Review

Estradiol Therapy in the Perioperative Period: Implications for Transgender People Undergoing Feminizing Hormone Therapy

Brendan J. Nolan[a,b,*] and Ada S. Cheung[a,b]

[a]Department of Endocrinology, Austin Health, Heidelberg, Victoria, Australia; [b]Department of Medicine (Austin Health), University of Melbourne, Heidelberg, Victoria, Australia

Venous thromboembolism is a documented risk of some estradiol formulations, but evidence evaluating the perioperative risk of continuation of estradiol therapy is limited. This narrative review summarizes literature related to the perioperative venous thromboembolic risk of estradiol, with a focus on feminizing genitoplasty for trans people undergoing feminizing hormone therapy. Given the dearth of evidence underlying gender-affirming hormone therapy regimens, much of the risk is based on the menopausal hormone therapy literature. However, the doses used for trans people undergoing feminizing hormone therapy can be significantly higher than those used for menopausal hormone therapy and escalating estradiol dose is associated with an increased thrombotic risk. Transdermal formulations are not associated with an increased risk in postmenopausal people. Feminizing genitoplasty is associated with a low thromboembolic risk. However, many patients are instructed to cease estradiol therapy several weeks preoperatively based on reports of increased thrombotic risk in trans people undergoing feminizing hormone therapy and hemostatic changes with the oral contraceptive pill. This can result in psychological distress and vasomotor symptoms. There is insufficient evidence to support routine discontinuation of estradiol therapy in the perioperative period. There is a need for high-quality prospective trials evaluating the perioperative risk of estradiol therapy in trans people undergoing feminizing hormone therapy to formulate evidence-based recommendations.

INTRODUCTION

There have been significant increases in the number of transgender (trans) people (with a binary and/or non-binary gender) seeking healthcare worldwide [1]. Trans people undergoing feminizing hormone therapy are typically treated with estradiol with or without anti-androgen to increase serum estradiol concentration and decrease serum testosterone concentration into a range similar to cisgender females [2]. This results in development of feminine physical characteristics, including softening of skin, a decrease in facial and body hair growth, breast development, and changes in body composition including body fat redistribution and decreased muscle mass [3,4].

Venous thromboembolism (VTE) is a recognized side effect of some formulations of estradiol therapy and is the

*To whom all correspondence should be addressed: Brendan J. Nolan, MBBS, FRACP, Department of Medicine (Austin Health), The University of Melbourne, Studley Road, Heidelberg 3084, Australia; E-mail: bjnolan@student.unimelb.edu.au.

Table 1. Typical estradiol doses in trans and postmenopausal individuals.

Formulation	Trans individuals	Postmenopausal individuals
Oral estradiol or estradiol valerate	2-6mg daily	0.5-2mg daily
Transdermal patch	100-150mcg daily	25-100mcg daily

most common side effect of feminizing hormone therapy [3]. However, estradiol formulations differ in their thrombotic risk and the incidence of VTE has decreased now that ethinyl estradiol is no longer recommended as part of the feminizing hormone therapy regimen [5].

Much of the evidence underlying the thrombotic risk of estradiol therapy is derived from the menopausal hormone therapy literature. Evidence suggests that oral but not transdermal formulations are associated with an increased VTE risk in post-menopausal people [6], potentially related to first-pass metabolism or the estradiol dose administered [7]. Escalating estradiol dose has been associated with increased VTE risk in some studies [8]. This is an important consideration, given that the estradiol doses administered as feminizing hormone therapy can be significantly higher than those used for menopausal hormone therapy.

Some trans people undergo gender-affirming surgery such as feminizing genitoplasty to align their physical characteristics with their gender identity. Due to the potential thrombotic complications of estradiol therapy and the increased risk of thrombosis perioperatively, guidelines including the Italian Society of Andrology and Sexual Medicine and National Observatory of Gender Identity recommend cessation of estradiol 2-4 weeks prior to feminizing genitoplasty or other major surgery [9-11]. However, these recommendations are based on evidence including estradiol formulations which are no longer used and many studies informing these recommendations were performed prior to introduction of routine VTE prophylaxis. Perioperative cessation of estradiol can result in psychological distress and vasomotor symptoms in trans people using feminizing hormone therapy [12].

Herein, we review the guidelines for feminizing hormone therapy, including the VTE risk of currently prescribed formulations. Next, we review the VTE risk and changes in hemostatic variables with different formulation of estradiol therapy. Finally, we discuss the thrombotic risk of estradiol therapy in the perioperative period, and implications for trans individuals undergoing feminizing genitoplasty. The material is based on peer-reviewed journals accessed within the PubMed database from January 1970 to 11 February 2020. The search terms "estradiol," "estrogen," "thrombosis," "thromboembolism," "surgery," "perioperative" were used. We also searched the references listed in relevant publications. Original research articles, reviews, and societal guidelines were considered.

FEMINIZING HORMONE THERAPY

Several clinical guidelines provide protocols for commencement and monitoring of gender-affirming hormone therapy (GAHT) [3,13,14]. Feminizing hormone therapy involves estradiol treatment, often in combination with an anti-androgen (commonly cyproterone acetate 12.5-50mg daily or spironolactone 100-200mg daily) in individuals without orchidectomy. Estradiol is most commonly administered via the oral or transdermal route, with oral estradiol valerate or micronized estradiol the most commonly prescribed formulations [1]. Oral estradiol is more frequently prescribed in the United States due to differences in cost and insurance coverage [15]. Ethinyl estradiol and conjugated equine estrogens are no longer recommended given a higher thrombotic risk and inability to measure serum estradiol concentrations.

Serum estradiol concentration can be used for monitoring, and Endocrine Society Clinical Practice Guidelines recommend maintenance of serum estradiol and testosterone concentrations in the range for premenopausal females (367-734 pmol/L (100-200 pg/mL) and <1.7 nmol/L (50 ng/dL), respectively) [3]. Maintenance of estradiol concentrations within this range often requires significantly higher estradiol doses than those used for menopausal hormone therapy (Table 1) [1]. For instance, a recent retrospective analysis from Australia reported a median estradiol concentration of 290 pmol/L (79 pg/mL) on median oral estradiol valerate 6mg daily [16]. The exact role of monitoring estradiol concentration is unknown other than to avoid supraphysiological estradiol concentrations, and some clinicians instead monitor testosterone suppression to assess efficacy.

RISK OF VENOUS THROMBOEMBOLISM IN TRANS INDIVIDUALS

Observational studies have shown an increased VTE risk in trans people using feminizing hormone therapy [5,17,18], compared to both cisgender men and women [19]. However, the relative thrombotic risk differs between estradiol formulations [7,10,20]. Initial studies evaluating safety of GAHT documented a 45-fold increased risk of VTE (occurring in 6.3%) in trans people treated with ethinyl estradiol 100mcg daily and cyproterone acetate 100mg daily [21]. Due to this, ethinyl estradiol is no longer recommended for feminizing GAHT [3]. Conjugated equine estrogens have also been asso-

Table 2. Venous thromboembolism in trans individuals undergoing feminizing hormone therapy.

Reference	Study type	Number of individuals	E2 regimen	Number of VTE (%)	Perioperative VTE
Asscheman et al., 1989 [21]	Retrospective cohort	303	EE 100mcg	19 (6.3%)	4/235 (1.7%)
Prior et al., 1989 [60]	Prospective cohort	61	CEE 2.5 mg BD ¾ weeks	0	N/A
van Kesteren et al., 1997 [5] Extension of [21]	Retrospective cohort	816	EE 100mcg Transdermal estradiol (n=138)	45 (5.5%)	5
Schlatterer et al., 1998 [61]	Retrospective cohort	46	Intramuscular estradiol valerate 40-100mg every 2 weeks	0	N/A
Dittrich et al., 2005 [62]	Prospective cohort	60	Oral estradiol valerate + GnRHa	1 (1.7%)	Nil
Wilson et al., 2009 [63]	Prospective cohort	30	CEE (n=23) Transdermal estradiol (n=7)	0	N/A
Ott et al., 2010 [27]	Retrospective cohort	162	Transdermal estradiol 100mcg/24hr	0	N/A
Seal et al., 2012 [22]	Retrospective, controlled audit	330	Estradiol valerate (n=163) EE (n=133) CEE (n=36)	4 (1.2%)	Not reported
Wierckx et al., 2012 [17]	Cross-sectional study	50	Various transdermal preparations (n=25) Various oral preparations (n=22)	3 (6%)	Nil
Wierckx et al., 2013 [18]	Cross-sectional study	214	Various transdermal preparations (n=105) Various oral preparations (n=99)	11 (5.1%)	3
Wierckx et al., 2014 [26]	Prospective cohort study	53	Oral estradiol valerate (n=40) Transdermal estradiol (n=13)	0	N/A
Arnold et al., 2016 [23]	Retrospective cohort	676	Oral estradiol (n=676) CEE (n=42)	1 (0.15%)	Nil
Getahun et al., 2018 [25]	Electronic medical record-based cohort study	2842	Not reported	61 (2.1%)	Not reported
Meyer et al., 2019 [24]	Retrospective cohort study	155	Transdermal preparations (n=82) Oral estradiol valerate or hemihydrate (n=73)	3 (1.9%)	2

CEE, conjugated equine estrogens; EE, ethinyl estradiol; GnRHa, gonadotropin-releasing hormone agonist

ciated with an increased VTE risk [22]. Modern GAHT regimens involving oral or transdermal estradiol have a lower risk of VTE; recent observational data suggests a risk between 0-2% [23-27]. A systematic review and meta-analysis found the overall risk approximates that of cisgender females prescribed estradiol [20]. Table 2 provides a summary of studies reporting VTE in trans people using feminizing hormone therapy.

INFLUENCE OF ROUTE OF ADMINISTRATION AND DOSE

The differential effects of VTE risk based on route of administration were first demonstrated in the EStrogen and THromboEmbolism Risk (ESTHER) study [28]. The case-control study enrolled 155 post-menopausal people with a first episode of VTE and 381 matched controls. Those treated with oral estradiol, compared to non-users, had a significantly higher estimated risk of VTE (odds ratio (OR) 3.5 (1.8–6.8)), whereas those treated with transdermal estradiol did not (OR 0.9 (0.5–1.6)) [28].

Following this, case-control [8,29,30] and cohort studies [31-34] in post-menopausal people have also documented an increased VTE risk with oral estradiol compared to transdermal estradiol (Table 3). Although the oral estradiol regimens differed between studies, with some reporting estradiol and/or conjugated equine estrogens, both preparations have independently been associated with an increased VTE risk.

Several studies in post-menopausal people have evaluated the influence of estrogen dose on VTE risk. High-dose (defined as >1mg estradiol [8,32], or >2mg estradiol or 0.625mg conjugated equine estrogens [30]) oral estradiol was associated with a higher risk of VTE in some studies [8,30] but not another [32]. There does not appear to be an increased VTE risk with high-dose (>50mcg/24hours) transdermal preparations [8,30,32]. However, one nested case-control study did suggest an increased risk of stroke in post-menopausal people treated with transdermal estradiol >50mcg/24hours compared to low-dose estradiol [35].

CHANGES IN HEMOSTATIC VARIABLES WITH ESTRADIOL THERAPY

Ethinyl Estradiol

Combined oral contraceptive agents are known to affect synthesis of coagulation factors. Levels of fibrinogen, factor VIII, von Willebrand factor, factor VII, factor X, and prothrombin increase while the level of protein S decreases [36]. Acquired resistance to activated protein C (APC) has also been reported [37]. Some parameters such as sex hormone-binding globulin increase in a dose-dependent manner, a potential biomarker of hepatic estradi-

ol exposure [38]. Overall, these changes may result in a prothrombotic state and an increase in VTE risk.

The timeline of changes in these parameters has been evaluated in one study. Robinson *et al.* evaluated changes in hemostatic variables in 24 people following cessation of the combined oral contraceptive pill containing 30mcg ethinyl estradiol. After 6 months of treatment, there were statistically significant increases in fibrinogen and factor X, with a decrease in antithrombin III [39]. Following cessation, a "rebound" in concentrations of fibrinogen and antithrombin III was seen between weeks 2-6. The authors postulated that surgery should be undertaken at least 4 weeks following cessation of the OC, at which stage fibrinogen is low, antithrombin III is high, and factor X has returned to baseline. This has formed the basis for perioperative recommendations in trans people using feminizing hormone therapy.

Menopausal Hormone Therapy

Hemostatic variables differ between oral and transdermal estradiol preparations, theoretically due to first-pass metabolism in the liver and a resultant increased synthesis of pro-coagulant proteins following oral administration. A lower anti-thrombin III has been reported with oral but not transdermal formulations [40]. Several randomized controlled trials have also demonstrated that oral [41] but not transdermal estradiol [42,43] results in an acquired resistance to APC. Therefore, transdermal estradiol formulations at doses used for menopausal hormone therapy do not appear to have a significant effect on hemostasis.

Studies in Trans People Undergoing Feminizing Hormone Therapy

The influence of feminizing hormone regimens on hemostatic variables has also been evaluated in trans people. In an open-label randomized study, hemostatic parameters were measured prior to and 4 months after commencement of: ethinyl estradiol 100mcg daily and cyproterone acetate 100mg daily; oral estradiol 2mg twice daily and cyproterone acetate 100mg daily; transdermal estradiol 100mcg daily and cyproterone acetate 100mg daily, or; cyproterone acetate 100mg daily. The group treated with ethinyl estradiol had the largest change in hemostatic variables, with a large increase in APC resistance (1.2±0.8 to 4.1±1.0; p<0.001), a 9% increase in plasma protein C (p<0.012), and a 30% decrease in plasma protein S (p<0.005) [44]. In comparison, small changes were seen in all other groups [44].

More recently, the potential utility of global coagulation assays has been investigated in a cross-sectional study of trans individuals. Overall, trans individuals on estradiol demonstrated increased clot strength (max-

Table 3. Studies evaluating VTE risk by estradiol formulation.

Reference	Study type	Number of individuals	Hormone therapy use	VTE risk
Scarabin et al., 2003 [28]	Case-control	155 with VTE 381 matched controls	62/155 (40%) VTE cases – 32 (51%) used oral E2 120/381 (31%) controls – 27 (22%) used oral E2	OR oral E2 vs. non-users: 3.5 (1.8-6.8) OR transdermal E2 vs. non-users: 0.9 (0.5-1.6) OR oral E2 vs. transdermal E2: 4.0 (1.9-8.3)
Canonico et al., 2007 [29]	Case-control	271 with VTE 610 matched controls	124/271 (45%) VTE cases – 57 (46%) used oral E2 226/610 (37%) controls – 46 (20%) used oral E2	OR oral E2 vs. non-users: 4.2 (1.5-11.6) OR transdermal E2 vs. non-users: 0.9 (0.4-2.1)
Renoux et al., 2010 [30]	Case-control	23505 with VTE 231562 matched controls	1004/23505 (4.3%) VTE cases – 729 (72%) used oral E2 7851/231562 (3.4%) controls – 5105 (65%) used oral E2	EE oral E2 vs. non-users: 1.49 (1.37-1.63) RR transdermal E2 vs. non-users: 1.01 (0.89-1.16) VTE risk increased with increasing E2 dose
Canonico et al., 2010 [31]	Cohort study	98995 individuals	549 VTE cases Oral E2 81 VTE Transdermal E2 174 E2	HR oral E2 vs. non-users: 1.7 (1.1-2.8) HR transdermal E2 vs. non-users: 1.1 (0.8-1.8)
Sweetland et al., 2012 [32]	Cohort study	1058259 individuals	2200 VTE cases Oral E2 194/51853 Transdermal E2 66/86250	RR oral E2 vs. non-users: 1.42 (1.22-1.66) RR transdermal E2 vs. non-users: 0.82 (0.64-1.06)
Simon et al., 2016 [33]	Matched cohort study	2551 individuals treated with transdermal E2 matched to 2551 individuals treated with oral E2	13/2551 VTE events in transdermal E2 group 22/2551 VTE events in oral E2 group	OR transdermal E2 vs. oral E2: 0.42 (0.19-0.96)
Laliberté et al., 2018 [34]	Matched cohort study	27018 individuals treated with transdermal E2 matched to 27018 individuals treated with oral E2	115/27018 VTE events in transdermal E2 group 164/27018 VTE events in oral E2 group	IRR transdermal E2 vs. oral E2: 0.67 (0.49-0.92)
Vinogradova et al., 2018 [8]	Case-control	80396 with VTE 391494 matched controls	5795/80396 (7.2%) VTE cases – 4915 (85%) used oral E2 21670/391494 (5.5%) controls – 16938 (78%) used oral E2	OR oral E2 vs. non-users: 1.58 (1.52-1.64) OR transdermal E2 vs. non-users: 0.93 (0.87-1.01) OR oral E2 vs. transdermal E2: 1.70 (1.56-1.85) OR oral E2 vs. CEE: 0.85 (0.76-0.95) VTE risk increased with increasing E2 dose

CEE, conjugated equine estrogen; E2, estradiol; HR, hazard ratio; OR, odds ratio; IRR, incidence rate ratio; VTE, venous thromboembolism

imum amplitude 65.2 vs 57.9 mm; p<0.001) on whole blood thromboelastography [45]. Fibrin generation was reduced with similar overall fibrinolytic potential. Interestingly, there was no difference in parameters between groups treated with oral (*n*=16) or transdermal (*n*=10) estradiol, however, the study was not powered to detect a difference between groups. Future prospective studies should evaluate the influence of various estradiol doses in a larger cohort.

Risk of Venous Thromboembolism in the Perioperative Setting

Limited observational studies have expressed concern regarding the VTE risk associated with continuation of estradiol therapy in the perioperative period (Table 4) [46]. Initial studies reported an increased perioperative VTE risk in people treated with oral contraceptives containing ethinyl estradiol [47-50]. However, more recent prospective studies did not find an association between ethinyl estradiol use and perioperative VTE [51,52].

Studies involving other oral or transdermal preparations are limited. A case-control study involving post-menopausal people following hip and knee arthroplasty evaluated 108 individuals with postoperative VTE matched to 210 controls without thrombosis [53]. Perioperative hormone replacement use was no more prevalent in the group with postoperative VTE. Eighteen (16.7%) people with postoperative VTE had taken perioperative hormone replacement compared to 49 (23.3%) of controls (odds ratio = 0.66; (95% CI 0.35-1.18; p=0.17)) [53]. Of note, over 50% used oral estrogen in this study. Retrospective studies evaluating VTE risk with spinal surgery have not found an association with estrogen use, though overall event numbers and patients treated with estradiol in these studies were low [54,55].

In summary, studies evaluating the perioperative risk of estradiol are largely based on ethinyl estradiol, which is no longer recommended as part of GAHT regimens. Similarly, many of these studies were performed prior to introduction of routine VTE prophylaxis. Limited evidence with modern GAHT regimens have not documented an increased risk.

Perioperative Guidelines in Trans People undergoing Feminizing Hormone Therapy

Current guidelines advise withholding estradiol 2 to 4 weeks prior to elective surgery and recommencing 3 to 4 weeks postoperatively and mobilizing [9-11]. Despite these recommendations, no study has evaluated perioperative continuation of estradiol in trans individuals, with studies informing us of thrombotic risk based on pre-menopausal women treated with ethinyl estradiol [39]. Cessation of estradiol renders an individual prone to side effects including vasomotor symptoms and mood disturbance that can impact quality of life [12]. Due to the lack of data, there is variability in clinical practice and some surgeons continue estradiol therapy perioperatively.

Rate of VTE with Feminizing Genitoplasty

There are limited data evaluating VTE risk with feminizing genitoplasty though retrospective cohort studies have documented a low risk. In a retrospective analysis of outcomes in 233 individuals who underwent feminizing genitoplasty between 1994-2004, two individuals (0.9%) reported postoperative deep vein thrombosis (DVT), one of whom had non-fatal pulmonary embolism (PE) [56]. Guidelines at this center are to cease feminizing hormone therapy 6 weeks pre-operatively. Hormonal regimens and other VTE risk factors were not reported.

Similarly, there were no patient-reported VTE in another cohort of 232 individuals undergoing penile inversion vaginoplasty [12]. Patients were instructed to cease estradiol 3 weeks preoperatively. Two-hundred-and-fourteen (92%) patients ceased their feminizing hormones pre-operatively with a mean duration of abstinence of 22 days.

In a more recent retrospective analysis of 330 trans individuals who underwent penile inversion vaginoplasty between 2011-2015, there were no reported cases of DVT [57]. This was despite a perioperative estradiol regimen that involved continuation of estradiol tapered to 2mg at least 2 weeks prior to surgery. Similarly, there were no reports of DVT using a protocol in which those under 50 (n=49) continued estradiol until surgery, and people aged 50 years or older (n=10) discontinued estradiol 6 weeks preoperatively but could choose to continue transdermal estradiol until 2 weeks preoperatively [58].

Patient-reported Outcomes of Preoperative Estradiol Cessation

Cessation of estradiol 2 or 6 weeks preoperatively results in virilization with testosterone and estradiol concentrations near the male reference range [59]. There are limited data examining patient-reported outcomes of preoperative estradiol cessation. In a retrospective analysis, among participants who discontinued hormones preoperatively, 74 (35%) reported that this had been difficult [12]. The most common symptoms reported by participants who stopped taking hormones were hot flushes (43 participants, 20% of those who stopped), mood swings or irritability (42 participants, 20% of those who stopped), and increases in facial or body hair growth (12 participants, 6% of those who stopped) [12].

Table 4. Studies evaluating perioperative VTE risk with estradiol treatment.

Reference	Study type	Hormone regimen	Population	Findings
Vessey *et al.*, 1970 [47]	Case-control	Oral contraceptives	30 women with postoperative (various surgeries) VTE 60 matched controls without VTE	12/30 (40%) women used OC in month prior to surgery vs. 9/60 (15%) controls (*p*=0.01), RR: 3.8
Greene *et al.*, 1972 [48]	Case-control	Oral contraceptives	60 women with postoperative, post-infection or post-traumatic VTE 60 matched controls without VTE	21/60 (35%) women used OC in month prior to admission vs. 10/60 (16.7%) controls RR (matched pair analysis): 6.5 (*p*=0.0074) RR (overall): 2.7 (*p*=0.01-0.02)
Sagar *et al.*, 1976 [49]	Case-control	Oral contraceptives	31 women with postoperative (Emergency abdominal surgery) VTE detected by fibrinogen uptake 19 controls without VTE	6/31 (19%) women used OC (2 symptomatic and 4 asymptomatic) vs. 0/19 (0%) controls. (*p*<0.05)
Astedt *et al.*, 1980 [50]	Prospective cohort	Ethinyl estradiol 50mcg or 200mcg	19 women aged >50 undergoing uterine prolapse surgery taking EE 50mcg (*n*=11) or 200mcg (*n*=8) 157 women in control group	Fibrin deposits found in 6/11 women taking 50mcg EE; 4/8 women taking 200mcg EE; 18/157 controls (*p*<0.001)
Bernstein *et al.*, 1980 [64]	Prospective cohort	Estrogens, not otherwise specified	276 women aged >50 undergoing gynecological surgery 31 of these treated with estrogen	12/31 (39%) women using estrogens vs. 35/245 (14%) those not using estrogens (*p*<0.01)
Gallus *et al.*, 1984 [51]	Prospective cohort	Oral contraceptive	221 women aged 21-49 undergoing abdominal or gynecological surgery 99 of these taking OC	0/99 (0%) women taking OC vs. 1/122 (0.8%) women not taking OC
Vessey *et al.*, 1986 [52]	Prospective cohort	Oral contraceptive	4359 not taking OC undergoing various surgeries 1244 women taking OC	12/1244 (0.96%) women taking OC in month prior to surgery vs. 22/4359 (0.5%) (*p*=NS)
Hurbanek *et al.*, 2004 [53]	Case-control	Oral or transdermal estrogens	108 patients with postoperative VTE following hip or knee arthroplasty 210 matched controls	18/108 (16.7%) women used estrogens vs. 49/210 (23.3%) controls: OR: 0.66 [95% CI, 0.35-1.18; p=0.17]
Barsoum *et al.*, 2010 [65]	Case-control	Oral contraceptive, oral or transdermal estrogens	726 women with VTE (302 hospitalized with or without surgery) 830 controls (71 matched hospitalized controls)	OC OR: 3.29 [95% CI, 1.72-6.27; (*p*<0.001] Non-contraceptive estrogen and progestin OR: 1.73 [95% CI, 1.04-2.87; *p*=0.03] Estrogen monotherapy OR: 1.32 [95% CI, 0.84-2.06; *p*=0.23]
Acuna *et al.*, 2011 [66]	Case-control	Oral contraceptive (*n*=2)	31 women with VTE following trauma 79 women without VTE	OC use vs. no use. OR: 0.70 [95% CI, 0.70-0.80]; *p*=0.41
Schulte *et al.*, 2013 [54]	Retrospective cohort	Estrogens, not otherwise specified	1469 patients following spine surgery 16 patients with postoperative VTE	Estrogens vs. no estrogens. Univariate RR: 6.2 [95% CI, 1.4-26.1]; *p*<0.01; multivariate RR, 3.1 [95% CI, 3.5-128.8]; *p*<0.07)
Park *et al.*, 2019 [55]	Retrospective cohort	Estrogens, not otherwise specified (*n*=10)	21261 patients who underwent spine surgery 444 patients with postoperative VTE	10 patients treated with estrogens, none with VTE No patients with VTE were treated with estrogens

EE, ethinyl estradiol; OC, oral contraceptives; OR, odds ratio; RR, relative risk; VTE, venous thromboembolism.

Future Directions

There is a need for prospective trials evaluating the perioperative risk of estradiol therapy in trans people. Based on safety in the menopausal hormone therapy literature, future research could give consideration to continuation of or transition to transdermal estradiol preparations in the perioperative period. Formal evaluation of the risks of cessation of estradiol on markers of quality of life, including vasomotor symptoms, mood disorders, and gender dysphoria should be undertaken.

CONCLUSION

There is currently limited evidence which supports routine cessation of estradiol regimens in the perioperative period in trans individuals at low thrombotic risk. Transdermal estradiol is not associated with VTE in postmenopausal women and could represent an alternative route of estradiol administration in the perioperative period although there is no supportive data. Future prospective trials should evaluate the safety of estradiol continuation in the perioperative period to enable evidence-based recommendations for this patient group.

REFERENCES

1. Cheung AS, Ooi O, Leemaqz S, Cundill P, Silberstein N, Bretherton I, et al. Sociodemographic and Clinical Characteristics of Transgender Adults in Australia. Transgend Health. 2018 Dec;3(1):229–38.
2. Greene DN, Schmidt RL, Winston McPherson G, Rongitsch J, Imborek KL, Dickerson JA, et al. Reproductive Endocrinology Reference Intervals for Transgender Women on Stable Hormone Therapy. J Appl Lab Med. 2020 Mar;j-faa028.
3. Hembree WC, Cohen-Kettenis PT, Gooren L, Hannema SE, Meyer WJ, Murad MH, et al. Endocrine Treatment of Gender-Dysphoric/Gender-Incongruent Persons: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab. 2017 Nov;102(11):3869–903.
4. Klaver M, de Blok CJ, Wiepjes CM, Nota NM, Dekker MJ, de Mutsert R, et al. Changes in regional body fat, lean body mass and body shape in trans persons using cross-sex hormonal therapy: results from a multicenter prospective study. Eur J Endocrinol. 2018 Feb;178(2):163–71.
5. van Kesteren PJ, Asscheman H, Megens JA, Gooren LJ. Mortality and morbidity in transsexual subjects treated with cross-sex hormones. Clin Endocrinol (Oxf). 1997 Sep;47(3):337–42.
6. Scarabin PY. Hormone therapy and venous thromboembolism among postmenopausal women. Front Horm Res. 2014;43:21–32.
7. Goldstein Z, Khan M, Reisman T, Safer JD. Managing the risk of venous thromboembolism in transgender adults undergoing hormone therapy. J Blood Med. 2019 Jul;10:209–16.
8. Vinogradova Y, Coupland C, Hippisley-Cox J. Use of hormone replacement therapy and risk of venous thrombo-embolism: nested case-control studies using the QResearch and CPRD databases. BMJ. 2019 Jan;364:k4810.
9. Asscheman H, T'Sjoen G, Lemaire A, Mas M, Meriggiola MC, Mueller A, et al. Venous thrombo-embolism as a complication of cross-sex hormone treatment of male-to-female transsexual subjects: a review. Andrologia. 2014 Sep;46(7):791–5.
10. Shatzel JJ, Connelly KJ, DeLoughery TG. Thrombotic issues in transgender medicine: A review. Am J Hematol. 2017 Feb;92(2):204–8.
11. Godano A, Maggi M, Jannini E, Meriggiola MC, Ghigo E, Todarello O, et al. SIAMS-ONIG Consensus on hormonal treatment in gender identity disorders. J Endocrinol Invest. 2009 Nov;32(10):857–64.
12. Lawrence AA. Patient-reported complications and functional outcomes of male-to-female sex reassignment surgery. Arch Sex Behav. 2006 Dec;35(6):717–27.
13. Coleman E, Bockting W, Botzer M, Cohen-Kettenis P, DeCuypere G, Feldman J, et al. Standards of Care for the Health of Transsexual, Transgender, and Gender-Non-conforming People, Version 7. Int J Transgenderism. 2011;13:165–232.
14. Cheung AS, Wynne K, Erasmus J, Murray S, Zajac JD. Position statement on the hormonal management of adult transgender and gender diverse individuals. Med J Aust. 2019 Aug;211(3):127–33.
15. Solotke MT, Liu P, Dhruva SS, Gulanski B, Shah ND, Ross JS. Medicare Prescription Drug Plan Coverage of Hormone Therapies Used by Transgender Individuals. LGBT Health. 2020 Apr;7(3):137–45.
16. Angus L, Leemaqz S, Ooi O, Cundill P, Silberstein N, Locke P, et al. Cyproterone acetate or spironolactone in lowering testosterone concentrations for transgender individuals receiving oestradiol therapy. Endocr Connect. 2019 Jul;8(7):935–40.
17. Wierckx K, Mueller S, Weyers S, Van Caenegem E, Roef G, Heylens G, et al. Long-term evaluation of cross-sex hormone treatment in transsexual persons. J Sex Med. 2012 Oct;9(10):2641–51.
18. Wierckx K, Elaut E, Declercq E, Heylens G, De Cuypere G, Taes Y, et al. Prevalence of cardiovascular disease and cancer during cross-sex hormone therapy in a large cohort of trans persons: a case-control study. Eur J Endocrinol. 2013 Sep;169(4):471–8.
19. Nota NM, Wiepjes CM, de Blok CJ, Gooren LJ, Kreukels BP, den Heijer M. Occurrence of Acute Cardiovascular Events in Transgender Individuals Receiving Hormone Therapy. Circulation. 2019 Mar;139(11):1461–2.
20. Khan J, Schmidt RL, Spittal MJ, Goldstein Z, Smock KJ, Greene DN. Venous Thrombotic Risk in Transgender Women Undergoing Estrogen Therapy: A Systematic Review and Metaanalysis. Clin Chem. 2019 Jan;65(1):57–66.
21. Asscheman H, Gooren LJ, Eklund PL. Mortality and morbidity in transsexual patients with cross-gender hormone treatment. Metabolism. 1989 Sep;38(9):869–73.
22. Seal LJ, Franklin S, Richards C, Shishkareva A, Sinclaire C, Barrett J. Predictive markers for mammoplasty and a comparison of side effect profiles in transwomen taking

various hormonal regimens. J Clin Endocrinol Metab. 2012 Dec;97(12):4422–8.

23. Arnold JD, Sarkodie EP, Coleman ME, Goldstein DA. Incidence of Venous Thromboembolism in Transgender Women Receiving Oral Estradiol. J Sex Med. 2016 Nov;13(11):1773–7.

24. Meyer G, Mayer M, Mondorf A, Fluegel AK, Herrmann E, Bojunga J. Safety and rapid efficacy of guideline-based gender affirming hormone therapy: an analysis of 388 individuals diagnosed with gender dysphoria. Eur J Endocrinol. 2019 Nov;EJE-19-0463.R2.

25. Getahun D, Nash R, Flanders WD, Baird TC, Becerra-Culqui TA, Cromwell L, et al. Cross-sex Hormones and Acute Cardiovascular Events in Transgender Persons: A Cohort Study. Ann Intern Med. 2018 Aug;169(4):205–13.

26. Wierckx K, Van Caenegem E, Schreiner T, Haraldsen I, Fisher AD, Toye K, et al. Cross-sex hormone therapy in trans persons is safe and effective at short-time follow-up: results from the European network for the investigation of gender incongruence. J Sex Med. 2014 Aug;11(8):1999–2011.

27. Ott J, Kaufmann U, Bentz EK, Huber JC, Tempfer CB. Incidence of thrombophilia and venous thrombosis in transsexuals under cross-sex hormone therapy. Fertil Steril. 2010 Mar;93(4):1267–72.

28. Scarabin PY, Oger E, Plu-Bureau G; EStrogen and THromboEmbolism Risk Study Group. Differential association of oral and transdermal oestrogen-replacement therapy with venous thromboembolism risk. Lancet. 2003 Aug;362(9382):428–32.

29. Canonico M, Oger E, Plu-Bureau G, Conard J, Meyer G, Lévesque H, et al.; Estrogen and Thromboembolism Risk (ESTHER) Study Group. Hormone therapy and venous thromboembolism among postmenopausal women: impact of the route of estrogen administration and progestogens: the ESTHER study. Circulation. 2007 Feb;115(7):840–5.

30. Renoux C, Dell'Aniello S, Suissa S. Hormone replacement therapy and the risk of venous thromboembolism: a population-based study. J Thromb Haemost. 2010 May;8(5):979–86.

31. Canonico M, Fournier A, Carcaillon L, Olié V, Plu-Bureau G, Oger E, et al. Postmenopausal hormone therapy and risk of idiopathic venous thromboembolism: results from the E3N cohort study. Arterioscler Thromb Vasc Biol. 2010 Feb;30(2):340–5.

32. Sweetland S, Beral V, Balkwill A, Liu B, Benson VS, Canonico M, et al.; Million Women Study Collaborators. Venous thromboembolism risk in relation to use of different types of postmenopausal hormone therapy in a large prospective study. J Thromb Haemost. 2012 Nov;10(11):2277–86.

33. Simon JA, Laliberté F, Duh MS, Pilon D, Kahler KH, Nyirady J, et al. Venous thromboembolism and cardiovascular disease complications in menopausal women using transdermal versus oral estrogen therapy. Menopause. 2016 Jun;23(6):600–10.

34. Laliberté F, Dea K, Duh MS, Kahler KH, Rolli M, Lefebvre P. Does the route of administration for estrogen hormone therapy impact the risk of venous thromboembolism? Estradiol transdermal system versus oral estrogen-only

hormone therapy. Menopause. 2018 Nov;25(11):1297–305.

35. Renoux C, Dell'aniello S, Garbe E, Suissa S. Transdermal and oral hormone replacement therapy and the risk of stroke: a nested case-control study. BMJ. 2010 Jun;340:c2519.

36. Connors JM, Middeldorp S. Transgender patients and the role of the coagulation clinician. J Thromb Haemost. 2019 Nov;17(11):1790–7.

37. Rosing J, Middeldorp S, Curvers J, Christella M, Thomassen LG, Nicolaes GA, et al. Low-dose oral contraceptives and acquired resistance to activated protein C: a randomised cross-over study. Lancet. 1999 Dec;354(9195):2036–40.

38. Stegeman BH, Raps M, Helmerhorst FM, Vos HL, van Vliet HA, Rosendaal FR, et al. Effect of ethinylestradiol dose and progestagen in combined oral contraceptives on plasma sex hormone-binding globulin levels in premenopausal women. J Thromb Haemost. 2013 Jan;11(1):203–5.

39. Robinson GE, Burren T, Mackie IJ, Bounds W, Walshe K, Faint R, et al. Changes in haemostasis after stopping the combined contraceptive pill: implications for major surgery. BMJ. 1991 Feb;302(6771):269–71.

40. Conard J, Samama M, Basdevant A, Guy-Grand B, de Lignières B. Differential AT III-response to oral and parenteral administration of 17 beta-estradiol. Thromb Haemost. 1983 Jun;49(3):252.

41. Høibraaten E, Mowinckel MC, de Ronde H, Bertina RM, Sandset PM. Hormone replacement therapy and acquired resistance to activated protein C: results of a randomized, double-blind, placebo-controlled trial. Br J Haematol. 2001 Nov;115(2):415–20.

42. Post MS, Christella M, Thomassen LG, van der Mooren MJ, van Baal WM, Rosing J, et al. Effect of oral and transdermal estrogen replacement therapy on hemostatic variables associated with venous thrombosis: a randomized, placebo-controlled study in postmenopausal women. Arterioscler Thromb Vasc Biol. 2003 Jun;23(6):1116–21.

43. Oger E, Alhenc-Gelas M, Lacut K, Blouch MT, Roudaut N, Kerlan V, et al.; SARAH Investigators. Differential effects of oral and transdermal estrogen/progesterone regimens on sensitivity to activated protein C among postmenopausal women: a randomized trial. Arterioscler Thromb Vasc Biol. 2003 Sep;23(9):1671–6.

44. Toorians AW, Thomassen MC, Zweegman S, Magdeleyns EJ, Tans G, Gooren LJ, et al. Venous thrombosis and changes of hemostatic variables during cross-sex hormone treatment in transsexual people. J Clin Endocrinol Metab. 2003 Dec;88(12):5723–9.

45. Lim HY, Leemaqz SY, Torkamani N, Grossmann M, Zajac JD, Nandurkar H, Ho P, Cheung AS. Global Coagulation Assays in Transgender Women on Oral and Transdermal Estradiol Therapy. J Clin Endocrinol Metab. 2020;105(7):dgaa262, https://doi.org/https://doi.org/10.1210/clinem/dgaa262..

46. Boskey ER, Taghinia AH, Ganor O. Association of Surgical Risk With Exogenous Hormone Use in Transgender Patients: A Systematic Review. JAMA Surg. 2018.

47. Vessey MP, Doll R, Fairbairn AS, Glober G. Postoperative thromboembolism and the use of oral contraceptives. Br Med J. 1970 Jul;3(5715):123–6.

48. Greene GR, Sartwell PE. Oral contraceptive use in patients with thromboembolism following surgery, trauma, or infection. Am J Public Health. 1972 May;62(5):680–5.

49. Sagar S, Stamatakis JD, Thomas DP, Kakkar VV. Oral contraceptives, antithrombin- III activity, and postoperative deep-vein thrombosis. Lancet. 1976 Mar;1(7958):509–11.

50. Astedt B, Bernstein K, Casslén B, Ulmsten U. Estrogens and postoperative thrombosis evaluated by the radioactive iodine method. Surg Gynecol Obstet. 1980 Sep;151(3):372–4.

51. Gallus AS, Chooi CC, Konetschnik F, Goodall KT. Oral contraceptives and surgery: reduced antithrombin and anti-factor Xa levels without postoperative venous thrombosis in low-risk patients. Thromb Res. 1984 Sep;35(5):513–26.

52. Vessey M, Mant D, Smith A, Yeates D. Oral contraceptives and venous thromboembolism: findings in a large prospective study. Br Med J (Clin Res Ed). 1986 Feb;292(6519):526.

53. Hurbanek JG, Jaffer AK, Morra N, Karafa M, Brotman DJ. Postmenopausal hormone replacement and venous thromboembolism following hip and knee arthroplasty. Thromb Haemost. 2004 Aug;92(2):337–43.

54. Schulte LM, O'Brien JR, Bean MC, Pierce TP, Yu WD, Meals C. Deep vein thrombosis and pulmonary embolism after spine surgery: incidence and patient risk factors. Am J Orthop (Belle Mead NJ). 2013 Jun;42(6):267–70.

55. Park JH, Lee KE, Yu YM, Park YH, Choi SA. Incidence and Risk Factors for Venous Thromboembolism After Spine Surgery in Korean Patients. World Neurosurg. 2019 Aug;128:e289–307.

56. Goddard JC, Vickery RM, Qureshi A, Summerton DJ, Khoosal D, Terry TR. Feminizing genitoplasty in adult transsexuals: early and long-term surgical results. BJU Int. 2007 Sep;100(3):607–13.

57. Gaither TW, Awad MA, Osterberg EC, Murphy GP, Romero A, Bowers ML, et al. Postoperative Complications following Primary Penile Inversion Vaginoplasty among 330 Male-to-Female Transgender Patients. J Urol. 2018 Mar;199(3):760–5.

58. Davidge-Pitts C, Herndon J, Nippoldt T, Imhof N, Gonzalez C, Martinez-Jorge J, et al. MON-197 Peri-operative Outcomes of Vaginoplasty Using an Individualized Approach to Hormone Management in Transgender Women. Journal of the Endocrine Society. 2019;3(Supplement_1).

59. Schneider F, Neuhaus N, Wistuba J, Zitzmann M, Heß J, Mahler D, et al. Testicular Functions and Clinical Characterization of Patients with Gender Dysphoria (GD) Undergoing Sex Reassignment Surgery (SRS). J Sex Med. 2015 Nov;12(11):2190–200.

60. Prior JC, Vigna YM, Watson D. Spironolactone with physiological female steroids for presurgical therapy of male-to-female transsexualism. Arch Sex Behav. 1989 Feb;18(1):49–57.

61. Schlatterer K, Yassouridis A, von Werder K, Poland D, Kemper J, Stalla GK. A follow-up study for estimating the effectiveness of a cross-gender hormone substitution therapy on transsexual patients. Arch Sex Behav. 1998 Oct;27(5):475–92.

62. Dittrich R, Binder H, Cupisti S, Hoffmann I, Beckmann MW, Mueller A. Endocrine treatment of male-to-female transsexuals using gonadotropin-releasing hormone agonist. Exp Clin Endocrinol Diabetes. 2005 Dec;113(10):586–92.

63. Wilson R, Spiers A, Ewan J, Johnson P, Jenkins C, Carr S. Effects of high dose oestrogen therapy on circulating inflammatory markers. Maturitas. 2009 Mar;62(3):281–6.

64. Bernstein K, Ulmsten U, Astedt B, Jacobsson L, Mattsson S. Incidence of thrombosis after gynecologic surgery evaluated by an improved 125I-fibrinogen uptake test. Angiology. 1980 Sep;31(9):606–13.

65. Barsoum MK, Heit JA, Ashrani AA, Leibson CL, Petterson TM, Bailey KR. Is progestin an independent risk factor for incident venous thromboembolism? A population-based case-control study. Thromb Res. 2010 Nov;126(5):373–8.

66. Acuña DL, Berg GM, Harrison BL, Wray T, Dorsch D, Sook C. Assessing the use of venous thromboembolism risk assessment profiles in the trauma population: is it necessary? Am Surg. 2011 Jun;77(6):783–9.