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# Serum Estradiol Concentrations With Estradiol 0.06% Gel in Transgender and Gender-Diverse Adults

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## ABSTRACT

**Objective:** Transgender and gender-diverse individuals undergoing estradiol therapy for gender affirmation are typically treated with oral or transdermal estradiol, with transdermal estradiol recommended for those aged > 45 years. There are limited data evaluating estradiol gel in gender-affirming hormone therapy regimens. We aimed to assess the serum estradiol concentrations achieved with estradiol 0.06% gel in transgender and gender-diverse adults.

**Design:** Retrospective cross-sectional audit of transgender and gender-diverse adults at endocrine clinics in Melbourne, Australia.

**Patients:** Eighty-one adults treated with estradiol 0.06% gel.

**Measurements:** Outcomes were estradiol 0.06% gel dose, serum estradiol concentration and proportion of individuals achieving target serum estradiol concentrations in consensus guidelines.

**Results:** Median serum estradiol concentration was 396 pmol/L (233–681) on 1.5 mg (1.5–2.25) estradiol 0.06% gel daily. Forty-six percent of individuals achieved serum estradiol concentrations within target range (250–600 pmol/L) of Australian consensus guidelines; 27% were below range and 27% were above range. There was a weak positive correlation between estradiol gel dose and serum estradiol concentration ($r = 0.23$, $p = 0.04$).

**Conclusion:** Estradiol 0.06% gel achieves target serum estradiol concentrations in a significant proportion of transgender and gender-diverse adults. This represents an alternative estradiol formulation for individuals desiring estradiol therapy for gender affirmation.

## 1 | Introduction

Estradiol therapy is a necessary component of management for some transgender and gender-diverse (trans) individuals to permit the development of physical characteristics that align with their gender identity. Treatment typically involves estradiol in combination with an anti-androgen such as spironolactone or cyproterone acetate [1–3].

Estradiol is mostly administered via the oral or transdermal route [4], with oral estradiol valerate the most prescribed first-line formulation in clinicians experienced in trans healthcare in Australia [5]. There is a lack of data in trans people, but given the association between oral estradiol and venous thromboembolic disease in cisgender postmenopausal women [6], transdermal estradiol is the recommended first-line option in trans individuals aged 40–45 years or older [7, 8]. Whether

transdermal is indeed less thrombotic than oral estradiol is unclear [9].

Transdermal 17ß-estradiol is available as a patch or gel. In Australia, estradiol 0.06% gel is available in a metered-dose pump in which each pump actuation delivers 0.75 mg estradiol. This allows for the rapid dispersing of estradiol into the stratum corneum, with ~10% of the applied dose absorbed by the skin prior to the solution drying [10]. From the stratum corneum, estradiol diffuses into the dermal capillaries over 2–14 h [10]. In menopausal hormone therapy for cisgender women, estradiol 0.06% gel is commonly prescribed at 0.75 mg estradiol/day, and titrated up to 3 mg daily as required to alleviate vasomotor symptoms [11]. However, there are limited data evaluating the use of estradiol 0.06% gel in trans individuals, in which estradiol is generally titrated to achieve specific serum estradiol concentration targets.

Consensus guidelines give recommendations for target serum estradiol concentrations to allow titration of estradiol therapy in trans adults [1–3]. Recommendations are largely based on expert opinion and known estradiol ranges in the cisgender female population, with no data demonstrating optimal estradiol concentrations for feminisation. The World Professional Association for Transgender Health (WPATH) Standards of Care Version 8 and Endocrine Society Clinical Practice Guideline recommend targeting serum estradiol concentrations 100–200 pg/mL (367–734 pmol/L) and total testosterone < 50 ng/dL (< 1.7 nmol/L) [2, 3]; whereas, Australian guidelines recommend targeting estradiol concentrations of 250–600 pmol/L and total testosterone concentrations < 2 nmol/L [2].

As such, in this retrospective audit of trans adults prescribed estradiol 0.06% gel, we aimed to assess the serum estradiol concentrations achieved, the estradiol dose prescribed and the proportion of individuals achieving serum estradiol concentrations recommended in consensus guidelines.

## 2 | Materials and Methods

A retrospective audit of electronic medical records was performed of consultations for trans adults at endocrine clinics in Melbourne, Victoria, Australia. Data were collected from consultations between 1 October 2019 and 2 August 2022. The audit was approved by the Austin Health Human Research Ethics Committee (Audit/21/Austin/76) that waived the need for informed consent.

This retrospective cross-sectional audit included trans and gender-diverse adults treated with estradiol 0.06% gel (EstroGel; Besins Healthcare, Sydney, Australia) who had at least one serum estradiol concentration available while on estradiol therapy. If an individual changed estradiol formulation, estradiol 0.06% gel dose and serum estradiol concentration were included in the analysis provided there was clear documentation of timing of previous formulation and adequate time from cessation of the previous regimen and subsequent serum results on estradiol 0.06% gel. Individuals were excluded if laboratory results were not available in our clinic databases. Individual laboratory results were also excluded if there was documentation of likely skin contamination at the venepuncture site.

The primary outcomes of interest were serum estradiol concentration and estradiol 0.06% gel dose. We also evaluated the proportion of individuals achieving serum estradiol concentrations recommended within consensus guidelines. Results were stratified in groups of < 250 pmol/L, 250–600 pmol/L and > 600 pmol/L, and < 367 pmol/L, 367–734 pmol/L and > 734 pmol/L as per Australian [2] and Endocrine Society [1] consensus guidelines, respectively. Finally, we assessed the correlation between estradiol 0.06% gel dose and serum estradiol concentration.

As data were obtained retrospectively, serum estradiol concentrations were measured using immunoassays available as standard care in Australia. All laboratories were accredited by the National Association of Testing Authorities (NATA, the national accreditation body for Australia). Serum estradiol concentrations are typically measured at baseline, every 3 months during the first year of estradiol treatment, and then every 6–12 months once stable. Notably, some individuals were still undergoing dose titration.

Statistical analyses were performed using STATA version 17.0 software. Data were not normally distributed so median (interquartile range, IQR) is reported. Categorical variables are reported as frequency (percentage). For individuals with more than one serum estradiol concentration available on one estradiol 0.06% gel dose, the data were averaged. Mann–Whitney *U* test was used to compare estradiol 0.06% gel dose and serum estradiol concentration between individuals aged < 45 and ≥ 45 years. Spearman's rank correlation coefficient was used to assess the correlation between variables. A $p$ value of < 0.05 was considered statistically significant.

## 3 | Results

Data were collected from 117 adults prescribed estradiol 0.06% gel, of whom 81 had documentation of serum estradiol concentration and estradiol dose. In total, 22 individuals did not have follow-up laboratory results in our database, 9 individuals were prescribed estradiol gel in combination with oral estradiol, 4 individuals had recently commenced estradiol gel therapy, and 1 individual was excluded due to estradiol gel application to the scrotum.

The median age was 29 years (23–40) and median duration of estradiol therapy was 29 months (17–48). Sixteen (20%) individuals were aged ≥ 45 years.

From 81 individuals, 152 individual laboratory results were available. Median serum estradiol concentration was 396 pmol/L (233–681) on 1.5 mg (1.5–2.25) estradiol 0.06% gel daily. Serum estradiol concentrations achieved with each estradiol 0.06% gel dose are shown in Table 1. There was no difference in estradiol 0.06% gel dose (1.5 mg (1.5–2.25) vs. 1.5 mg (1.5–2), $p = 0.55$) or serum estradiol concentration (392 pmol/L (210–681) vs. 474 pmol/L (289–580), $p = 0.34$) in individuals aged < 45 years compared to those ≥ 45 years.

In the overall cohort, there was a weak positive correlation between estradiol 0.06% gel dose and serum estradiol concentration ($r = 0.23$, $p = 0.04$) (Figure 1).

**TABLE 1** | Serum estradiol concentration by estradiol 0.06% gel dose.

| Estradiol 0.06% gel dose | Number of individuals | Serum estradiol concentration (pmol/L) |
|---|---|---|
| 0.75 mg | 5 | 223 (221, 388) |
| 1.5 mg | 66 | 285 (173, 478) |
| 2.25 mg | 18 | 447 (301, 729) |
| 3 mg | 17 | 529 (267, 818) |
| > 3 mg | 5 | 552 (465, 1163) |

*Note:* Median (IQR) are presented. If an individual had more than one serum estradiol concentration available on a particular dose, the average of these readings was taken.
Abbreviation: IQR, interquartile range.

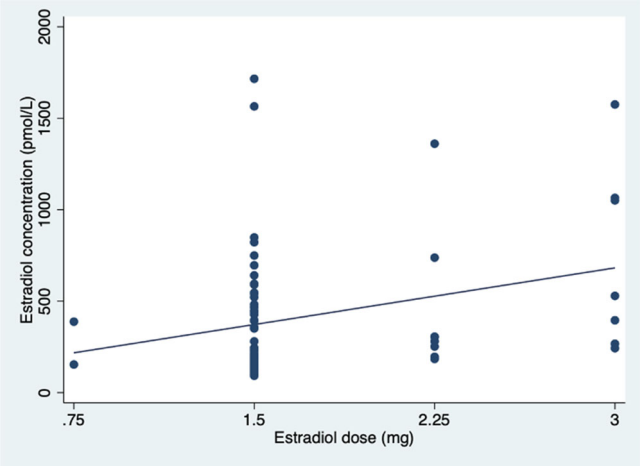


**FIGURE 1** | Correlation between estradiol 0.06% gel dose and serum estradiol concentration. [Color figure can be viewed at wileyonlinelibrary.com]

Thirty-seven (46%) individuals achieved serum estradiol concentrations within the target range of 250–600 pmol/L in Australian guidelines. Twenty-two (27%) achieved serum estradiol concentrations below target range (< 250 pmol/L) and 22 (27%) individuals achieved serum estradiol concentrations above target range (> 600 pmol/L). However, if using the Endocrine Society Clinical Practice Guidelines serum estradiol concentration target of 367–734 pmol/L (100–200 pg/mL) [1], 28 (35%) individuals achieved target concentrations, with 39 (48%) below target and 14 (17%) above target.

Supratherapeutic serum estradiol concentrations (range, 1630–6559 pmol/L) with documentation in clinical records of likely skin contamination at venepuncture site occurred in 13 individuals.

## 4 | Discussion

The results from this retrospective audit demonstrate that estradiol 0.06% gel can achieve serum estradiol concentrations in the target range recommended in consensus guidelines with a median dose 1.5 mg daily. There was a weak positive correlation between estradiol 0.06% gel dose and serum estradiol concentration.

### 4.1 | Comparison With Other Studies

There are limited data evaluating serum estradiol concentrations with transdermal estradiol formulations in trans individuals. Studies have more commonly reported on serum estradiol concentrations with oral estradiol, with an Australian study reporting a median serum estradiol concentration of 328 pmol/L in 259 individuals treated with oral estradiol [12]. Another retrospective analysis demonstrated a median serum estradiol concentration of 293 pmol/L in 17 trans individuals aged ≥ 45 years treated with various transdermal estradiol preparations [13].

In a retrospective study of 99 trans people receiving estradiol for gender affirmation in Denmark, of whom 94 (95%) received transdermal estradiol (predominantly estradiol spray), the median serum estradiol concentration achieved was 386 pmol/L (193–579) [14]. Only 11 of 38 individuals (29%) achieved serum estradiol concentrations within the target range of 100–200 pg/mL (367–734 pmol/L) after 11–19 months of treatment, with more than 40% returning subtherapeutic serum estradiol concentrations throughout the study period. Nineteen individual laboratory tests in 17 individuals measured > 1000 pmol/L.

Other studies have compared the serum estradiol concentrations achieved with transdermal estradiol to other estradiol formulations. In a cohort study from Australia [15], transdermal estradiol (gel and/or patches) achieved comparable serum estradiol concentrations to oral estradiol (median 262 pmol/L (158–408) with transdermal estradiol and 264 pmol/L (176–364) with oral estradiol); however, this was lower than the serum estradiol concentrations achieved with subdermal estradiol implants (median 341 pmol/L (263–435)). Overtreatment (defined as serum estradiol concentration > 800 pmol/L), occurred in 4 (12%) individuals treated with transdermal estradiol.

A retrospective cohort study from the United States reported a median serum estradiol concentration of 71 pg/mL (260 pmol/L) in those using transdermal estradiol formulations, lower than that achieved with oral estradiol of 102 pg/mL (374 pmol/L), though this study was limited by a small number of individuals treated with transdermal estradiol ($n = 39$ individual laboratory results) compared to intramuscular ($n = 242$) and oral estradiol ($n = 366$) formulations [16]. Another cross-sectional study found that serum estradiol concentrations achieved in trans individuals were 80 pg/mL (294 pmol/L, $n = 9$) with transdermal patch (median dose 175 mcg/day), and 154 pg/mL (567 pmol/L, $n = 54$) with sublingual estradiol; there were no serum estradiol concentrations > 200 pg/mL (> 734 pmol/L; the upper limit of American guidelines) using transdermal estradiol patches [17].

### 4.2 | Serum Estradiol Concentrations in Cisgender Women

In a pharmacokinetic cross-over study enroling 15 postmenopausal cisgender women, mean serum estradiol concentration over days

11–13 was 68.1 ± 27.4 pg/mL (250 ± 101 pmol/L) with estradiol 0.06% gel 1.5 mg daily and 102.9 ± 39.9 pg/mL (378 ± 146 pmol/L) with estradiol 0.06% gel 3 mg daily [18]. Serum estradiol concentrations achieved with 1.5 mg estradiol gel were higher than those achieved with an estradiol patch 50 mcg/24 h and similar to those achieved with 2 mg oral micronised estradiol.

In a 12-week phase 3 randomised controlled trial in symptomatic postmenopausal cisgender women, median serum estradiol concentrations at week 12 were 33.5 pg/mL (123 pmol/L) for 0.75 mg estradiol gel daily and 65 pg/mL (239 pmol/L) for 1.5 mg estradiol gel daily [19]. Importantly, estradiol 0.06% gel has been shown to be bioequivalent to 0.1% estradiol gel (Sandrena, Organon Laboratories) [20].

### 4.3 | Clinical Implications

Estradiol 0.06% gel is able to achieve serum estradiol concentrations within the target range of consensus guidelines and represents an alternative option for trans individuals desiring feminisation. Although oral estradiol is the most prescribed formulation [4], transdermal formulations should be considered for aging trans individuals or those at high risk of venous thromboembolic disease.

From a clinical perspective, it is important to note that studies have not documented a difference in breast development [21, 22] or feminine body fat redistribution [21, 23] between individuals treated with oral or transdermal estradiol. Similarly, changes in areal bone mineral density over the 12 months following initiation of estradiol for gender affirmation were not different between those treated with oral or transdermal estradiol [24]. Based on long-term bone outcomes [25], the Amsterdam Cohort of Gender dysphoria (ACOG) now recommends targeting serum estradiol concentrations > 200 pmol/L for bone health [26]; our data suggest that this can be achieved with estradiol 0.06% gel.

In the assessment of dosing adequacy, it is important to consider that contamination of the venepuncture site by transdermal gel can lead to spuriously high sex steroid concentrations. In the current study, 13 individuals had documentation of supratherapeutic serum estradiol concentrations in the setting of likely skin contamination. Similar findings have been reported with both testosterone and estradiol gels [27, 28]. Clinicians should consider education of patients regarding avoidance of gel application to the cubital fossa to prior to venesection to mitigate this risk.

### 4.4 | Limitations

Limitations to this analysis are related to its retrospective design, including missing data as these were not collected in a standardised manner. Serum estradiol concentration results were collected via different immunoassays available for routine clinical care, and not collected in a standardised time in relation to the timing of the last gel application. We did not have consistent documentation of the timing of the laboratory test in relation to the last dose or the site of gel application. Although liquid chromatography–mass spectrometry (LC–MS) is considered the reference standard for sex steroid measurement, it is not routinely available in Australia [29]. Prescriber preference and the rationale for estradiol 0.06% gel dose or prescription, and individualised serum estradiol concentration targets were not consistently documented in medical records. Given the retrospective design, we did not have data on clinically relevant outcomes including treatment satisfaction, clinical markers of feminisation, or quality of life.

## 5 | Conclusion

In conclusion, transdermal estradiol 0.06% gel is able to achieve target serum estradiol concentrations in a significant proportion of trans individuals undergoing estradiol for gender affirmation. Given its stable pharmacokinetics and demonstrated safety in larger cisgender population studies, estradiol 0.06% gel should be considered a first-line option for trans individuals undergoing estradiol for gender affirmation. Further studies are required to assess clinical feminisation outcomes in this population.

#### Acknowledgements

Dr. Brendan Nolan is supported by a Royal Australasian College of Physicians-Endocrine Society of Australia Research Establishment Fellowship. A/Prof Ada Cheung is supported by an Australian Government National Health and Medical Research Council Investigator Grant (#2008956).

#### Conflicts of Interest

Brendan J. Nolan. and Ada S Cheung have received product from Besins Healthcare for separate investigator-initiated clinical studies using estradiol and progesterone. No monetary support from Besins Healthcare has been received for any studies and Besins Healthcare have had no input into study design, data analysis or writing of any manuscripts. Raquel A Maggacis has no declarations.

#### Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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