Predicting ovarian response in artificial insemination with low stimulation

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This large prospective multi-center cohort study aims to identify patient*s characteristics that significantly influence ovarian response to mild stimulation with a fixed dose of 75 IU recombinant FSH

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Sexual function and fertility disorders
Study type	Observational invasive

Summary

ID

NL-OMON43894

Source
ToetsingOnline

Brief title
PRORAILS study

Condition

- Sexual function and fertility disorders

Synonym
infertility, subfertility

Research involving
Human

Sponsors and support

Primary sponsor: Isala Klinieken
Source(s) of monetary or material Support: Merck Serono

Intervention

Keyword: AMH, IUI, subfertility

Outcome measures

Primary outcome

* To assess the relationship between AMH serum levels and ovarian response

(defined by the number of dominant follicles >15mm) in IUI cycles stimulated

with a fixed dose of 75 IU recFSH. All follicles > 11 mm will be documented.

Secondary outcome

* To assess the relationship between age, weight, BMI, smoking, AFC, FSH/E2 on

CD3 and ovarian response (defined by the number of dominant follicles >15mm) in

IUI cycles stimulated with a fixed dose of 75 IU recFSH.

* Pregnancy rate per started cycle.

* Multiple pregnancy rate per started cycle.

* Miscarriage rate per started cycle.

* Cancellation rate per stimulated cycle.

- Correlation between ovarian response and pregnancy rate after IUI

- Correlation between ovarian response and live birth rate after IUI.

Study description

Background summary

Intra-uterine insemination in combination with mild ovarian hyperstimulation (COH) has been proven effective in couples with unexplained (including minimal to mild endometriosis) and mild male subfertility. Gonadotrophins seem to be the most effective drugs to achieve this mild stimulation. Successful stimulation is defined as the achievement of 2 to maximal 3 dominant follicles > 15 mm at the moment of hCG administration. On the other hand, the achievement

of multiple pregnancies should be kept to a minimum and strict cancellation criteria are mandatory.

Retrospective analysis reveals that stimulation with a fixed dose of 75 IU rec FSH (follicle stimulating hormone) per day results often in mono-follicular development (49% of the stimulated cycles) and only rarely to excessive response (8% of the cycles) (unpublished data). To optimize treatment outcome one should be able to predict ovarian response in mild stimulation cycles before hand. A small trial published in Denmark showed that antral follicle count (AFC) and weight seem to influence stimulation response significantly whereas a trend was observed for Anti-Müllerian hormone levels (AMH) . However, numbers were far too small to reach firm conclusions.

Study objective

This large prospective multi-center cohort study aims to identify patient*s characteristics that significantly influence ovarian response to mild stimulation with a fixed dose of 75 IU recombinant FSH

Study design

A multi-center, open-label, prospective cohorts study.
Patients with a regular indication for COH/IUI (controlled ovarian stimulation/ intra uterine insemination) will be asked to participate. Patient*s characteristics will be documented including age, weight, BMI, waist- hip ratio, smoking status, cycle day 2 or 3 FSH /Estradiol levels, antral follicle count, and AMH. AMH and FSH/Estradiol will be determined centrally after completion of inclusion of all patients in the study. All patients will receive a fixed 75 IU recFSH per day stimulation protocol starting from cycle day 3, 4 or 5 after exclusion of ovarian cysts by ultrasound. Ovarian response will be documented by ultrasound only. Once the dominant follicle(s) reach a mean diameter of 16-18 mm, hCG (5000IU or 250 mcg) will be applied and insemination will be scheduled 36-42 hours later. Cancellation criteria will be defined according to the national guidelines provided by the NVOG. This is treatment is conform normal stimulation protocol.

Study burden and risks

On cycle day 2 or 3, one blood sample will be taken for investigation of FSH, Estradiol and AMH levels. Questionnaires about patient characteristics have to be filled in at the beginning of the study. Patients will visit the clinic on cycle day 2, 3 of 4 for their first ultrasound of their cycle and measuremet of their waist- hip ratio. When no contra-indications are detected, patients will receive a fixed dose of 75IU recFSH per day stimulation conform normal ovarian stimulation protocol. After 5 to 7 days a second ultrasound will be performed. This will be repeated until ovulation is induced. RecFSH is administered by

subcutaneous injections. There are no other specific burdens other than taking a blood sample on cycle day 2 or 3 associated with participation and extended (several minutes) transvaginal ultrasound. A questionaire based on reguarly used questionnaires after delivery will be send to the participants. All other investigations (transvaginal ultrasound and the insemination) are normal routine in an IUI program.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

Subfertile couples presenting at fertility clinics with an indication for IUI in stimulated cycles: couples with unexplained or mild male subfertility and a spontaneous chance of conception below 30% (Hunault score) or higher when couples have waited for 6 months after calculation of the initial Hunault score. Unexplained subfertility including minimal to mild endometriosis

(AFS grade 1 or 2) is defined as the failure to conceive after at least one year of unprotected intercourse whereas the standard fertility work-up was unable to detect any factors that might influence fertility negatively. Thus semen analysis should be normal according to the WHO guidelines and ovulation should be documented (by BBT charts, ovulation detection by ultrasound or normal luteal progesterone values). In principle, a negative history (for genital infections among others) in combination with a negative Chlamydia Antibody testing is sufficient to exclude tubal pathology. If there is any doubt or if the local protocol requires further tubal testing, a HSG, fertiloscopy or laparoscopy should be performed. Mild male subfertility is defined as abnormal semen parameters according to the WHO but an average total motile sperm account before processing of at least 10 million.

Exclusion criteria

- Hunault score * 30%
- Endometriosis AFS grade 3 or 4
- Contra-indications for the use of gonadotrophins (cysts larger than 2 cm, allergy for gonadotrophins)
- Total motile sperm count after sperm processing below 1 million
- Women aged younger than eighteen years or older than 45 years.
- Previous treatment with COH/IUI for treating current subfertility
- Unable to speak or read the Dutch language

Study design

Design

Study phase:	2
Study type:	Observational invasive
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Diagnostic

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	10-12-2012
Enrollment:	530
Type:	Actual

Ethics review

Approved WMO Date:	05-12-2012
Application type:	First submission
Review commission:	METC Isala Klinieken (Zwolle)
Approved WMO Date:	03-12-2013
Application type:	Amendment
Review commission:	METC Isala Klinieken (Zwolle)
Approved WMO Date:	27-02-2014
Application type:	Amendment
Review commission:	METC Isala Klinieken (Zwolle)
Approved WMO Date:	16-06-2014
Application type:	Amendment
Review commission:	METC Isala Klinieken (Zwolle)
Approved WMO Date:	22-09-2014
Application type:	Amendment
Review commission:	METC Isala Klinieken (Zwolle)
Approved WMO Date:	19-08-2016
Application type:	Amendment
Review commission:	METC Isala Klinieken (Zwolle)

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
ClinicalTrials.gov	NCT01662180
CCMO	NL41198.075.12

Study results

Date completed:	06-06-2017
Actual enrolment:	527