Cost-effectiveness of perioperative vaginally administered oestrogen in postmenopausal women undergoing prolapse surgery.

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Primary Objective: This study aims to comprehensively compare the effectiveness and costs of perioperative topical oestrogen for postmenopausal women undergoing POP surgery. In this trial, the perioperative use of oestrogen is considered superior to...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Menopause related conditions
Study type	Interventional

Summary

ID

NL-OMON55535

Source
ToetsingOnline

Brief title
EVA trial

Condition

- Menopause related conditions
- Obstetric and gynaecological therapeutic procedures

Synonym
pelvic organ prolapse; female genital prolapse;

Research involving
Human

Sponsors and support

Primary sponsor: Academisch Medisch Centrum
Source(s) of monetary or material Support: 'Leading the Change' programma van Stichting Zorgevaluatie

Intervention

Keyword: Cost-effectiveness, Oestrogen, Postmenopausal, Prolapse surgery

Outcome measures

Primary outcome

Subjective cure (PGI-I)

Secondary outcome

- Compound measure:

[1] no prolapse in compartment of surgery or past the hymen

[2] no bothersome complaints of prolapse

[3] no re-intervention for prolapse in the compartment of surgery within the

follow-up period;

- QALY (EQ-5D-6L);

- Disease specific quality of life: micturition, defecation and sexual

function;

- Vaginal pH;

- Signs of vaginal atrophy during gynaecological examination;

- Complaints of vaginal atrophy;

- Morbidity and adverse events;

- Interventions for pelvic floor pathology;

- Costs;

- Adherence to treatment.

Study description

Background summary

Pelvic organ prolapse (POP) is a common disorder affecting about 40% of postmenopausal women. Women with POP are bothered by a sagging sensation and problems with micturition, defecation and sexual functioning. The body image of these women is often negatively affected, and their loss of productivity can have financial impact. Surgery is often indicated to relieve symptoms, but is successful in only 70% of treated women since 30% needs surgery for recurrent prolapse. The group of women in the postmenopausal age is growing rapidly, the societal impact of this health problem is large and ways to improve treatment outcomes of POP surgery is needed.

It has been shown that women with pelvic floor pathology benefit from vaginal oestrogen therapy. A reduction of symptoms has been described in women with stress urinary incontinence, overactive bladder symptoms, recurrent cystitis, and prolapse symptoms after using vaginal oestrogen.Vaginal atrophy can be solved by the use of vaginal oestrogen therapy, effectively treating bothersome symptoms like vaginal dryness, and itching of the vulva. The hypothesized underlying mechanism is that oestrogen results in a thickening of the vaginal wall or urothelium, and improves vascularization of the pelvic floor. Apart from the above described clinical evidence, there are basic scientific data available that support this hypothesis. In our clinic, several studies have been performed to investigate the potential beneficial effects of vaginal oestrogen therapy. Using an objective outcome measurement, we showed that vaginal wall thickness more than doubles within 6 weeks after start of vaginal oestrogen supplementation. An randomized trial showed that the use of vaginal oestrogen prior to prolapse surgery increased the production of collagen and reduced degradative enzyme activity. Therefore, it is assumed that women with low oestrogen levels who undergo surgery for POP have a higher risk of recurrence of their POP symptoms because poor vascularization and a thin vaginal wall compromise their healing capacity. Administering vaginal oestrogen is expected to improve healing conditions and consequently reduce risk of recurrence. Oestrogens act on the cutaneous wound healing response by modulating the inflammatory response, cytokine expression and matrix deposition. They also accelerate re-epithelialization, stimulating angiogenesis and wound contraction, and regulate proteolysis.

Vaginal oestrogen therapy has been used in practice for over 30 years in 74 different countries and is considered to be safe. Although vaginally administered oestrogen could result in a minimal systemic uptake, serum

oestrogen levels remain within the normal range for postmenopausal women.(19) Also no endometrial or myometrial effects are seen with the use of vaginal oestrogen. In literature, an increased risk of breast cancer or endometrial cancer has never been proven for vaginal oestrogen therapy (only for systemic use of oestrogen).
A review identified two studies that investigated the use of vaginal oestrogen as compared to placebo or no treatment for treating POP. These studies show that POP treatment with oestrogen led to a significant difference in POP symptoms and in vaginal health composite score. Although there is benefit that vaginal oestrogen therapy improves pelvic floor function following POP surgery, and improves healing conditions, there is no comparative study to evaluate whether vaginal oestrogen therapy before and after POP surgery improves outcome. Based on the theoretical background, such study would need to be performed in postmenopausal women as they have low levels of oestrogen. For that reason, we propose a multicentre RCT comparing perioperative vaginal oestrogen therapy to placebo in post-menopausal women undergoing vaginal POP surgery.

Health care efficiency problem: Worldwide 30% of all POP operations is performed for recurrent prolapse. The costs associated with the treatment of recurrent POP are huge, and the burden by the women who encounter recurrent POP has negative impact on quality of life. Oestrogen has a proven beneficial effect on the healing process of the vagina after POP surgery. It is easy to administer, cheap, and easy to obtain. Based on research performed in our institute, is has been shown that vaginal oestrogen in low dosages is very efficient: in women with vaginal atrophy the vaginal wall thickness doubles after 6 weeks of use. There is also evidence that oestrogen improves wound healing, by reducing the inflammatory responses and promoting angiogenesis. If peri-operative oestrogen therapy would reduce the risk on recurrence by 2%, this intervention would be cost-effective. Based on our own research, data in literature, and theoretical background, the reduction in recurrent POP surgery is expected to be 15% or more. This would mean a cost-saving of 5.1 million euros per year in the Netherlands.

Study objective

Primary Objective: This study aims to comprehensively compare the effectiveness and costs of perioperative topical oestrogen for postmenopausal women undergoing POP surgery. In this trial, the perioperative use of oestrogen is considered superior to placebo which results in cost reduction.

Secondary Objective(s): Other aims are to investigate adverse effects and reasons for the discontinuation of treatment.

Study design

This study will be a multicentre, double-blind, randomised placebo-controlled trial. After inclusion, subjects will receive either topical oestrogen treatment or placebo treatment 4-6 weeks before their POP surgery till 12 months postoperative.

Recruitment of postmenopausal women to the study will take place in a multicentre setting across the Netherlands. Recruitment will be done by gynaecologists.

Randomisation:
Subjects will be randomised 1:1 to perioperative treatment with oestrogen and perioperative treatment with placebo by the method of online block randomisation with randomly varying block sizes (in Castor).

Blinding:
Study medication will be blinded. All physicians, researchers, research nurses, outcome assessors and patients will remain blinded to treatment allocation until the primary analysis is completed.

Intervention

Intervention group:
The intervention group receives 0,5 mg oestriol cream (1mg/g, topical administration) 4-6 weeks preoperative till 12 months postoperative. (First 2 weeks 0,5 mg once a day, thereafter 0,5 mg twice per week).

Control group:
The other group receives a placebo cream (equal schedule as intervention group).

Study burden and risks

- The subject will apply a vaginal cream 4-6 weeks preoperatively till 12 months postoperatively. Frequeny: first 2 weeks 1x/day, thereafter 2x/week.(Except the first two weeks postoperative)
- Questionnaires at 4 different time points - baseline, 2, 6, and 12 months postoperative. (4x 30 minutes).
- Perioperative diary on cream application (from beginning till 6 weeks postoperative).
- Hospital visit 12 months postoperative, including gynaecological examination

Contacts

Public

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

- Postmenopausal women (>1 year amenorrhoea) with a minimum age of 18 years old
- Pelvic organ prolapse; POP Quantification stage 2 or higher
- Women that will undergo primary POP surgery with native tissue repair; including at least anterior OR posterior vaginal wall repair

Exclusion criteria

- Previous POP surgery in concerning compartment
- Prolapse repair using mesh
- Current vaginal infection
- Use of oestrogens in the past 12 months
- Contraindication for use of topical oestrogen
- Known, past or suspected oestrogen-dependent malignant tumours (e.g. breast cancer, endometrial cancer);

- Insufficient knowledge or understanding of the Dutch language

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	07-09-2018
Enrollment:	300
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Synapause
Generic name:	Oestriol (vaginal)
Registration:	Yes - NL intended use

Ethics review

Approved WMO

Date:	28-02-2018
Application type:	First submission
Review commission:	METC Amsterdam UMC

Approved WMO

Date:	19-04-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	16-05-2018
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	29-05-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	04-06-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	26-06-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	17-07-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	24-07-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	28-08-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	19-10-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO	

Date:	08-11-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	11-02-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	02-08-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	17-03-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	01-04-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	18-02-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	16-02-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

ID: 28340
Source: Nationaal Trial Register
Title:

In other registers

Register	ID
EudraCT	EUCTR2017-003144-21-NL
CCMO	NL62764.018.17
Other	NTR: NL6853
OMON	NL-OMON28340