

THE EFFECT OF VAGINAL OESTROGEN ON SUBJECTIVE AND OBJECTIVE SYMPTOMS OF SUI AND VAGINAL ATROPHY: AN INTERNATIONAL MULTI-CENTRE OBSERVATIONAL PILOT STUDY

Hypothesis / aims of study:

Vaginal oestrogen cream has been used to treat stress urinary incontinence (SUI) in postmenopausal women for many decades. However, the existing literature on the efficacy of local oestrogen for SUI is not consistent in its conclusions. Out of 9 trials in the 2012 Cochrane review on this subject, 4 are not clinically applicable (Premarin is no longer available). Although improvement is generally reported, due to the small sample size, different types, dosages and durations of treatments, the evidence was judged to be inadequate. Similarly, a 2011 review (1) states that, currently, insufficient data is available to support the use of topical oestrogen in postmenopausal women with SUI.

We aimed to study the subjective and objective cure of local oestrogen in post-menopausal women with SUI. We also intended to study whether the efficacy is related to the effect of treatment on vaginal atrophy. A secondary aim was to determine the variability of the data for a range of outcome measures, so as to allow the calculation of an adequate sample size for a subsequent RCT (comparing vaginal oestrogen cream with placebo).

Study design, materials and methods:

A prospective multinational observational pilot study was performed in 3 participating metropolitan centres (in African continent, the Antipodes and Europe). Postmenopausal women (age 50-80 years) with complaints of SUI (with or without complaints of prolapse and other forms of incontinence) were approached at their first visit to the Centre. Women who used any topical or systemic oestrogen replacement, who had too little understanding of the common spoken language in the country, and women who were otherwise unable to give informed consent, were excluded. Objective outcome measures were a) standardized erect cough pad test (at a minimum bladder volume of 200ml on ultrasound), and b) vaginal pH accurate to 0.2 units (MColorpHast TM, strip pH 4.0-7.0). Subjective outcomes were disease specific quality of life as measured with: a) ICIQ-UI-SF, b) UDI-6, c) IIQ-7, and d) MBS (2) for the measurement of vaginal atrophy symptoms.

The participants used 1mg/g oestriol cream, daily for the first 3 weeks, and then 3 times per week from weeks 4-6, as per written instructions. Thus, there were 21 + 9 occasions of application, with compliance scored as % of 30 applications. No other treatment was allowed during the 6 weeks, when follow up occurred, and a questionnaire about treatment compliance was collected. The Patients Global Impression of Improvement (PGI-I) (3) was given at this visit, and was chosen as the Primary Outcome Measure. *Statistical analyses:* The changes in outcome measures after treatment were analysed (Wilcoxon signed rank test for paired numerical data, and McNemar test for paired categorical data). In order to examine the relationship between the primary outcome measure (PGI-I) and the other variables, Spearman's correlation coefficient between the post treatment change on pH, stress test, and QOL etc were analysed.

Results:

At present, 20 participants from Africa, 23 women from the Antipodes, and 3 from Europe have enrolled. Total follow up data from 11, 18, and 0 women in each country respectively is available (n=46, with 29 complete). Target sample size is 90 patients (30 from each country) and study completion date is 31st August 2014. Median age of women was 61 yr [range 50-75 yr]. Table 1 shows the baseline outcome measures for all participants and the available post treatment changes. The median baseline pH was not as high as expected (5.2, IQR 4.4-6.5). The baseline cough stress test demonstrated wide variation (median 3.3g, IQR 0.2-19.5g). The degree of incontinence on ICIQ was quite substantial. Compliance was generally high.

The vaginal pH fell significantly by a median of 0.2 units (p=0.02). After treatment, the median total UDI score was significantly lower (50.0 vs 44.4, p=0.03), patients showed a significant

improvement on the irritative and stress domains. ICIQ scores and IIQ domain scores did not change significantly.

Table 2 shows that 30.2% of participants experienced "little" to "much" improvement on PGI-I.

Table 1: Baseline features of participants (Numbers are median [range] or n (%)).

	Baseline (n=43)	6 weeks follow-up (n=29)	p-value
Vaginal pH	5.2 [4.0-8.0]	5.0 [4.0-6.1]	0.022*
Cough test (grams)	3.3 [0.0-127.5]	5.3 [0.0-89.2]	0.302*
ICIQ total	13 [5-21]	13 [3-21]	0.299*
IIQ total	47.6 [0-100]	38.1 [4.8-100]	0.272*
- physical activity	41.7 [0-100]	33.3 [0-100]	0.724*
- travel	33.3 [0-100]	33.3 [0-100]	0.132*
- social/relationships	66.7 [0-100]	33.3 [0-100]	0.190*
- emotional health	50.0 [0-100]	33.3 [0.100]	0.225*
UDI total	50.0 [5.6-100]	44.4 [5.6-100]	0.027*
- irritative	66.7 [0-100]	66.7 [0-100]	0.044*
- stress	66.7 [0-100]	50.0 [0-100]	0.033*
- obstructive/discomfort	33.3 [0-100]	16.7 [0-100]	0.310*

Most bothersome symptom			
- vaginal dryness	9 (20.9)	4 (13.8)	1.0**
- vaginal itching/irritation	4 (9.3)	3 (10.3)	1.0**
- vaginal soreness	3 (7.0)	3 (10.3)	1.0**
- difficulty during urination	6 (14.0)	4 (13.8)	1.0**
- dyspareunia	3 (7.0)	3 (10.3)	1.0**
- bleeding after intercourse	0 (0.0)	1 (3.4)	1.0**
- none	17 (39.5)	10 (34.5)	0.727**
- missing	1 (2.3)	1 (3.4)	

*Wilcoxon signed rank test

**McNemar test

Table 2: PGI-I results

PGI-I	n (%)
Very much better	0 (0.0)
Much better	5 (11.6)
A little better	8 (18.6)
No change	13 (30.2)
A little worse	1 (2.3)
Much worse	0 (0.0)
Very much worse	2 (4.7)

Table 3: Correlation between PGI-I and post treatment changes in other variables.

	Correlation coefficient (r value)	P value
pH	-0.06563	0.7450
Cough pad test	-0.1669	0.3961
ICIQ	-0.3279	0.0825
IIQ	-0.4593	0.0063*
UDI	-0.3519	0.0612
MBS	-0.3875	0.0378*

Interpretation of results: Our experience at this stage of recruitment indicates that the erect cough stress test is cumbersome (achieving a volume consistently >200ml is problematic), with large variability. Vaginal pH appears to measure the biological effect of oestriol cream. The irritative and stress domains of the UDI score appear to be sensitive to change. The post treatment change in IIQ and MBS correlate significantly with PGI-I (table 3).

Concluding message: Preliminary data of this pilot study show that local oestrogen therapy reduces SUI symptoms in women with vaginal atrophy. Once recruitment is complete, careful evaluation of individual outcome measures will be needed in order to choose the most sensitive primary outcome, allowing the design of a RCT comparing oestriol therapy with placebo for women with SUI in a multi-centre RCT.

References

1. Robinson D, Cardozo L. The role of oestrogen in female lower urinary tract dysfunction. Urology 62 (Suppl 4A): 45-51, 200
2. Ettinger B, Hait H, Reape KZ, Shu H. Measuring symptom relief in studies of vaginal and vulvar atrophy: the most bothersome symptom approach. Menopause 2008 Sep;15(5):885-9.
3. Tincello D, Owen R, Slack M, Abrams K. Validation of the Patient Global Impression scales for use in detrusor overactivity: secondary analysis of the Relax study. BJOG 2013;120:212-216.

Disclosures

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