A phase IIIB, multicentre, multinational, randomized, open-label trial to compare the efficacy and safety of ovarian stimulation with GONAL-f day 1 to day 5 followed by Pergoveris starting day 6 to Pergoveris starting day 1 in women between 36 and 40 years of age undergoing assisted reproductive technique (ART)

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The overall objective of this trial is to generate data on the ovarian stimulation profile obtained when Pergoveris® is started either on stimulation day 1 or stimulation day 6 in ART patients between 36 and 40 years of age (both inclusive). A...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Pregnancy, labour, delivery and postpartum conditions
Study type	Interventional

Summary

ID

NL-OMON36626

Source
ToetsingOnline

Brief title
PERSIST study (PERgoveriS In Stratified Treatment) for ART

Condition

- Pregnancy, labour, delivery and postpartum conditions
- Gonadotrophin and sex hormone changes

Synonym
hormonal deficiency, reduced natural fecundity (infertility)

Research involving
Human

Sponsors and support

Primary sponsor: Merck
Source(s) of monetary or material Support: industrie

Intervention

Keyword: assisted reproductive technique, infertility, oocyte, ovarian stimulation

Outcome measures

Primary outcome

Generate data on the ovarian stimulation profile obtained when Pergoveris® is

started either on stimulation day 1 or stimulation day 6 in ART patients

between 36 and 40 years of age.

Secondary outcome

To further investigate the efficacy and safety profile of Pergoveris® in ART

patients between 36 and 40 years of age.

Study description

Background summary

Ongoing data collection from the UK HFEA has demonstrated that a combination of delayed childbearing and reduced natural fecundity with increasing age has resulted in a steady increase in the number and proportion of women above the age of 34 who are seeking assisted reproductive technology (ART) treatment.

Although ART treatments are available for patients experiencing fertility problems, the likelihood of successful ART outcomes decreases with increasing age of the woman, and is closely linked to the number and quality of oocytes retrieved. Biological ageing leads to depletion of the size of the ovarian pool of oocytes and a reduction in oocyte quality.

Ovarian stimulation with follicle stimulating hormone (FSH) has been the central component to the success of ART procedures. By daily injection of recombinant human follicle stimulating hormone (r hFSH), exogenous FSH levels are maintained for a number of days above the threshold for follicle development, allowing multiple follicles to develop and multiple oocytes to be retrieved. The ideal yield of oocytes varies according to chronological as well as ovarian age, and in women less than 40 years of age, reports in the literature have considered 8 to 10 oocytes (range 5-14 oocytes) per stimulation cycle as adequate. Such a yield should result in sufficient high quality embryos being available to allow a choice in transferring 1 to a maximum of 3 embryos. The remaining embryos or in some countries, the oocytes are cryopreserved, allowing multiple attempts of embryo transfer (ET) per stimulation cycle and contributing to higher cumulative pregnancy rates.
As the ovaries become less sensitive to FSH with increasing age, a poor ovarian response to stimulation is more common in women aged >=35 years, leading to a multitude of treatment strategies. The probability of embryo implantation and successful live birth after IVF declines progressively in women above the age of 35 years. However, the outcome in patients using donor eggs remains relatively constant with increasing age, demonstrating that poor outcomes in older women relate to the oocyte rather than to uterine factors.

Despite major advances in medical technology, there is currently no ART treatment strategy that can fully compensate for the natural decline of fertility with increasing age. However, several useful biomarkers are emerging that can identify women with accelerated biological ovarian ageing, and potential options for improving ovarian response in these patients include the use of luteinising hormone (LH) supplementation, and adjuvant therapies. Treating patients with biologically older ovaries will require a tailored approach based on the individual patient characteristics, to maximize the chances of the low numbers of healthy follicles developing successfully.

LH promotes ovarian androgen production, and hence oestrogen formation, throughout folliculogenesis, and therefore plays a key role in promoting steroidogenesis and growth of the leading follicle. It is known that stimulation of ovarian androgen production by LH starts to decline during the third decade of life. Given the association between diminishing ovarian response to gonadotrophins and increasing age, it is not surprising that some studies have suggested a trend towards an increasing benefit of LH supplementation during ART with increasing age, however there is not a consensus view on this, nor on when is the optimum time to start LH supplementation.

Among women who did not receive r-hLH supplementation, pregnancy and implantation rates were shown to be significantly lower in those >=35 years of age compared with those <35 years of age; this difference was not observed in the group given r-hLH supplementation. Similarly, Marrs et al. found that in patients aged >=35 years at their first ART cycle, the clinical pregnancy rate was significantly higher if patients received r-hLH than if they did not. In a clinical trial including patients aged <39 years, the data obtained suggested that LH supplementation, in the form of r-hLH or HMG, may optimize follicle steroidogenesis in women treated with gonadotrophin-releasing hormone (GnRH)-antagonists. Nevertheless, the evidence is insufficient to evaluate the effect of such a treatment on implantation and pregnancy rates, at least in unselected patients. The efficacy of an LH activity supplementation to a flexible GnRH-antagonist protocol in patients at risk of poor ovarian response (aged >37 years), having as control reference standard the GnRH-agonist flare up protocol was conducted. No significant difference was observed in the total number of oocytes retrieved, however, a statistically significant higher number of mature oocytes was found in the group receiving LH supplementation. Thus, a stimulation regimen provided in association with exogenous LH activity in form of r-hLH, seems to be able to significantly improve the ovarian response in women. This might be due to the quite physiological and stable hormonal environment. Bosch and colleagues also recently described the effect of LH supplementation in ART cycles where a GnRH-antagonist was used. This was a randomized controlled trial in two age subgroups: a) patients aged < 35 years or b) patient aged >= 36 and up to 39 years. The two treatment arms received either 300 IU FSH alone or 225 IU FSH and 75 IU LH i.e. a total of 300 IU gonadotrophin injected per day. They reported less oocytes retrieved in the LH supplemented group (probably due to lower FSH dose used) but higher implantation rates (26.7% vs. 18.9%; P=0.03) in patients aged 36 to 39, but not in the younger sub-population. In contrast, young ovaries may be more sensitive to LH levels and, thus, may experience a detrimental effect of LH supplementation by exceeding the *LH ceiling*. Thus, the patient population receiving LH supplementation should be carefully selected.

It is known that in the less sensitive ovaries, simply increasing the amount of FSH stimulation is of limited use during ART and there may therefore be a place for LH supplementation. Indeed, high doses of FSH could even be postulated to have an adverse effect. It is interesting to note that a large study has shown reduced pregnancy rates, despite the production of at least five oocytes, if a high dose of FSH is required for ovarian stimulation during ART in a long GnRH agonist protocol. One putative explanation for this is that continuously high FSH drive combined with strong LH suppression can result in elevation of late follicular phase progesterone from the follicular cohort being stimulated (Fleming et al 2008), and this has been associated with a reduced implantation potential. Thus, in such a situation, ability to adjust the FSH dose and/or supplementation with LH may be beneficial for the treatment response. A study in women aged 35-39 years undergoing ovarian stimulation with r-hFSH; 300-450 IU/day day1-5 and on day 6 were randomized to receive r-hFSH alone or r-hFSH +

r-hLH; 150 IU/day for the remainder of the stimulation period. No significant differences were observed in markers of either oocyte or embryo quality or quantity. However, higher rates of implantation and live birth per started cycle were observed with r-hLH supplementation than with r-hFSH alone. Although additional large studies are required to further investigate these findings, r-hLH supplementation for women aged 35-39 years undergoing ICSI has been recommended as it may have a beneficial action on implantation. In a study by Bühler et al., 2009, the use of Pergoveris® in routine clinical practice in ART was evaluated in 857 patients. It was found to be effective in achieving clinical pregnancies and was associated with a favourable safety profile. The study also concluded that Pergoveris® seemed to be beneficial in patients aged >35 years, poor responders and those with low LH.

Although chronological age is the most important predictor of ovarian response to follicle stimulating hormone (FSH), the rate of reproductive ageing varies considerably among individuals. Both environmental and genetic factors contribute to biological ovarian ageing. (Individual variation in response to r-hFSH treatment may in part reflect genetic variation such as functional differences in the FSH receptor (FSH-R), as activating and inactivating mutations within the gene have been associated with ovarian dysfunction. Polymorphisms in the gene coding for the LH beta subunit have also been shown to influence the dose of r hFSH needed to achieve an apparently normal ovarian response in ART (i.e. > 5 oocytes obtained).

In summary, certain sub-populations such as women with a higher chronological age seem to benefit from the addition of LH and when used with FSH, in women with severe gonadotrophin deficiency (as occurs during concomitant GnRH agonist use) supports use of a 2:1 ratio of FSH to LH to optimise follicular response.

In this trial, administration of Pergoveris®, a fixed combination product containing recombinant human follicle stimulating hormone (r-hFSH) and recombinant human luteinising hormone (r-hLH) will be initiated at day 1 and day 6 in the two study arms respectively. The primary endpoint will be the total number of oocytes retrieved following stimulation in the two study arms and to document the stimulation characteristics and secondary endpoint measures

Study objective

The overall objective of this trial is to generate data on the ovarian stimulation profile obtained when Pergoveris® is started either on stimulation day 1 or stimulation day 6 in ART patients between 36 and 40 years of age (both inclusive). A secundary objective is to further investigate the efficacy and safety profile of Pergoveris® in ART patients between 36 and 40 years of age.

Study design

This is a multicentre, multi-national, randomized, open-label comparative trial. At the screening visit, the prospective subject will be informed of the trial objectives and overall requirements. Informed consent will be obtained prior to any assessments being made. The subjects who have completed the screening assessments and fulfil all of the eligibility criteria will start down-regulation treatment on day 21-22 of the cycle. Down-regulation treatment must start within 2 months following the screening visit. The routine long luteal phase protocol for GnRH agonist treatment will be followed. Once down-regulation has been confirmed, a pregnancy test will be performed just before randomisation and start of recombinant human follicle stimulating hormone (r-hFSH) treatment to rule out any pre-existing pregnancy. If the result is negative, the subject will be randomly assigned to one of the two treatment arms of the trial:
- GONAL-f® (Liquid Pen; 300 IU of per day) stimulation day 1-5 followed by Pergoveris® (vial/powder, 300 IU per day) from stimulation day 6 and until required r-hCG level is met. The dose can be adjusted from stimulation day 6 (increased or decreased) based upon the subject*s ovarian response and according to the centre*s standard practice.
- Pergoveris® (vial/powder, 300 IU per day) from stimulation day 1 and until the required r-hCG level is met. The dose can be adjusted from stimulation day 6 (increased or decreased) based upon the subject*s ovarian response and according to the centre*s standard practice.
Randomisation across the two treatment arms will be kept balanced in a 1:1 ratio. Follicular development will be monitored according to the centre*s standard practice by US and/or E2 levels, until the protocol r hCG requirement is met (i.e., at least 1 follicle ³ 18 mm and 2 follicles ³ 16 mm). After this, a single injection of 250 mcg of r hCG (Ovidrel®/Ovitrelle®), will be administered in order to induce final oocyte maturation.
At a time of 34-38 hours after r hCG administration, oocytes will be recovered vaginally under US monitoring. Oocytes will then be fertilized in vitro and embryos replaced 2-5 days after oocyte recovery. Ovum Pick Up (OPU), in vitro fertilization (IVF), ET and luteal support will be performed as per centre*s standard practice.
A post-treatment safety visit will be performed for all subjects who received r hCG (pregnant and non-pregnant) on day 15-20 post-hCG. For subjects who have withdrawn from treatment (i.e. after starting Pergoveris® or GONAL-f® but before hCG is given) this visit will take place 20-30 days after their first Pergoveris® or GONAL-f® treatment injection (excluding pregnancy testing).

Intervention

* GONAL-f® (Liquid Pen; 300 IU of per day) stimulation day 1-5 followed by Pergoveris® (vial/powder, 300 IU per day) from stimulation day 6 and until required r-hCG level is met. The dose can be adjusted from stimulation day 6 (increased or decreased) based upon the subject*s ovarian response and according to the centre*s standard practice.
* Pergoveris® (vial/powder, 300 IU per day) from stimulation day 1 and until

the required r-hCG level is met. The dose can be adjusted from stimulation day 6 (increased or decreased) based upon the subject*s ovarian response and according to the centre*s standard practice.
Randomisation across the two treatment arms will be kept balanced in a 1:1 ratio.

Study burden and risks

The safety of Pergoveris® relies on extensive data cumulated during product development and from data on GONAL-f® and Luveris®. Based on the pre-clinical and clinical data available to date, the conduct of the trial is regarded as justifiable at the planned dose ranges. The risk benefit ratio is determined to be favourable

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

* Female subject justifying an IVF/ET treatment,
* Between her 36th and 40th birthday (both included) at the time of the randomisation visit,
* Early follicular phase (day 2-4) serum level of basal FSH £ 12 IU/L measured in the centre*s local laboratory during the screening period (i.e. within 2 months prior to down regulation start),
* Body mass index (BMI) < 30 kg/m2,
* Regular spontaneous ovulatory menstrual cycle between 21 and 35 days in length,
* Presence of both ovaries,
* Normal uterine cavity, which in the Investigator*s opinion is compatible with pregnancy,
* Negative cervical PAP test within the last 6 months prior to randomisation,
* At least one wash-out cycle (defined as ³ 30 days since the last dose of clomiphene citrate or gonadotrophin treatment) since the last ART cycle and/or clomiphene citrate or gonadotrophin treatment prior to starting GnRH agonist therapy,
* Willing and able to comply with the protocol for the duration of the trial,
* Having given written informed consent, prior to any trial-related procedure not part of normal medical care, with the understanding that consent may be withdrawn by the subject at any time without prejudice to her future medical care,
* Having a male partner with semen analysis within the past 6 months prior to randomisation considered adequate to proceed with regular insemination or ICSI according to the centre*s standard practice. If these criteria are not met, the subject can only be entered if donor sperm will be used.

Exclusion criteria

* Had >= 2 previous ART cycles with a poor response to gonadotrophin stimulation defined as £ 6 mature follicles and/or £ 4 oocytes collected in any previous IVF cycle or previous cycles with a hyper response defined as ³ 25 oocytes retrieved,
* Had >= 3 previous ART cycles,
* Any medical condition, which in the judgment of the Investigator may interfere with the absorption, distribution, metabolism or excretion of the drug. In case of doubt, the subject in question should be discussed with Merck Serono's Medical Responsible,
* Previous severe OHSS,
* Patients with primary ovarian failure,
* Polycystic ovary syndrome (PCOS; Rotterdam criteria) to reduce the risk of the occurrence of OHSS,
* Presence of endometriosis requiring treatment,
* Uterine myoma requiring treatment,
* Any contraindication to being pregnant and/or carrying a pregnancy to term,
* Extra-uterine pregnancy within the last 3 months prior to screening,
* History of 3 or more miscarriages (early or late miscarriages) due to any cause,
* Tumours of the hypothalamus and pituitary gland,
* History or presence of ovarian enlargement or cyst of unknown aetiology,

* Ovarian, uterine or mammary cancer,
* A clinically significant systemic disease,
* Known infection with Human Immunodeficiency Virus (HIV), Hepatitis B or C virus in the trial subject or her male partner,
* Abnormal gynaecological bleeding of undetermined origin,
* Known allergy or hypersensitivity to human gonadotrophin preparations,
* Smoking >= 10 cigarettes per day,
* Any active substance abuse or history of drug, medication or alcohol abuse in the past 5 years prior to the screening visit,
* Entered previously into this trial or simultaneous participation in another clinical trial,
* Pregnancy and lactation period,
* Participation in another clinical trial within the past 30 days

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:	Recruitment stopped
Start date (anticipated):	02-08-2011
Enrollment:	10
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	GONAL-f
Generic name:	Follitropin alpha
Registration:	Yes - NL intended use

Product type:	Medicine
Brand name:	Pergoveris
Generic name:	follitropin alfa / lutropin alfa
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	25-01-2011
Application type:	First submission
Review commission:	METC Isala Klinieken (Zwolle)
Approved WMO Date:	09-05-2011
Application type:	First submission
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
EudraCT	EUCTR2010-023534-23-NL
CCMO	NL35069.075.11