

1 **Venous thrombotic Risk in Transgender Women Undergoing Estrogen Therapy: A Systematic Review**  
2 **and Meta-Analysis**

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20 Keywords:

21 Transgender, Transsexual, Trans women, Male to female, Cross-sex hormone therapy,  
22 Hormones, Estrogen, Thrombosis, Thromboembolism, Embolism

23

## 24 **ABSTRACT (250 Words)**

### 25 Background

26 Transgender women are individuals who were assigned as male at birth based on their biological sex,  
27 but who identify as female. Supporting a transgender person's gender identity can improve their  
28 psychological health, preventing gender dysphoria and its associated morbidities. One important  
29 component of medical care is estrogen administration for feminization. Previous reviews have reported  
30 conflicting literature on the thrombotic risk of estrogen therapy in transgender women and have  
31 highlighted the need for more high quality research.

### 32 Content

33 To help address the gap in understanding of thrombotic risk in transgender women on estrogen therapy,  
34 we performed a systematic review and meta-analysis of the literature. Two evaluators independently  
35 assessed study quality using the Ottawa Scale for Cohort Studies. The Poisson-normal model was used  
36 to estimate the study-specific incidence rates and the pooled incidence rate. Heterogeneity was  
37 measured using Higgins  $I^2$  statistic. The overall estimate of the incidence rate was 0.0023 (95% CI:0.0008  
38 – 0.0069). The heterogeneity was significant ( $I^2 = 74%$ ,  $p = 0.0039$ ).

### 39 Summary

40 Our data suggest that the overall risk of thrombotic events in transgender women taking estrogen  
41 therapy is slightly higher than in the general population and comparable to the risk of thrombotic events  
42 associated with oral contraceptives in premenopausal women, making them a clinically acceptable  
43 therapy. There was insufficient data for subgroup analysis. Additional studies of current estrogen  
44 formulations, modes of administration, and combination therapies, as well as studies in the aging  
45 transgender population, are needed to confirm thrombotic risk and clarify optimal therapy regimes.

## 46 INTRODUCTION

47

48 Biological sex is defined at birth, typically by the visual appearance of the infant genitalia indicating the  
49 reproductive organs specific to the chromosomal make up. In contrast, gender is a psychosocial  
50 characteristic that develops with a sense of self. Social norms are generally based on the assumption  
51 that sex and gender are synonymous, but this is an unfortunate overgeneralization that leads to  
52 stereotypes and biases against those who experience gender/sex incongruence.

53

54 People who are transgender do not experience their gender as defined by their sex. This experience is  
55 not pathological, but the distress compounded from daily encounters of identity misrepresentation can  
56 lead to gender dysphoria, which is associated with depression, anxiety, and suicidal ideation(1). A  
57 national survey that solicited feedback from over 6,000 transgender people indicated that the suicide  
58 attempt rate for the transgender population is approximately 9 times that of the general population  
59 (40% vs 4.6%)(2). Standards of care endorse that supporting a transgender person's gender identity,  
60 rather than trying to identify the etiology or impose the natal sex as gender, significantly improves their  
61 psychosocial health(3). Not all transgender people seek medical interventions to affirm their gender  
62 but, for those who do, hormone therapy and/or gender affirmative surgeries are common.

63

64 Transgender women (also referred to as trans women or MtF) were assigned male at birth, but identify  
65 as female. Trans feminine individuals will also have been assigned male at birth, but identify on a  
66 gender spectrum rather than a distinct binary. Medical management of these populations includes  
67 estrogen administration, the goal of which is to feminize by softening skin, altering hair growth patterns,

68 redistributing body fat, altering mood, and decreasing erections (4). Estrogen can be administered  
69 orally, topically, or intramuscularly and is most often co-administered with androgen inhibitors such as  
70 spironolactone or cyproterone. Although guidelines have been published, there is international  
71 variation in prescribing practices, as well as variability in individual compliance and self-medication (3, 5,  
72 6).

73

74 Although hormone therapy is considered a vital component of care by clinicians familiar with treating  
75 transgender individuals, many primary care physicians are not familiar with management and may be  
76 hesitant to prescribe hormone therapy (7). Lack of access to physicians competent in prescribing  
77 gender-affirming hormones has been shown to play a role in unprescribed hormone use (8).

78 Documenting the risks associated with hormone treatment may allow for physicians to feel more  
79 comfortable with prescribing practices, allowing for better overall management of transgender people  
80 (9).

81

82 Previous studies on the clinical effects of combined oral contraceptives or hormone replacement  
83 therapy indicate that exogenous estrogen and/or progesterone is associated with an increased risk of  
84 thrombotic events (10, 11). This is not unexpected, as both of these hormones are responsible for  
85 hemostasis during pregnancy and delivery, and result in increased thrombotic risk during this time.  
86 Given this background, it was generally assumed that hormone therapies would also increase the risk of  
87 thrombotic events in trans women. While this is a reasonable hypothesis, it is not clear that studies  
88 focused on hormone replacement therapy in peri/post menopausal women or on oral contraceptives in  
89 premenopausal women can be generalized to predict the risk of hormone therapy in transgender  
90 women. Transgender women differ in important ways. For example, transgender women use different

91 estrogen formulations, different doses, differ in age, and, of course, differ with respect to biological sex.  
92 For that reason, studies specific to populations of trans women are necessary.

93

94 There have been several previous reviews describing the potential for estrogen to increase thrombotic  
95 risk in transgender women (4, 12, 13). These reviews have highlighted the conflicting literature, but no  
96 one has attempted to combine the results of individual studies to estimate the risk of estrogen therapy  
97 in transgender women. This is problematic because most studies in this area tend to be small and  
98 estimates from individual studies will have low reliability. A recent review highlighted thrombosis as a  
99 priority in outcomes-based research for transgender women because understanding risk can allow  
100 physician and patient to make informed decisions (14). Meta-analysis can combine the results of  
101 previous studies to provide better risk estimates. The objective of this study was to conduct a systematic  
102 review and meta-analysis to provide an estimate of the risk of venous thrombotic events associated with  
103 estrogen therapy in transgender women based on all available evidence.

104

## 105 **METHODS**

106 This systematic review and meta-analysis was conducted according the Cochrane Guidelines for  
107 studies on interventions(15). We also followed Preferred Reporting Items for Systematic Reviews and  
108 Meta-analysis (PRISMA) guidelines(16). A protocol was registered in the Prospero database.

109 Literature Search: Search strategies were developed in consultation with a medical reference librarian  
110 (see Supplementary Materials) and executed on April 11, 2018. In brief, we searched PubMed and  
111 Embase for studies that included the incidence of thrombotic events in MtF transsexuals receiving

112 estrogen therapy. There were no language or date restrictions. Two additional articles were identified  
113 by hand searching the references of the included articles.

114 Study Selection: References were stored and reviewed using Covidence software for systematic reviews  
115 (<https://www.covidence.org>). Titles and abstracts were independently evaluated for inclusion by two  
116 authors (DG, JK) and discrepancies were resolved by discussion. Full-text review of the potentially  
117 relevant articles was independently performed by (DG, JK) and discrepancies were resolved by  
118 discussion and third-party review (RS). Each article had data extraction performed independently by  
119 two authors (either RS, JK or DG, KS). Studies were included if they had extractable data on the number  
120 of thrombotic events per formulation and mode of administration of estrogen therapy. Authors were  
121 contacted for clarification if studies lacked data components necessary for analysis.

122 Quality Appraisal: Study quality (risk of bias, lack of generalizability) was independently evaluated by  
123 two authors (DG, RS) using the Ottawa Scale for Cohort Studies(17). Discordant results were resolved  
124 by discussion.

125 Data Extraction: We used a data collection form to extract data from included articles. We extracted  
126 data on the following items: author, date, and language of publication; study design and control group;  
127 location and timeframe of the treatment cohort; age range and underlying conditions of the patient  
128 population; and doses and treatment duration of estrogen therapy. We created a tabulation of the  
129 number of treated patients with and without a thrombotic event by mode and formulation of estrogen  
130 therapy.

131 Statistical Methods: We evaluated thrombotic risk by calculating the incidence rate of venous  
132 thrombotic events (events per person year). Most studies did not categorize thrombotic events as  
133 provoked (e.g. post-surgery, related to trauma) or unprovoked. Thus, the incidence rate includes all  
134 thrombotic events (provoked and unprovoked).

135 Meta-analysis was performed using the *metafor* package in R (R Foundation for Statistical  
136 Computing)(18). We used the Poisson-normal model to estimate the study-specific incidence rates and  
137 the pooled incidence rate. We used this model because in 7 of our 12 studies there were zero events  
138 meaning that the estimates could not be calculated using standard meta-analysis methods. The Poisson-  
139 normal has been shown previously to estimate these parameters without bias in studies with structural  
140 zeros (19). Heterogeneity was measured using Higgins  $I^2$  statistic(20).

141

## 142 **RESULTS**

143 Literature Search: Initial search results selected 2,032 references for abstract screening (Figure 1). Of  
144 these, 1,080 duplicates were removed and the remaining 952 abstracts were screened. Abstract  
145 screening indicated that 868 of the references were irrelevant; 84 references proceeded to full text  
146 review. Case reports and review articles were the most common exclusion (n=18 each), while wrong  
147 outcome (n=10) and wrong study design (n=11) also excluded a significant percent. After excluding  
148 commentaries (n=9), duplicates (n=4), and wrong patient population or wrong setting (n=1 each) 12  
149 articles/abstracts remained for data extraction(21-32).

150 Characteristics of included studies: We identified twelve studies with data that allowed us to make  
151 quantitative estimates of the risk of thrombotic events in MtF transsexuals receiving estrogen therapy  
152 (Table 1). All of the studies were single arm (no controls) cohort studies. Ten of the studies (83%) were  
153 conducted in Europe, mainly in the Netherlands and Belgium; one study was conducted in the US and  
154 one in Canada. The crude incidence rate varied from 0 to 0.009 in individual studies (Figure 2).

155 Earlier studies (before approximately year 2000) administered oral conjugated equine estrogen or  
156 ethinyl oestradiol treatment; those after were more likely to administer oral, topical, or intramuscular  
157 estradiol valerate. Studies that spanned the time periods included a mixed cohort. Anti-androgen

158 administration remained consistent, with some European countries preferring cyproterone and others  
159 preferring GnRH agonists; spironolactone is the commonly prescribed anti-androgen in the US.

160 Duration of monitoring for thrombotic events ranged from 1-10 years, with 7 of the studies having a  
161 duration less than or equal to 2 years and 6 of the studies having a duration of greater than or equal to  
162 3.8 years.

163 Sample sizes were variable across the different studies and ranged from 32-816 individuals, 7 of the  
164 studies included less than or equal to 60 participants.

165  
166 Venous thrombotic risk: The overall estimate of the incidence rate was 0.0023 (95% CI:0.0008 – 0.0069)  
167 (Table 1, Figure 2). The heterogeneity was significant ( $I^2 = 74%$ ,  $p = 0.0039$ ).

168 Quality Appraisal: Studies had variable quality, depending on the metric. All studies had excellent  
169 rankings for representativeness of the exposed cohort, ascertainment of exposure, demonstrating that  
170 the outcome of interest was not present at the start of the study, assessment of outcome and adequacy  
171 of follow-up. Studies had moderate ratings for length of follow-up being sufficient for outcomes to  
172 occur (assuming one event/500 patient-years). The most apparent quality limitation of the studies was  
173 their ability to utilize control groups, which was indicated by the poor scores for selection of exposed  
174 cohort and comparability of cohorts.

## 175 **DISCUSSION**

176 This review provides an estimate of the crude incidence rate for venous thrombotic events in  
177 transgender women treated with estrogen therapy. We used meta-analysis to combine the results from  
178 12 studies and estimated that the incidence rate was 0.0023 (95% CI:0.0008 – 0.0069). The estimated  
179 incidence rate of thrombotic events in the general population is between 0.00104 and 0.00183(33). The

180 estimated relative risk of thrombotic events in pre-menopausal women prescribed combined oral  
181 contraceptives is 3.5 (95% CI: 2.9-4.3) (10). Our data suggest that the risk of thrombotic events in trans  
182 women taking estrogen therapy is slightly higher than the risk of thrombotic events in the general  
183 population and comparable to the risk of thrombotic risks associated with oral contraceptives in  
184 premenopausal women.

185 We found significant heterogeneity in the estimates of thrombotic risk between studies. This is  
186 consistent with the informal findings of previous narrative reviews. Unfortunately, the number of  
187 studies was insufficient to perform subgroup analyses to explore the sources of heterogeneity. There  
188 are many potential sources of heterogeneity. These include mode of administration (oral vs  
189 transdermal), dose, type of androgen blocker (spironolactone vs cyproterone acetate). Given the  
190 variation in these factors, it is not surprising that we found significant heterogeneity in the estimated  
191 incidence rates. Although the heterogeneity is statistically significant, it is unlikely that it is clinically  
192 significant. Oral contraception is widely accepted and, as noted above, is about 3.5 times greater than  
193 the background risk in the general population. By comparison, our results suggest that the risk of  
194 therapy in trans women is approximately 50 to 80% greater than the background risk. When compared  
195 to the risk associated with oral contraception, the heterogeneity in results in thrombotic risk to trans  
196 women has little practical impact. Thus, despite the presence of statistically significant heterogeneity,  
197 our results suggest the risk of thrombosis associated with estrogen treatment in transgender women is  
198 clinically acceptable.

199 Our study may overestimate the risk of thrombosis because we included several older studies  
200 (i.e., pre ~2000) that included data prior to the introduction of estrogen valerate. The conjugated and  
201 synthetic estrogens previously prescribed are thought to pose more of a thrombotic risk. There is  
202 controversy regarding if this increased risk is due to the type of estrogen or the route of administration  
203 (34). The earlier estrogens were administered orally only; estrogen valerate is administered orally,

204 intramuscularly, and topically. The existing data isn't partitioned in a way that allows us to discriminate  
205 between modes of estrogen valerate administration. Additionally, we wanted to include all available  
206 studies from the literature. Thus, our meta-analysis most likely over-estimates thrombotic risk of  
207 contemporary prescribing practices.

208 A gap in the literature is that the majority of studies were performed in Europe, which has different  
209 prescribing practices compared to the US. In general, European countries will have nationalized  
210 healthcare that allows for the standardized treatment of trans feminine gender incongruence. In  
211 contrast, the US has a diverse range of patients with differing access to care (9). Additionally, the anti-  
212 androgens commonly used in Europe are not FDA cleared for use in the US (cyproterone acetate) or are  
213 cost prohibitive (GnRH agonists). This distinction is not only relevant for calculating thrombotic risk, but  
214 also relevant to almost any study that seeks to investigate the influence of hormonal treatment on  
215 transgender women. Of the 12 articles included in our study, 10 were from European countries (and  
216 one was from Canada), which did not allow for sufficient data to perform a sub-group analysis.  
217 Determining whether there is a difference in rate of thrombotic events between the European and  
218 American therapeutic regimens should be an area of future study. In general, there is a need for more  
219 clinical data particular to the transgender population in the US.

220

221 There are several limitations to our analysis. First, there was insufficient data to compare risk  
222 associated with different therapies. We could not perform subgroup analysis to investigate sources of  
223 heterogeneity. Second, the studies did not include control groups, which limited our analysis to  
224 reporting the crude incidence rate rather than the incidence rate ratio. Finally, the incidence rate  
225 includes the background risk.

226

227 Additional studies are needed to address the relative contribution of estrogen formulation,  
228 mode of administration, and co-administered anti-androgen medications to thrombotic risk. Some  
229 researchers have speculated that the increased thrombotic risk is a function of first pass liver  
230 metabolism of oral estrogens. This may not be true, as oral estradiol valerate may impose little risk  
231 relative to topical. A recent study demonstrated an eight-fold higher incidence of VTE with CEE  
232 compared to oral estradiol suggesting that the formulation of estrogen used rather than the route of  
233 delivery may be more important for determining thrombotic risk (Seal 2012). Cyproterone acetate is a  
234 highly potent anti-androgen typically used in Europe and has been reported to have procoagulant  
235 effects. As it is not available in the USA and spironolactone is the more commonly used anti-androgen,  
236 current literature may overestimate the thrombosis risk in the USA.

237 Future studies should also address the overall risk in the aging population. The average age for  
238 participants in these studies was 30 years old. This average age is representative of many trans women,  
239 but may not adequately predict risk in those who are aging or have underlying co-morbidities,  
240 particularly smoking and obesity.

241  
242 Conclusion: The risk of venous thrombotic events associated with estrogen therapy for trans women is  
243 less/comparable to the risk associated with oral contraceptives in premenopausal women. There is no  
244 evidence to suggest that there is a difference in the response to estrogen (thrombotic risk) in sex-  
245 assigned men and women.

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341 Table 1: Characteristics of Included Studies (Submitted as supplemental table due to formatting issues  
342 inserting such a large document into word document)

343

344

345 Figure Legends

346 Figure 1: PRISMA Diagram illustrating literature search results

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348 Figure 2: Forest plot of included studies. The squares indicate the incidence rate (IR) of each individual  
349 study. The size of the square is proportional to the weight given each study in the meta-analysis. The  
350 whiskers indicate the 95% confidence interval for the IR for each individual study. The diamond at the  
351 bottom is the overall estimate based on all studies. The width of the diamond is the 95% confidence  
352 interval of the overall estimate. The numbers follow each study are the individual study estimate and  
353 the 95% confidence interval. RE = random effects.

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