Approximating Systemic Estrogen Exposure from Vaginal Estrogen Cream Therapy

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OBJECTIVE

It is not clear if vaginal application of estrogen results in clinically significant systemic effects, though this would likely only occur at high doses. Collecting real-world data regarding systemic estrogen exposure from vaginal estrogen use is difficult as serum collection is invasive and no other sampling method has been shown to provide reliable and accurate results. One objective of this study was to determine if high dose vaginal estrogen cream use showed expected dose-dependent increases in urinary estrogen levels. Secondarily, cases with high dose vaginal therapy were examined to test the urine assay's ability to successfully remove any potential contamination for accurate analysis of systemic estrogen exposure.

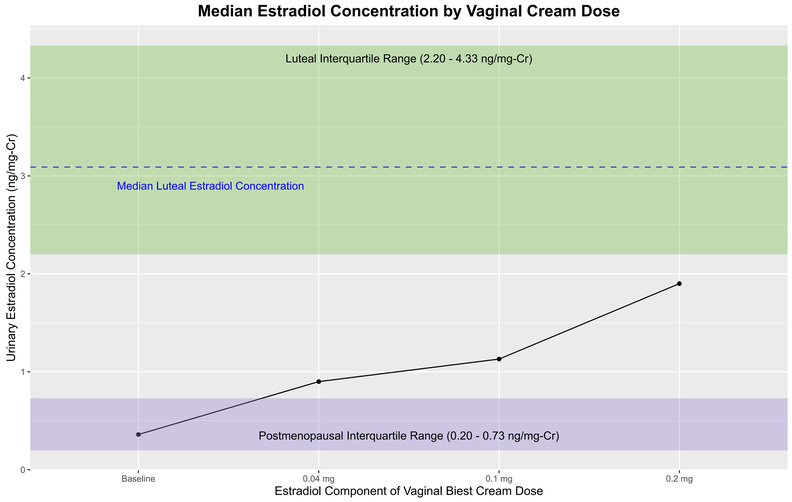
DESIGN

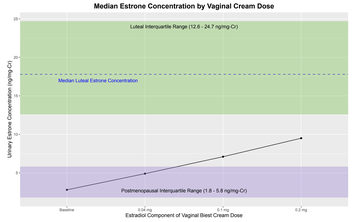
This was a retrospective observational study conducted using data from the database of a diagnostic laboratory (Clinical Trials ID: NCT04305093). Results included urinary concentrations of 10 different estrogen metabolites including estrone (E1), estradiol (E2), and estriol (E3). From this database of over 100,000 results, 58 postmenopausal women met inclusion criteria and had both baseline results and results while using a 0.1 mg dose of vaginal estrogen cream, Biest (60% E3, 40% E2; applied to the labia daily). From this group, 30 women had an additional measurement while using 0.25 mg and 17 women (non-overlapping) had a measurement while using 0.5 mg. The assay method used in this study has previously been shown to systematically remove more than 97% of any free hormone contamination via a methyl tert-butyl ether (MTBE) wash and this removal of contamination was confirmed in each sample. The Jonckheere-Terpstra trend test was used to assess for ordered trends across dose categories.

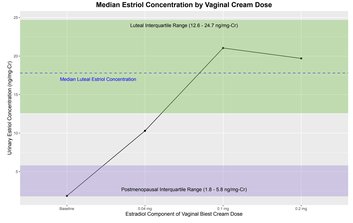
RESULTS

The mean age of study participants was 55.7 years. Increasing doses of the vaginal estrogen cream resulted in dose-dependent increases in median urinary concentrations of E1, E2, and E3. All 3 metabolites showed statistically significant ordered trends across dose categories ($p<.00001$ Jonckheere-Terpstra trend test). The median E2 concentration increased from 0.36 ng/mg-Cr at baseline to 0.9 ng/mg-Cr at a dose of 0.1mg, 1.13 ng/mg-Cr at a dose of 0.25 mg and 1.90 ng/mg-Cr at 0.5 mg.

Urinary Estrogen Profile Changes in Response to Vaginal Estrogen Cream



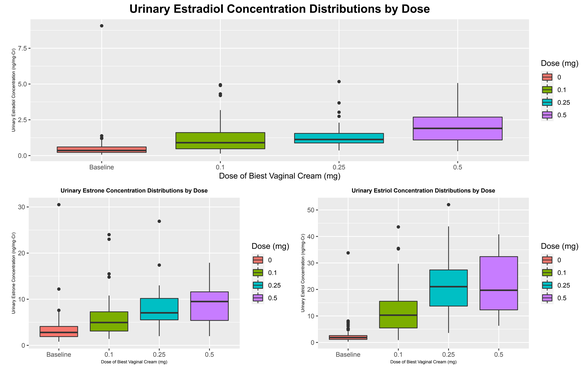




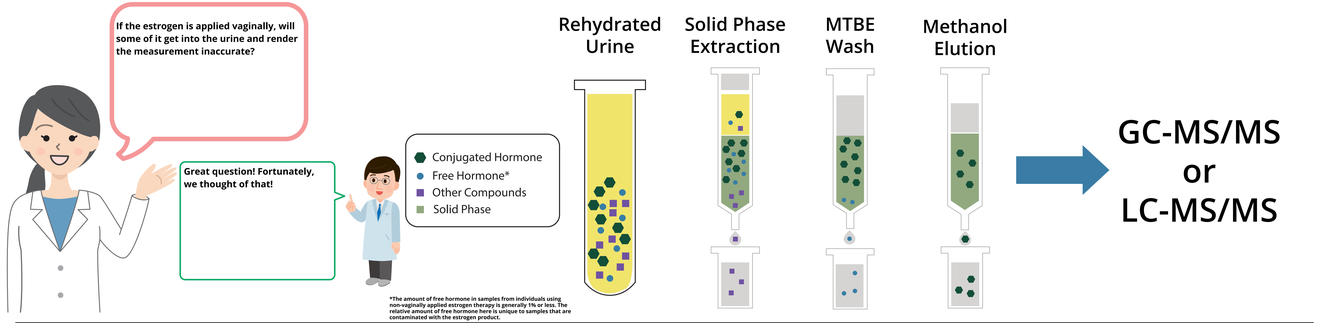
Patient Characteristics and Estrogen Metabolite Concentrations by Dose

	Dose of Biest Vaginal Cream (mg)			
Variable	**Baseline**, N = 58[†]	**0.1**, N = 58[†]	**0.25**, N = 30[†]	**0.5**, N = 17[†]
Age at Collection	56.0 (52.0, 59.8)	56.0 (52.0, 59.8)	56.0 (52.0, 61.8)	56.0 (53.0, 58.0)
BMI	27.6 (24.0, 31.9)	27.6 (25.3, 32.4)	25.9 (23.2, 29.9)	27.3 (25.7, 31.0)
Estrone (ng/mg-Cr)	2.80 (1.90, 4.10)	4.95 (3.10, 7.27)	7.05 (5.53, 10.18)	9.50 (5.40, 11.60)
Estradiol (ng/mg-Cr)	0.36 (0.22, 0.60)	0.90 (0.47, 1.61)	1.13 (0.88, 1.55)	1.90 (1.09, 2.69)
Estriol (ng/mg-Cr)	1.85 (1.15, 2.60)	10.30 (5.47, 15.55)	21.05 (13.72, 27.38)	19.70 (12.30, 32.40)
Total Estrogens (ng/mg-Cr)	8.30 (6.03, 12.43)	20.30 (13.60, 28.02)	35.80 (26.20, 48.80)	39.50 (29.50, 52.30)

[†] Median (IQR)



Why The Method Works



CONCLUSION

The results of this study suggest that vaginal estrogen cream at doses of 0.04 mg (E2) and higher may be absorbed systemically in significant amounts. This indicates a need for further investigation, ideally with larger, prospective studies. The sampling method and accompanying assay used in this study may represent an ideal tool for further study due to the ease of sample collection and the ability of urine to capture and represent a greater proportion of the pharmacokinetic patterns exhibited by estrogen cream.