European Review for Medical and Pharmacological Sciences 2022; 26: 2511-2517

Continuing perioperative estrogen therapy does not increase venous thromboembolic events in transgender patients: a systematic review and meta-analysis

J. BADREDDINE[1], M.H. LEE[2], K. MISHRA[3], R. POPE[1], J.Y. KIM[2], S.H. HONG[4], S. GUPTA[1], J.M. SONG[5], J.I. SHIN[6], R.A. GHAYDA[1]

[1]Urology Institute, University Hospitals Cleveland Medical Center, Cleveland, OH, USA; Case Western Reserve University School of Medicine, Cleveland, OH, USA
[2]Yonsei University College of Medicine, Seoul, Republic of Korea
[3]NYU Langone Health, Department of Urology, New York, USA
[4]Severance Hospital, Yonsei University Health Systems, Seoul, Republic of Korea
[5]Keimyung University School of Medicine, Daegu, Republic of Korea
[6]Department of Pediatrics, Yonsei University College of Medicine, Seoul, Republic of Korea

J. Badreddine and M.H. Lee are co-first authors

Abstract. – OBJECTIVE: The aim of this study is to compare the risk of venous thromboembolic events (VTE) between patients suspending and continuing estrogen therapy perioperatively, in male to female gender-affirming surgery (vaginoplasty).

MATERIALS AND METHODS: The authors conducted a systematic review and meta-analysis of existing research on male to female gender-affirming study, which compared the risk of VTE among the usage of estrogen perioperatively.

RESULTS: A total of 209 studies were identified as potentially eligible among PubMed, Embase, and Cochrane library databases. Among the studies, 191 studies were excluded due to their abstract inappropriateness. Out of the remaining 18 studies, only 3 articles were eligible and were finally included. Meta-analysis was performed and showed odds ratio of 0.77 (95% CI: 0.04, 14.01).

CONCLUSIONS: Perioperative estrogen therapy does not increase VTE risk on male to female gender-affirming surgery. Therefore, estrogen therapy may be continued perioperatively in vaginoplasty. More prospective studies are needed.

Key Words:
Gender-affirming surgery, Hormone replacement therapy, HRT, Vaginoplasty, Transgender, Perioperative estrogen.

Introduction

Awareness about transgender health and recognition of their health needs has significantly increased over the past few decades. This has subsequently led to a steep surge in the medical and surgical offerings in order to cater to the well-being and health of the transgender society. Within these advancements, there are several possible options for treating transgender patients, but to sum up, patients usually start with hormone replacement therapy and then move up to gender affirming surgeries[1]. While these treatment options brought great advancement in transgender society, hormonal and surgical treatments have their risks. In hormonal treatments, venous thromboembolic events (VTE) is rare but is the most consistent and eminent complication[2]. A study[2] shows that the estrogen-progestin trial doubles the risk of VTE, with an actual increase of 0.18% points, and the estrogen-only trial increases the risk by 33%, with an actual increase of 0.07% points. In contrast, in gender affirming surgeries, neo-vaginal stenosis was the most reported complication (7% to 12% in penile inversion vaginoplasty; 1.2% to 43% in bowel vaginoplasty), followed by rectal injury such as rectovaginal fistula (2% to 4.2%). Other complications include urethral meatal stenosis (1% to

Corresponding Author: Jae Il Shin, MD, Ph.D; e-mail: shinji@yuhs.ac

6%), wound dehiscence (12% to 33%), bleeding (3.2% to 10%), and VTE[3,4]. Therefore, both gender affirming surgeries and the use of hormone replacement therapy are independent risk factors for VTE[5,6]. Plus, hormone management in the perioperative transgender surgery period and the associated risk of VTE has always been a controversial debate in this field due to the absence of evidence-based recommendations and expert consensus as to suspend or continue hormone replacement therapy in the perioperative period. Small cohort studies and a lack of randomization have limited the estimation of the lifetime risk of venous thrombosis in the transgender population. As a result, different centers have established their own institutional protocols on the interruption, or not, of hormone replacement therapy before and/or after transgender surgery[7,8]. There have been very few studies that addressed this issue. So, we have performed a systemic review and meta-analysis to summarize the overall effect of the use of perioperative estrogen on the incidence of VTE in patients receiving male to female transgender surgery.

Materials and Methods

Literature Search Strategy and Study Selection

This review was conducted with in accordance with Preferred Reporting Items for Systemic Review and Meta-Analysis (PRISMA) statement. Two investigators (JB and MHL) independently searched in PubMed, Embase, and Cochrane library databases up to January 31, 2021, for studies evaluating the risk of VTE in transgender patients using perioperative estrogen with the following keywords and their MeSH terms*:* male-to-female transition, transgender, gender reassignments/affirming surgery, estrogen, perioperative, vaginoplasty. Within the searched articles, investigators progressively examined the titles, abstract, and the full-text. Furthermore, the investigators searched for the reference articles to find out additional eligible articles. The selected articles were then reviewed and determined by other coauthors for final inclusion. If there was disagreement between the coauthors, third senior author (JIS) held a discussion and agreement was made between the reviewers.

Studies were considered eligible if they included patients undergoing gender-affirming vaginoplasty that either continued or intentionally discontinued estrogen therapy and documented the incidence of postoperative VTE in both cohorts. The quality of observational studies was evaluated using the Newcastle-Ottawa Scale. The primary outcome of interest measured the occurrence of post-operative VTE in the two groups. With the extracted data, meta-analysis was performed to aggregate odds ratio of VTE among the two groups after gender-affirming vaginoplasty.

Data Extraction

From each eligible article, study design, risk of bias, quality, number of patients, control group characteristics, type of hormone used, outcome, type of surgery, relevant results, and recommendations were extracted. Then, meta-analysis was performed

Statistical Analysis

Odds ratio between two groups (hormone therapy suspended *vs.* hormone therapy continued after the surgery) were calculated. Adjusted measures of association and the corresponding 95% confidence intervals (CIs) from each study were pooled using a random-effects model. The "tau" measurement and related metric, the I^2 statistics, were used to evaluate heterogeneity across studies. The meta-analysis was performed using Review Manager 5.4.1 and R 4.0.4 and its packages.

Results

Figure 1 exhibits PRISMA diagram of the study process. A total of 209 reports (PubMed 93, Embase 115, Cochrane library 1) were identified as potentially relevant studies after completing our database searches. 191 studies were excluded through screening after assessing their eligibility based on the title and abstract and removing duplicates. 18 studies were subjected to full-text screening, of which 15 were excluded for the following reasons: 6 did not report the outcome of interest, 6 were only abstracts, 1 was a review article, 1 was not related to the topic, and 1 was written in a language other than English. At last, a total of 3 articles were included in our description. The characteristics of the 3 included studies are summarized in Table I[9-11]. All reports were retrospective cohort studies and are deemed good quality with a Newcastle-Ottawa Scale score of 7 except for one article (Table II)[9].

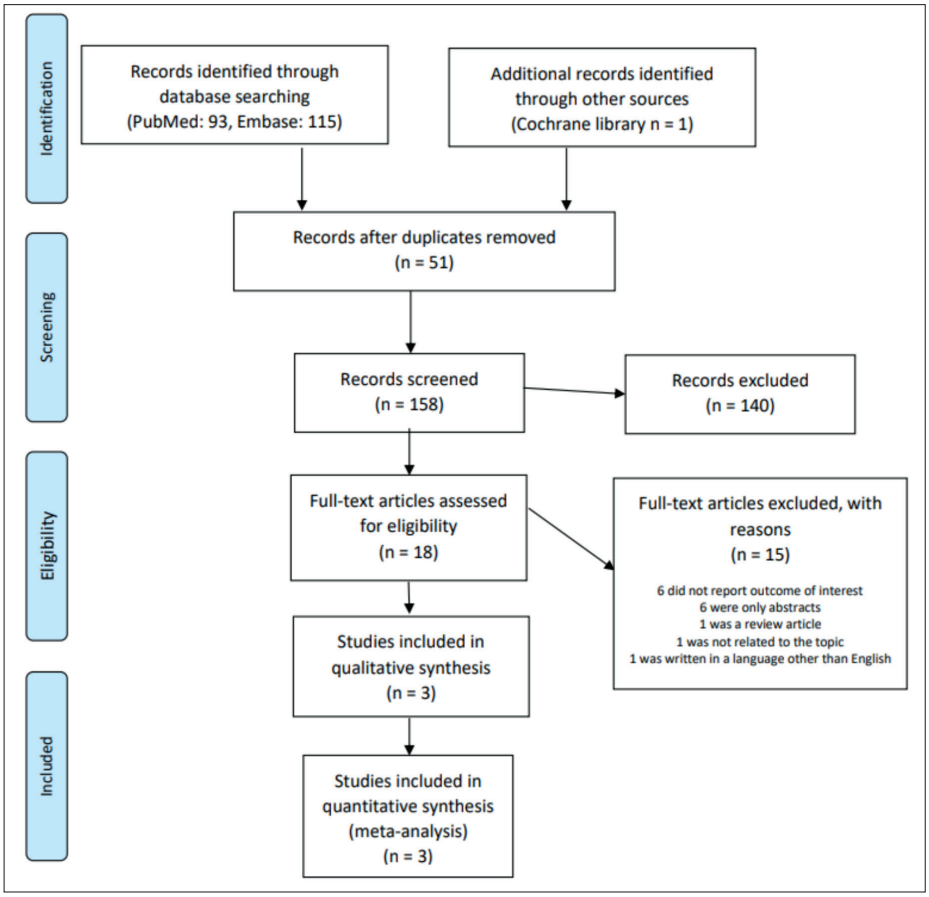

Figure 1. PRISMA flow diagram.

In Nolan et al[11], a total of 178 patients had penile inversion vaginoplasty in the United States, and the patients were divided into two groups. Group 1 were consisted of 117 patients who discontinued estrogen two weeks before the surgery and continued after one week of the surgery. On the contrary, 61 patients in group 2 did not stop the estrogen and continued it perioperatively. The primary outcome of the study was 90-day VTE rate. Other complications and Caprini score, which is a measurement of risk of VTE, was also measured[12]. In this study, results differed from conventional idea. Group 1, estrogen discontinued group, had higher Caprini Score of 4 compared to group 2 (Caprini Score of 3), estrogen continued group. Also, complications were higher in the group 1 (group 1 2.2 *vs.* group 2 0.9, $p < 0.001$) and rates of 90-day VTE did not have statistically meaningful difference (0.0% *vs.* 1.6%, $p = 0.166$).

In Kozato et al[10], a total of 407 patients had primary vaginoplasty. Similar to Nolan et al[11], these patients were divided into two groups. In the first group of 190 patients, estrogen was discontinued from one week before the surgery and in the second group 212 patients continued estrogen throughout the perioperative period. 5 patients did not have hormone replacement therapy. Within the mean postoperative follow-up of 285 days, only one patient in the first (estrogen discontinuing group) group had VTE and none suffered from VTE in the second group, stating the risk of VTE among the vaginoplasty and hormone therapy being fairly low.

In Gaither et al[9], 330 patients had penile inversion vaginoplasty and the post operational records were reviewed. Within the stud population, the most common complication was formation of granulation tissue (24, 7.3%), wound separation (17, 5.2%), rectoneovaginal fistula (3, 0.9%), vesiconeovaginal fistula (3, 0.9%). No patient had VTE or related complications of thrombosis. In this study, multivariable logistic regression was performed between risk factors (age, body mass index, years on hormone replacement therapy, and clinic distance) and major three complication occurrences (fistula, wound separation or granulation tissue, and vaginal stenosis). Only

Table I. Baseline characteristics of studies included.

Source	Design	Risk of bias/ Quality*	Population	Control or comparison population	Hormones studied	Outcome	Type of surgery	Relevant results	Recommendations
Nolan, 2021[11]	Retrospective pre/post study	Low/7	178 patients who have undergone Penile Inversion Vaginoplasty	Group 1: 117 patients who stopped estrogen therapy for 2 weeks before surgery and resumed 1 week postoperatively Group 2: 61 patients who continued estrogen therapy perioperatively	Estrogen therapy	90-day VTE rate	Penile Inversion Vaginoplasty	Median Caprini Score was 4 in group 1 and 3 in group 2. Complications per patient were higher in group 1. Rates of 90-day VTE were not different between groups	This study suggests that perioperative estrogen continuation may be safe for patients undergoing Penile Inversion Vaginoplasty
Kozato, 2021[10]	Retrospective study	Low/7	919 patients who underwent gender-affirming surgery	662 transfeminine patients (407 vaginoplasties): 190 cases performed with estrogen suspended for 1 week prior to surgery, 212 continued HT, and 5 patients had no perioperative HRT	Hormone therapy including estrogen therapy	VTE events, Caprini score	Gender-affirming surgery	Perioperative VTE was not a significant risk in a large, homogenously treated cohort of TGNB patients independent of whether HT was suspended or not prior to surgery	Estrogen HT suspension is not necessary for the transfeminine patient undergoing gender-affirming surgery
Gaither, 2018[9]	Retrospective study	Serious/4	330 men presented for primary penile inversion vaginoplasty	NA	Hormone replacement therapy including estradiol Estradiol tapered to 2 mg at least 2 weeks before surgery, progesterone and spironolactone discontinued	Incidence of vaginal pain, wound separation, labial asymmetry), vaginal stenosis, fistula, a deflecting, vaginal fissure, vaginal bleeding, difficulty dilating, DVT or pulmonary embolism	Primary penile inversion vaginoplasty	No DVT or PE reported	Age, BMI and hormone replacement therapy are not associated with complications and, thus, they should not dictate the timing of surgery

Table II. New-Castle Ottawa scale.

Cohort studies	Selection				Comparability	Outcome			Total quality score	Ref
Author, year	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Demonstration that the current outcome of interest was not present at start of study	Comparability of cohorts on the basis of the design or analysis	Assessment of outcome	Was follow-up long enough for outcomes to occur	Adequacy of follow up of cohorts		
Nolan, 2021		*	*		**	*	*	*	7	11
Kozato, 2021	*	*	*		**	*	*		7	10
Gaither, 2018		*	*			*	*	*	5	9

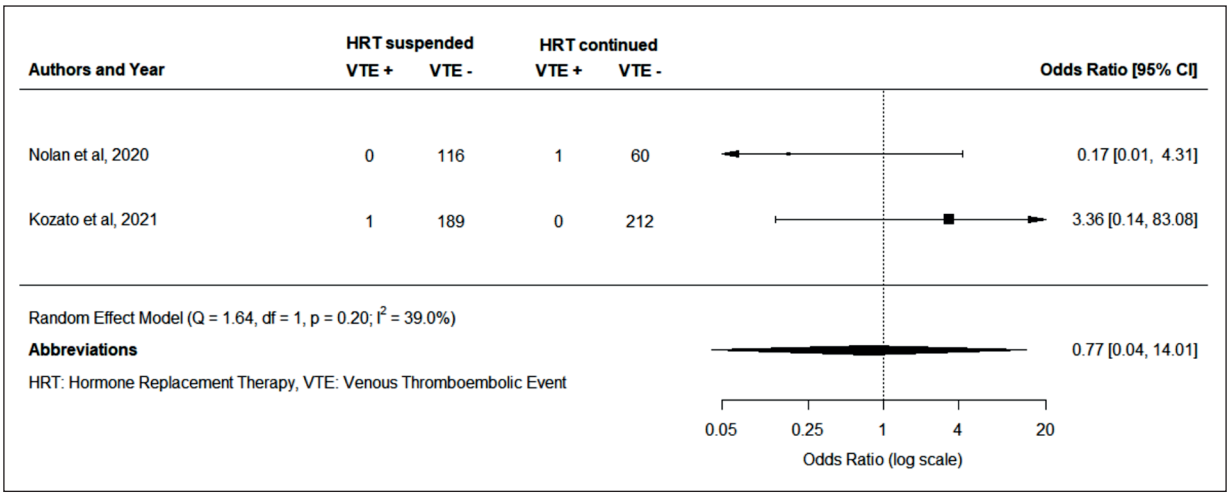

Figure 2. Meta-analysis of two retrospective studies.

clinic distance showed statistically significance for the wound separation or granulation tissue (odds ratio 0.93, 95% CI 0.88-0.97) and other risk factors, such as age, body mass index, years on hormone replacement therapy were irrelevant to the complications.

Out of three eligible studies, two studies, which presented odds ratio of VTE among perioperative estrogen therapy, were able to be included. With those two studies[10,11], meta-analysis was performed and non-significant association between the perioperative use of estrogen and postoperative risk of VTE was shown (Figure 2; pooled OR = 0.77; 95% CI, 0.04 to 14.01).

Discussion

Gender-affirming surgery is a definite solution to the transgender patients, while hormone replacement therapy such as estrogen therapy is essential for morphological and psychological integrity[13]. However, until current days, many debates about continuing estrogen therapy have been unresolved.

While there are few studies on transgender patients among this subject, it is clear that the risk of VTE is minimal among the gender affirming surgery and estrogen therapy. The finding of our meta-analysis suggests continuing estrogen therapy perioperatively may be safe for patients undergoing penile inversion vaginoplasty. In other words, discontinuing estrogen perioperatively seems unnecessary due to low risk of VTE. Nevertheless, physicians should evaluate each case carefully, engage their patients with an active discussion in making this decision, and weigh the risks and benefits of suspending/continuing estrogen therapy in the perioperative period.

The findings of this systemic review and meta-analysis should be interpreted in light of its limitations. First, our meta-analysis only included studies of the retrospective design, and the generalizability of the findings may be limited. Prospective studies are required to substantiate our findings. Second, number of studies are relatively small and there may be a publication bias. Nevertheless, estimating and presenting the odds ratio into concrete number instead of ambiguous words would be more beneficial when consulting patients.

Conclusions

Perioperative estrogen therapy does not increase the risk of VTE in male to female gender-affirming surgery.

Conflict of Interest

The Authors declare that they have no conflict of interests.

Consent for Publication

All authors confirmed the final version and gave their approval to be published.

Availability of Data and Materials

The datasets analysed during the current study are available from the corresponding author on reasonable request.

Funding
No financial support was provided for research conduct and/or preparation of the article.

Authors' Contribution
All authors made substantial contributions to this manuscript; (1) conception and design of the study, data acquisition, or analysis and interpretation of data; (2) drafting or critical revision of the article for intellectual content; and (3) final approval of version to be submitted.

References

1) Atkinson SR, Russell D. Gender dysphoria. Aust Fam Physician. 2015; 44: 792-796.
2) Randolph JF, Jr. Gender-Affirming Hormone Therapy for Transgender Females. Clin Obstet Gynecol 2018; 61: 705-721.
3) Baumeister S, Sohn M, Domke C, Exner K. [Phalloplasty in female-to-male transsexuals: experience from 259 cases]. Handchir Mikrochir Plast Chir 2011; 43: 215-221.
4) Salim A, Poh M. Gender-Affirming Penile Inversion Vaginoplasty. Clin Plast Surg 2018; 45: 343-350.
5) Pan S, Honig SC. Gender-Affirming Surgery: Current Concepts. Curr Urol Rep 2018; 19: 62.
6) Zucker R, Reisman T, Safer JD. Minimizing Venous Thromboembolism in Feminizing Hormone Therapy: Applying Lessons From Cisgender Women and Previous Data. Endocr Pract 2021; 27: 621-625.
7) Tangpricha V, den Heijer M. Oestrogen and anti-androgen therapy for transgender women. Lancet Diabetes Endocrinol 2017; 5: 291-300.
8) Wylie K, Knudson G, Khan SI, Bonierbale M, Watanyusakul S, Baral S. Serving transgender people: clinical care considerations and service delivery models in transgender health. Lancet 2016; 388: 401-411.
9) Gaither TW, Awad MA, Osterberg EC, Murphy GP, Romero A, Bowers ML, Breyer BN. Postoperative Complications following Primary Penile Inversion Vaginoplasty among 330 Male-to-Female Transgender Patients. J Urol 2018; 199: 760-765.
10) Kozato A, Fox GWC, Yong PC, Shin SJ, Avanessian BK, Ting J, Ling Y, Karim S, Safer JD, Pang JH. No Venous Thromboembolism Increase Among Transgender Female Patients Remaining on Estrogen for Gender-Affirming Surgery. J Clin Endocrinol Metab 2021; 106: e1586-e1590.
11) Nolan IT, Haley C, Morrison SD, Pannucci CJ, Satterwhite T. Estrogen Continuation and Venous Thromboembolism in Penile Inversion Vaginoplasty. J Sex Med 2021; 18: 193-200.
12) Golemi I, Salazar Adum JP, Tafur A, Caprini J. Venous thromboembolism prophylaxis using the Caprini score. Dis Mon 2019; 65: 249-298.
13) Nguyen HB, Chavez AM, Lipner E, Hantsoo L, Kornfield SL, Davies RD, Epperson CN. Gender-Affirming Hormone Use in Transgender Individuals: Impact on Behavioral Health and Cognition. Curr Psychiatry Rep 2018; 20: 110.