl estradiol daily for 3 wk; 8 women taking 200-µg oral estradiol for 12 d	VTE, detected by fibrinogen uptake	Uterine prolapse	Fibrin deposits found in 6 of 11 women (54%) taking 50 µg, 4 of 8 (50%) taking 200 µg, and 18 of 157 untreated participants (11.5%), representing a significant increase in VTE for women on ethinyl estradiol (P < .001).	Recommended discontinuing estrogen prior to surgery.

(continued)

Table 2. Studies Evaluating the Association of Drugs Used in Cross-Sex Hormone Treatment With Perioperative Outcomes (continued)

Source	Design	Level of Evidence[20]/ Quality[21]	IRB Review	Population	Control or Comparison Population	Hormones Studied	Outcome	Type of Surgery	Relevant Results	Recommendations
Bernstein et al,[27] 1980	Prospective cohort	3/Very low	No	31 Women older than 50 y taking preoperative estrogen	245 Women older than 50 y not taking preoperative estrogen	Estrogen, type and route not specified	VTE, detected by fibrinogen uptake	Gynecologic	12 of 31 Active participants (39%) and 35 of 245 control participants (14%) developed postoperative thrombosis ($P < .01$).	Researchers suggested that estrogen treatment should be completed before surgery.
Gallus et al,[28] 1984	Prospective cohort	3/Low	No	99 Women aged 18-49 y taking oral contraceptives	122 Women aged 18-49 y not taking oral contraceptives	Oral contraceptives, 81% containing 30-50 µg of estrogen	VTE, detected by fibrinogen uptake	Elective or emergency general intra-abdominal or gynecologic	No active participant and 1 control participant had an abnormal fibrinogen scan.	Concluded that the added risk is "very small when patients are young and lack other clinical risk factors for postoperative thrombosis, and when abdominal or pelvic surgery is of limited extent." Stated that it may not be necessary to discontinue oral contraceptives prior to surgery in low-risk patients, but standard thromboprophylaxis should be used for such patients.
Vessey et al,[29] 1986	Prospective cohort	3/Very low	No	1244 Women taking oral contraceptives	4359 Women not taking oral contraceptives in the month before surgery	Oral contraceptives	VTE diagnosis within 3 mo of surgery	Various	12 of 1244 Women taking oral contraceptives (0.96%) had a postsurgical thrombosis compared with 22 of 4359 controls (0.5%), but the difference was not significant.	The risk of thromboembolism associated with oral contraceptive use is limited to current users.
Hurbanek et al,[31] 2004	Case-control	4/Very low	Yes	108 Patients with postoperative thrombosis (<45 d after surgery); including 9 taking oral estrogen, 6 taking oral estrogen and progesterone, 1 using estrogen patches, 2 taking SERMs	210 Control participants, matched on age, date, surgeon, and type of surgery	Hormone therapy, oral or transdermal	VTE	Hip and knee arthroplasty	Found no difference in perioperative hormone therapy use for individuals with and without VTE. Results did not vary significantly by route of hormone administration.	Concluded it is probably not necessary to routinely discontinue hormone therapy use; noted that hormone therapy users had lower rates of coronary disease and prior thrombosis, which could confound results.

(continued)

Table 2. Studies Evaluating the Association of Drugs Used in Cross-Sex Hormone Treatment With Perioperative Outcomes (continued)

Source	Design	Level of Evidence[20]/ Quality[21]	IRB Review	Population	Control or Comparison Population	Hormones Studied	Outcome	Type of Surgery	Relevant Results	Recommendations
Barsoum et al,[32] 2010	Case-control	4/Very low	Yes	726 Individuals with thromboembolism, 302 hospitalized with or without surgery	830 Control participants, 71 hospitalized, matched on age, sex, and medical care near the event date	Oral contraceptives and hormone therapy (various routes of administration)	Objectively diagnosed VTE	Hospitalized patients (with or without surgery)	In a subanalysis, after adjusting for hospitalization with or without surgery, oral contraceptives (odds ratio, 3.29 [95% CI, 1.72-6.27]; $P < .001$), progestin alone (odds ratio, 3.92 [95% CI, 1.50-10.23]; $P = .01$), and noncontraceptive estrogen and progestin (odds ratio, 1.73 [95% CI, 1.04-2.87]; $P = .03$) were all significantly associated with VTE risk, but estrogen alone (odds ratio, 1.32 [95% CI, 0.84-2.06]; $P = .23$) was not.	Authors concluded that hormones are independent risk factors for VTE but did not specifically discuss implications for surgery.
Acũna et al,[33] 2011	Case-control	4/Very low	No	31 Patients with VTE	79 Patients without VTE	2 Patients taking oral contraceptive in study population	VTE	Trauma patients	Oral contraceptive use was not found to be a significant risk factor for VTE in trauma patients (odds ratio, 0.70 [95% CI, 95% CI, 0.70-0.80]; $P = .41$).	It cannot be concluded that estrogen use is not associated with VTE because estrogen use was poorly documented in the population.
Schulte et al,[34] 2013	Retrospective cohort	3/Low	Yes	16 Patients with DVT after spine surgery	1469 Individuals who underwent spinal surgery	Estrogen therapy, route not specified	DVT and PE	Spine surgery	Full cohort included 817 women and 668 men. Estrogen therapy is linked to postoperative VTE (univariate relative risk, 6.2 [95% CI, 1.4-26.1]; $P < .01$; multivariate relative risk, 3.1 [95% CI, 3.5-128.8]; $P < .07$, adjusted for prior DVT/PE, discharge to rehabilitation, and depression).	No conclusions about whether it is valuable to stop estrogen therapy prior to surgery.
Testosterone in cisgender men										
Argalious et al,[35] 2017	Retrospective cohort	2/Moderate	Yes	947 Male patients >40 y receiving testosterone	4598 Male patients >40 y, matched on type of surgery and propensity score	Testosterone, route unspecified	Perioperative mortality and cardiovascular events	Noncardiac surgery	No difference in postoperative in-hospital mortality or cardiovascular events (including myocardial infarction, stroke, PE, and DVT) for patients receiving exogenous testosterone preoperatively.	Concluded that preoperative testosterone does not affect in-hospital mortality or cardiac outcomes.

(*continued*)

Table 2. Studies Evaluating the Association of Drugs Used in Cross-Sex Hormone Treatment With Perioperative Outcomes (continued)

Source	Design	Level of Evidence[20]/ Quality[21]	IRB Review	Population	Control or Comparison Population	Hormones Studied	Outcome	Type of Surgery	Relevant Results	Recommendations
Other medications used in cross-sex hormonal treatment										
Özaydin et al,[36] 2010	Prospective cohort	3/Low	No	37 Patients taking spironolactone for 13-60 d	232 Patients not taking spironolactone	Spironolactone	Atrial fibrillation after surgery	Coronary artery bypass or valve surgery	No association found between spironolactone and postoperative atrial fibrillation.	Conclusions cannot be drawn about the safety of spironolactone owing to the low proportion of patients receiving it.
Simopoulos et al,[37] 2015	Retrospective cohort	4/Low	No	132 Patients with reduced ejection fraction heart failure treated with an aldosterone agonist	200 Patients with reduced ejection fraction heart failure treated with standard therapy	Spironolactone	Atrial fibrillation after cardiac surgery	On-pump cardiac surgery	Aldosterone agonists (including spironolactone) reduced the risk of postoperative atrial fibrillation after on-pump cardiac surgery (odds ratio, 2.10 [95% CI, 1.18-3.73]; $P = .01$ for nonusers compared with users).	Randomized clinical trials are needed to determine if aldosterone agonists can reduce atrial fibrillation after cardiac surgery.
Barba-Navarro et al,[38] 2017	Placebo-controlled Randomized clinical trial	2/Low	Yes	115 Patients taking spironolactone 12-24 h before surgery	118 Patients taking placebo 12-24 h before surgery	100 mg of Spironolactone or placebo	Acute kidney injury	Cardiac surgery	Results suggested that a single dose of spironolactone did not protect against acute kidney injury; subanalysis of patients in the placebo group did not find a significant increase in risk for patients receiving long-term spironolactone treatment compared with nonusers.	No clear conclusions for spironolactone use in the perioperative period.
Billon et al,[39] 2017	Retrospective cohort	4/Very low	No	48 Patients taking SERMs, 39 taking aromatase inhibitors (anastrozole, letrozole, or exemestane)	145 Patients not taking hormone therapy	Antiestrogens	Perioperative complications	Breast reconstruction	No difference in interoperative vascular complications, postoperative thrombosis, flap loss, or thromboembolitic events for women on aromatase inhibitors. Odds of wound healing complications were 4.2 (95% CI, 2.39-7.39; $P < .001$) for women receiving any hormone therapy. Increases were seen for rates of infection, fat necrosis, and delayed wound healing.	Antiestrogens may complicate wound healing after surgery. Temporary discontinuation may be advisable.
Batra et al,[30] 2003	Case-control	4/Low	No	16 Postmenopausal women with estrogen exposure and 6 premenopausal women with estrogen exposure	22 Matched controls	Oral contraceptives and oral hormone therapy	Wound healing	Laser skin resurfacing	Found no significant differences in wound healing for women taking estrogen.	There is no need to stop estrogen prior to this type of procedure. There is some evidence estrogen may promote healing, but not enough evidence to prescribe it.

Abbreviations: DVT, deep vein thrombosis; IRB, institutional review board, PE, pulmonary embolism; SERMs, selective estrogen receptor modulators; VTE, venous thromboembolism.

Table 3. Summary of Evidence on Perioperative Risk of Transgender Hormone Treatments

Type of Hormone	Population Using Hormone	Major Surgical Concerns	Summary of Evidence
Estrogens	Transgender women	Thrombosis	Evidence is inconsistent as to whether estrogen use increases the risk of perioperative thrombosis. Surgeons may want to discuss the pros and cons of discontinuing treatment with patients. Most perioperative research has studied oral contraceptives and hormone therapy rather than the transdermal estrogens used for transgender women. The effect of route of estrogen administration on perioperative risk has not been studied directly, but transdermal estrogen is associated with a lower overall risk of venous thromboembolism.
Antiandrogens	Transgender women	Unclear	Limited evidence that spironolactone does not affect perioperative morbidity, but research is limited to cardiac surgery.
Testosterone	Transgender men	Thrombosis, hematoma	Limited evidence suggests that testosterone does not affect perioperative morbidity.
Gonadotropin-releasing hormone agonists	Transgender adolescents prior to initiating cross-sex hormone treatment	Not applicable	There is no direct evidence of how these medications affect perioperative morbidity, to our knowledge.

study[27] found postoperative thrombosis in 12 of 31 oral contraceptive users (39%) and 35 of 245 nonusers (17%) who were undergoing gynecologic surgery ($P < .10$). Another 2 other studies[28,29] on a total of 5824 women did not see a significant increase in risk, and a small case-control study[30] of 44 women saw no difference in wound healing between those who did and those who did not receive estrogen in the form of oral contraception or hormone therapy.

We also located 1 large prospective study[34] of patients undergoing spine surgery, including 817 women. This study found that estrogen therapy significantly increased postoperative VTE risk (univariate relative risk, 6.2 [95% CI, 1.4-26.1]; $P < .01$; adjusted risk, 3.1 [95% CI, 3.5-128.8]; $P < .07$). However, a case-control study[31] of 318 women undergoing hip and knee arthroplasty found no difference in VTE between women receiving hormone therapy and those who did not receive it, and an additional case-control study[32] with an active arm of 302 hospitalized women within a larger cohort of 726 individuals with thromboembolism found that oral contraceptives (odds ratio, 3.29 [95% CI, 1.72-6.27]; $P < .001$), progestin (odds ratio, 3.92 [95% CI, 1.5-10.23]; $P = .01$), and noncontraceptive combined estrogen and progestin (odds ratio, 1.73 [95% CI, 1.04-2.87]; $P = .03$) were associated with VTE in hospitalized women, but estrogen alone was not (odds ratio, 1.32 [95% CI, 0.84-2.06]; $P = .23$) (Table 2). One additional study[33] of 110 trauma patients, including 2 individuals taking oral contraceptives, found no significant risk associated with VTE risk in patients taking oral contraceptives (odds ratio, 0.70 [95% CI, 0.70-0.80]; $P = .41$).

Perioperative Morbidity and Mortality Associated With Other Drugs Used in Cross-Sex Hormone Therapy

We located 3 studies examining the use of spironolactone in the perioperative period. One prospective cohort study[36] of 269 patients, 37 of whom were taking spironolactone, found no increase in atrial fibrillation after cardiac surgery for patients taking the drug compared with those who were not. A second retrospective cohort study[37] of 332 patients found that 132 individuals taking aldosterone agonists, including spironolactone, experience a decrease in the risk of atrial fibrillation, although the difference was not significant from that of the 200 control participants. A placebo-controlled randomized clinical trial[38] of spironolactone to prevent acute kidney injury after cardiac surgery found an increased risk of kidney injury in 115 patients given spironolactone compared with 118 individuals given a placebo, but a subanalysis did not see an increased risk in patients who were prescribed spironolactone prior to the study compared to those who were not.

In addition, a study[39] looking at use of selective estrogen receptor modulator use in 48 women and aromatase inhibitor use in 39 women in an overall cohort of 223 women undergoing breast reconstruction found a significant increase in the odds of wound healing complications (odds ratio 4.2 [95% CI, 2.39-7.39]; $P < .001$). However, it found no difference in the rate of interoperative vascular complications, postoperative thrombosis, or thrombolytic events.

Discussion

Current evidence does not support the need to routinely discontinue all cross-sex hormone therapy prior to surgery (**Table 3**). Although it may seem like a straightforward decision to discontinue hormone use as a protective measure, it is important to balance the risks of thrombosis in the perioperative period with the risks of stopping therapy. Unfortunately, to date and to our knowledge, there are few data that directly address the question of how stopping CSHT in the perioperative period affects vascular, emotional, and general health.

Evidence suggests there is no need to routinely discontinue testosterone treatment in transgender men prior to scheduled or elective surgery. Testosterone can be aromatized to estradiol,[40] which theoretically provides a pathway through which testosterone supplementation could be associated with increased clotting risk. In this review, we found that moderately sized cohort studies in both cisgender[35] and transgender[22] men have not shown any increase in perioperative morbidity associated with exogenous testosterone use. Previous studies of CSHT in transgender men have also not shown testosterone to significantly increase the risk of thrombosis or cardiovascular mortality outside of the surgical setting.[6,9] Furthermore, in cisgender men, adverse cardiovascular events have primarily been seen with short-term testosterone treatment or shortly after initiation of treatment, with no increase in risk associated with long-term use.[41-45] This suggests the possibility that stopping and restarting testosterone could itself elevate the risk of thrombosis, although to date and to our knowledge, that hypothesis has not been studied directly.

The decision of whether it is necessary to routinely discontinue estrogen treatment in transgender women undergoing sur-

gery is less clear. There is an extensive body of evidence showing the thrombogenic potential of estrogen in cisgender women. However, researchers have questioned whether estrogen increases the rate of VTE above and beyond the risk already associated with various surgical procedures.[46,47] To our knowledge, there has been little research directly examining the effects of CSHT on transfeminine surgical outcomes, and it is difficult to get retrospective data, because surgeons routinely discontinue estrogen treatment despite an acknowledged lack of evidence supporting that practice.[10,14,48] Although we found a number of studies that have examined the effects of oral contraceptives and hormone therapy in cisgender women undergoing surgery, the results have been inconsistent,[23-32,34] and it appears that there have not been any studies of the safety of the estrogen formulations generally prescribed for transgender women in the perioperative period.

Discussions of whether to discontinue hormonal contraception in cisgender women prior to surgery often focus on balancing the increased risk of thrombosis with the risk of pregnancy in the perioperative period. Although transgender women are not at risk of pregnancy, there can be physical and behavioral consequences of stopping estrogen use. These include emotional lability, anxiety, and depression, as well as other perimenopausal-like symptoms associated with estrogen withdrawal.[3,15] These symptoms can start within a few days. As such, some women may be reluctant to discontinue estrogen for long periods surrounding surgery. In such situations, it becomes the role of treating physicians to factor in the patient's overall risk of thrombus formation, the type of surgery, and the type of estrogen being prescribed to the patient when counseling the patient about the risks of continuing CSHT, as well as the possible risks and benefits of thromboprophylaxis.

Outside of the perioperative period, there is substantial evidence suggesting a prothrombotic role of estrogen supplementation in cisgender women and men as well as in transgender women. However, inconsistent research results mean that it remains unclear to what extent that risk is additive with the risk of thrombosis associated directly with surgery. Specifically for transgender women, the evidence of increased clotting risk is strongest for treatments including oral ethinyl estradiol and much weaker for certain other estrogens, including the transdermal 17β estradiol that is most often used in current treatment.[2,6,8-10] Similar data on the reduced risk of transdermal estrogens compared to oral estrogens have also been seen in other populations including cisgender women and men.[49-55]

These risk differences may be explained by the fact that the way in which sex hormones are metabolized, and thus their potential effects on the clotting cascade, appears to be highly dependent on the route through which they are administered. Oral estrogens have been shown to stimulate production of liver proteins when they initially pass through that organ during the process of digestion, which is known as the hepatic first-pass effect.[56] Oral estrogen administration has been linked to changes in hepatic markers, including C-reactive protein, sex hormone binding globulin, corticosteroid-binding globulin, growth hormone-binding protein, insulin-like growth factor 1, and angiotensin, as well as enhanced clearance of tissue plasminogen activator.[57,58] Similar effects are either greatly reduced or not seen at all when estrogen is given by nonoral routes, and administration of multiple hormone regimens transdermally has not been shown to increase hemostatic parameters associated with thrombosis.[57-59] There are also some data suggesting that the type of progestins used in oral contraceptives and hormone therapy might also affect thrombogenic risk, which further complicates the generalizability of existing research data to transgender women, who are generally prescribed unopposed estrogens.[52,60-65]

As with transdermal estrogens, it is unclear whether it is necessary to stop spironolactone, gonadotropin-releasing hormone agonists, and other antiandrogens prior to surgery for transfeminine patients. Stopping these medications can be psychologically problematic for transfeminine patients because of the strongly virilizing activity of endogenous testosterone.[16] There is some limited, inconsistent evidence that these medications may be prothrombotic.[10,66-68] However, there is also a moderate amount of evidence suggesting that these medications are safe in the perioperative period, although that evidence is restricted to patients undergoing cardiac surgery.[36-38]

The effects of sex hormones and other medications used for CSHT on the cardiovascular system are clearly complex, and there needs to be further research on the various pathways through which the use of these drugs can affect cardiovascular risk. There is also a need for a clearer understanding of how and when current hormone formulations are associated with thrombosis in the perioperative period. Although the hemostatic effects of combined oral contraceptives have been shown to wear off 4 to 6 weeks after therapy is stopped and several months after oral and injectable testosterone therapies are stopped, it is unclear how long any washout period is for the specific formulations used in treating transgender patients.[69,70] Further research is needed to answer those questions as well as to determine whether there are any metabolic risks associated with stopping and restarting CSHT. This is a biologically plausible concern, because there is some evidence that the risk of thrombosis with certain hormone treatments is highest shortly after therapy initiation.[41-45]

The lack of evidence to support routine discontinuation of CSHT prior to undergoing planned surgeries is reflected in inconsistencies in practice for transgender individuals and the population as a whole. Several studies have found that surgeons' beliefs and practices around the role of perioperative hormone use in thrombotic events are highly variable and often internally inconsistent.[71,72] The same is true for their use of antithrombotic prophylaxis.[73,74] These inconsistencies demonstrate a need for further research to inform the development of clear, evidence-based guidelines on both perioperative hormone use and antithrombotic prophylaxis in transgender patients and other individuals using exogenous hormones.

Conclusions

There is insufficient evidence to support routine discontinuation of testosterone or spironolactone in transgender patients undergoing scheduled surgical procedures. Given inconsistent risk data about the risks associated with estrogen, decisions about whether or not to discontinue estrogen treatment should keep individual risk factors and concerns in mind.

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