Open-label randomized controlled trial for the effects of continuous ethinylestradiol/levonorgestrel (30/150 µg/day) compared with vitamin E (400 IU/day) in the treatment of menstrually-related migraine and migraine during perimenopause

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Ethical review	Approved WMO
Status	Recruiting
Health condition type	Headaches
Study type	Interventional

Summary

ID

NL-OMON52418

Source
ToetsingOnline

Brief title
WHAT! - RCT

Condition

- Headaches

Synonym
headache, migraine

Research involving
Human

Sponsors and support

Primary sponsor: Leids Universitair Medisch Centrum
Source(s) of monetary or material Support: ZonMW,Hersenstichting

Intervention

Keyword: Hormones, Migraine, Treatment, Women

Outcome measures

Primary outcome

Number of monthly migraine days

Secondary outcome

- number of monthly headache days

- number of monthly migraine and probable migraine attacks

- 50% response rates for migraine days

- number of (severe) adverse events

Study description

Background summary

The incidence and prevalence of migraine is three times higher in women than in men. Clinical and epidemiological studies suggest a prominent role for sex hormones in female migraine patients. Menstruation is an important factor increasing the susceptibility for an upcoming attack.1 Perimenstrual migraine attacks are also more disabling, longer lasting, and more difficult to treat than other attacks.2-5 Hormonal fluctuations during menopausal transition are associated with increased susceptibility for migraine as well.6 Thus, sex hormonal conditions are known to affect the susceptibility for migraine attacks in women, but there is a lack of understanding the underlying pathophysiological mechanism. Currently, there is no evidence-based hormonal intervention for the treatment of migraine in women.

Study objective

This study has been transitioned to CTIS with ID 2024-517127-40-00 check the CTIS register for the current data.

To study the effects of continuous use of ethinylestradiol/levonorgestrel (30/150 µg/day) compared to vitamin E (400 IU/day) in the treatment of menstrually-related migraine and migraine during perimenopause.

Study design

Open-label randomized controlled trial

Intervention

Continuous ethinylestradiol/levonorgestrel 30/150 µg/day versus vitamin E 400 IU/day

Study burden and risks

The study will encompass a period of 4 months (1 baseline month and 3 treatment months). Patients have to fill out daily headache diaries throughout the study using a web-based app (5 minutes daily). Patients visit the headache clinic thrice, once for inclusion, once during the baseline period and once after 3 months of therapy. During the first and last visit blood samples will be taken. Patients will fill out one baseline questionnaire (1 hour), one expectations questionnaire (5 minutes) and one follow-up questionnaire (15 minutes). Patients will be contacted twice during follow-up to evaluate (S)AE*s. Treatment with the oral contraceptive pill is accompanied by a very low risk of developing thromboembolisms. In- and exclusion criteria are formulated to decrease this risk (exclusion of smokers and migraine with aura). In addition, a DSMB will be established.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

- female
- menstrually-related migraine OR migraine in the early menopausal transition phase
- age >= 18
- demonstrated at least 80% compliance with eDiary during baseline period
- no or stable for at least two months on prophylactic medication

Exclusion criteria

- Smoking
- Migraine with aura
- Chronic migraine with 15 or more headache days per month/with 8 or more migraine days per month
- Medication-overuse headache (ICHD-3 criteria)
- Women who are breastfeeding, pregnant, or planning to become pregnant
- Oral contraceptive use and not willing to undergo washout period (stop for two consecutive months)
- Vitamin E use at start of the study
- Use of other sex hormone containing treatments
- Increased risk of VTE: history of VTE or thrombophlebitis, hereditary predisposition for VTE (APC resistance, protein C or S deficiency, antithrombin deficiency), VTE in first-degree family member with young age, long term immobilisation
- Increased risk of ATE: history of ATE, hereditary predisposition for ATE

(hyperhomocysteinemia, antiphospholipid antibodies), ATE in first-degree family member with young age, diabetes mellitus, total cholesterol >= 6.5
- Other contraindication for oral contraceptives: liver malignancy, schistosomiasis, HIV/aids, use of immunosuppressives, tuberculosis, sex-hormone-dependent malignancies (breast, endometrial or ovary carcinomas), pancreatitis, vaginal bleeding with unknown cause, other diseases that can influence vessels (malignancies, heart valve disorders, atrial fibrillation, SLE, haemolytic uremic syndrome, chronic inflammatory bowel disease, sickle cell disease)
- Contraindication for vitamin E: vitamin K deficiency
- Hypersensitivity for any of the compounds in oral contraceptive or vitamin E
- Spontaneous postmenopausal status (menstrual bleedings have ceased for 12 consecutive months)
- Iatrogenic postmenopausal status
- Inability to complete the electronic diary in an accurate manner
- Any serious illness that can compromise study participation

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	10-09-2019
Enrollment:	360
Type:	Actual

Medical products/devices used

Product type:	Medicine

Brand name:	Ethinylestradiol
Generic name:	Ethinylestradiol
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Microgynon30
Generic name:	ethinylestradiol/levonorgestrel (30/150)
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Vitamin E
Generic name:	D-alfatocoferol, 400 IE
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	18-04-2019
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
	metc-ldd@lumc.nl

Approved WMO Date:	03-06-2019
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
	metc-ldd@lumc.nl

Approved WMO Date:	02-09-2019
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
	metc-ldd@lumc.nl

Approved WMO Date:	22-10-2019
Application type:	Amendment

Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	13-03-2020
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	15-02-2021
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	26-03-2021
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	08-04-2021
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	05-08-2022
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	14-12-2023
Application type:	Amendment

Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	02-01-2024
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

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

No registrations found.

In other registers

Register	ID
EU-CTR	CTIS2024-517127-40-00
EudraCT	EUCTR2018-004096-12-NL
CCMO	NL67994.058.19