Continuous use of Oral contraceptives as an alternative for long term Pituitary down-regulation with a GnRH agonist prior to IVF/ICSI in Endometriosis patients: a randomised controlled trial and prospective cohort study

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To show a non-inferiority of continuous use of oral contraceptives for three months to long term pituitary down-regulation with a GnRH agonist for three months prior to present-day IVF/ICSI protocols in patients with severe endometriosis (ASRM…

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Sexual function and fertility disorders
Study type	Interventional

Summary

ID

NL-OMON55530

Source
ToetsingOnline

Brief title
COPIE trial

Condition

- Sexual function and fertility disorders

Synonym
appearance of endometrial tissue outside the womb, Endometriosis

Research involving

Human

Sponsors and support

Primary sponsor: Vrije Universiteit Medisch Centrum
Source(s) of monetary or material Support: Stichting Wetenschappelijk Onderzoek Gynaecologie (SWOG)

Intervention

Keyword: Endometriosis, GnRH agonist, IVF/ICSI, Oral contraceptives

Outcome measures

Primary outcome

Primary outcome: live birth rate after fresh embryo transfer.

Secondary outcome

Secondary outcomes: cumulative live birth rate after one IVF/ICSI treatment cycle including fresh and frozen embryo transfers up to 12 months after start IVF/ICSI, ongoing pregnancy rate, time to pregnancy, treatment outcome parameters (like number of oocytes), adverse events, complications, recurrences, quality of life, safety, effect of GnRH agonist treatment on cognition and costs effectiveness (direct and indirect costs).

Study description

Background summary

It is shown in a number of publications that long term pituitary down-regulation for three to six months prior to IVF/ICSI improves clinical pregnancy rates in patients suffering from endometriosis. However, discussion about this treatment strategy exists, as both the Cochrane and ESHRE recommendation are based on only three small studies. These studies are executed in a different IVF/ICSI treatment era in which more aggressive stimulation was used followed by transferring two or more embryos instead of single embryo transfer which is the current standard. Being afraid that

prolonged down-regulation with a GnRH agonists may lower the response to ovarian stimulation (especially in patient with a poor response in previous IVF/ICSI treatments), it is conceivable that clinicians nowadays may be sceptical about this treatment regime. In addition, uncomfortable side effects, such as vasomotor instability, are often related to this treatment regime, which make patients frequently unwilling to use GnRH agonists for a longer period of time. Alternatively, the effect of continued use of oral contraceptives (OCs) for six to eight weeks prior to IVF/ICSI has also been investigated. These observational data show that this treatment might be beneficial in patients with severe endometriosis undergoing IVF/ICSI, as clinical pregnancy rates were improved compared to endometriosis patient treated without OCs and similar to that of control patients without endometriosis. Those results in combination with the direct costs of GnRH agonists (¤ 370,- per 3 months) versus oral contraceptives (¤ 41,- per 3 months) and indirect costs (higher loss of productivity during GnRH agonist treatment) makes it interesting to investigate whether the outcome of continuous use of OCs is as effective as long term pituitary down-regulation with a GnRH agonist prior to IVF/ICSI, which has not been investigated yet.

Study objective

To show a non-inferiority of continuous use of oral contraceptives for three months to long term pituitary down-regulation with a GnRH agonist for three months prior to present-day IVF/ICSI protocols in patients with severe endometriosis (ASRM stages III and IV).

Study design

Prospective randomised controlled, parallel two-arm study and a prospective cohort

Intervention

Continuous use of oral contraceptives for three months (intervention group) versus long term pituitary down-regulation with a GnRH agonist for three months (reference group) prior to IVF/ICSI.

Study burden and risks

As both treatment protocols are not experimental and already used in daily practice, no additional risks or burdens are expected from the study. All measurements will be combined as much as possible with routine investigations. All possible sides effects and severe adverse events will be monitored and evaluated. No untoward effects of continuous use of oral contraceptives prior to IVF/ICSI on treatment outcome (i.e. ongoing pregnancy) are expected. Non inferiority of continuous use of oral contraceptives can improve patients

comfort by eliminating the side effects related to long term pituitary down-regulation with a GnRH agonist. An IVF/ICSI treatment strategy with continuous use of oral contraceptives holds promise to be more patient friendly as well as cost-effective compared with long term pituitary down-regulation with a GnRH agonist.
Participants will be asked to complete questionnaires every three months. Women who participate in the cohort study, will receive the same questionnaires except for the questionnaire on cost effectiveness.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

- Patients with presence of endometriosis (ASRM III-IV) confirmed by previous surgery or likely to be present based on TVUS or MRI (including presence of uni- or bilateral ovarian endometrioma and deep endometriosis).

- First, second or third IVF or ICSI cycle for this current wish to conceive.
- Signed informed consent.

Exclusion criteria

- Patients aged over 41 years (excluding patients from the day they have celebrated their 41 year birthday).
- Patients with known contraindications for oral contraceptives (history of venous trombo-embolic events, positive family history for venous trombo-emblic events and/or known thrombophilic abnormalitie) or GnRH agonist.
- Patients who previously participated in this trial.
- Pregnancy.
- Malignancy.
- non-Dutch speaking patients
- Azoospermia in partner/donor

Study design

Design

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):	30-10-2018
Enrollment:	730
Type:	Actual

Medical products/devices used

Product type:	Medicine

Brand name:	Livial
Generic name:	Tibolone
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Lupron Depot
Generic name:	Leuproreline-acetaat
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Microgynon '30
Generic name:	ethinylestradiol, levonorgestrel
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	07-12-2016
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	30-03-2017
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	06-08-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	29-08-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	07-12-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO	

Date:	21-12-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	14-05-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	20-06-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	27-07-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	27-08-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	05-12-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	25-02-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	16-03-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	27-11-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO	

Date:	15-12-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	24-02-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	25-02-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	05-07-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	12-07-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	18-08-2021
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: 26777
Source: Nationaal Trial Register
Title:

In other registers

Register	ID
EudraCT	EUCTR2016-004545-91-NL
CCMO	NL59874.029.16
OMON	NL-OMON26777