

Endometrial response to long-term testosterone therapy: histological insights from transgender individuals undergoing gender affirming hormone therapy

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Background and Introduction

Assigned female at birth (AFAB) individuals undergoing gender-affirming hormone therapy (GAHT) may also undergo gender-affirming surgery (GAS). However, the long-term impact of prolonged testosterone exposure on the endometrium in AFAB individuals who do not undergo GAS—specifically hysterectomy with or without bilateral salpingo-oophorectomy—remains poorly defined representing a significant gap in clinical knowledge. Therefore, we conducted a prospective observational study to assess whether testosterone therapy suppresses estrogen levels sufficiently to induce endometrial atrophy.

Materials and Methods

Twenty-one adults attending the Endocrinology and Gynecology Units of the University Hospital of Padua between 2021 and 2025 were included after ≥ 12 months of gender-affirming hormone therapy (GAHT). Serum LH, FSH, 17β -estradiol, and total testosterone levels were measured. In participants undergoing gender-affirming surgery, hormonal assessments were repeated ≥ 2 months postoperatively, and surgical specimens were analyzed for endometrial and ovarian histopathology.

Results

Six participants underwent hysterectomy with bilateral salpingo-oophorectomy, and one underwent hysterectomy alone. Baseline median 17β -estradiol levels were 37 pg/mL, exceeding postmenopausal reference values. Postoperative median hormone levels were LH 9.20 mIU/mL, FSH 17.3 mIU/mL, 17β -estradiol 41.50 pg/mL, and total testosterone 5.75 ng/mL. Histopathological evaluation of hysterectomy specimens ($n = 7$) revealed no cases of endometrial atrophy; all samples showed persistent endometrial stimulation consistent with a proliferative phase.

Conclusions

Estrogen levels above the postmenopausal range may reflect residual ovarian activity, consistent with the postoperative increase in gonadotropins. Persistently stable estrogen concentrations after surgery may result from peripheral androgen aromatization. This relative estrogen dominance, if not unopposed by adequate progestin exposure, may increase the risk of endometrial atypical hyperplasia or carcinoma.

	LH (mU/mL)	FSH (mU/mL)	E2 (pg/mL)	T (ng/mL)
Median [IQR]	4.79 [1.33–9.73]	4.58 [2.43–7.08]	37.0 [23.5–77.6]	4.95 [3.64–6.51]
Range	0.22–32.0	0.90–89.0	4.63–784	1.10–9.53

Table 1. Hormonal concentrations of the whole study population are expressed as median [IQR], with minimum and maximum values.

	Before Surgery Median [IQR]	Range	After Surgery Median [IQR]	Range	<i>p</i>
LH (mU/mL)	2.80 [1.03–7.03]	0.22–10.0	9.20 [6.75–27.1]	0.28–72.9	0.156
FSH (mU/mL)	3.45 [2.0–7.5]	0.98–8.20	17.3 [9.00–45.3]	0.80–128	0.109
E2 (pg/mL)	28.45 [20.9–52.0]	17.4–299	41.50 [26.0–67.0]	22.34–82.99	0.813
T (ng/mL)	5.61 [5.15–7.44]	2.40–8.21	4.69 [3.62–7.59]	3.03–9.00	0.469

Table 2. Values are reported as median [IQR] and range. Comparisons were performed using the Wilcoxon signed-rank test.

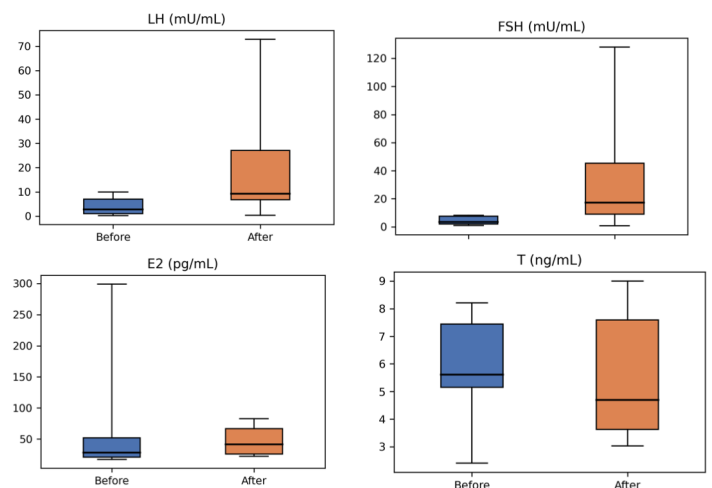


Figure 1. Hormonal levels before and after surgery are shown as box plots (median, IQR, and range).