

Corifollitropin α followed by menotropin for poor ovarian responders' trial (COMPORT): a protocol of a multicentre randomised trial

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ABSTRACT

Background: Poor response to ovarian stimulation affects a significant proportion of infertile couples undergoing in vitro fertilisation (IVF) treatment. Recently, the European Society of Human Reproduction and Embryology developed new criteria to define poor ovarian response, the so-called Bologna criteria. Although preliminary studies in these patients demonstrated very low pregnancy rates, a recent pilot study has shown promising results in women <40 years old fulfilling the criteria, after treatment with corifollitropin α followed by highly purified menotropin (hpHMG) in a gonadotropin-releasing hormone (GnRH) antagonist setting. Corifollitropin α followed by menotropin for poor ovarian responders' trial (COMPORT) is a randomised trial aiming to investigate whether this novel protocol is superior to treatment with recombinant follicle-stimulating hormone (FSH) in an antagonist setting for young poor responders.

Methods/design: COMPORT is a multicentre, open label, phase III randomised trial using a parallel two-arm design. 150 patients <40 years old fulfilling the 'Bologna criteria' will be randomised to corifollitropin α followed by hpHMG (group A) or recombinant FSH (group B) in a GnRH antagonist protocol for IVF/intracytoplasmic sperm injection (ICSI). The primary outcome is the ongoing pregnancy rate (defined as the presence of intrauterine gestational sac with an embryonic pole demonstrating cardiac activity at 9–10 weeks of gestation). Secondary outcomes are clinical and biochemical pregnancy rates and number of oocytes retrieved. Central randomisation will be performed using a computer-generated list and allocation concealment will be secured with the use of sealed-opaque envelopes. A sample size of 150 women is essential to detect a difference of 19.5% in ongoing pregnancy rates between group A (28%) and group B (8.5%) with a power of 85% and a level of significance at 0.05 using a two-sided Fisher's exact test.

ARTICLE SUMMARY

Article focus

- Recently, the European Society of Human Reproduction and Embryology (ESHRE) developed new criteria to define women with poor ovarian response after ovarian stimulation for in vitro fertilisation (IVF), 'The Bologna criteria'.
- Up to date no randomised trial has been published to evaluate the effectiveness of ovarian stimulation protocols in poor ovarian responders according to the new ESHRE definition.
- Although poor ovarian responders according to the Bologna criteria have very low pregnancy rates after ovarian stimulation for IVF, recently a pilot study demonstrated that corifollitropin α followed by highly purified menotropin (hpHMG) may result in very promising pregnancy rates.

Key messages

- Corifollitropin α followed by menotropin for poor ovarian responders' trial will provide conclusive evidence regarding the superiority of a novel protocol with corifollitropin α followed by hpHMG versus recombinant follicle-stimulating hormone in a gonadotropin-releasing hormone antagonist setting for the treatment of young (<40 years old) poor ovarian responders according to the Bologna criteria.

Strengths and limitations of this study

- This is the first randomised study to examine the efficacy of two stimulation protocols in poor ovarian responders as described by the newly developed ESHRE definition.
- To ensure sufficient power, the study's sample size calculation was based on a previous pilot study with the use of corifollitropin α followed by hpHMG in the antagonist setting. A sample size of 150 patients has 85% power to detect significant differences.
- The study is focusing only in young poor responders (<40 years). Women of advanced age (≥ 40 years) were not included in the study.

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INTRODUCTION

According to the Human Fertilisation and Embryology Authority, live-birth rate per started cycle after in vitro fertilisation (IVF) has increased fairly consistently from 14% in 1991 to 24.5% in 2010.¹ Nonetheless, despite this substantial increase in live-birth rates over the years, specific patient populations experience low-pregnancy rates due to their limited ovarian response after ovarian stimulation for IVF.² Poor ovarian responders are women who fail to respond to ovarian stimulation treatment and represent up to 20% of the population seeking fertility advice.³

Despite the numerous trials conducted in women with poor ovarian response, pregnancy rates remain low, with studies reporting a live-birth of less than 10% irrespective of the treatment protocol used and the age of the patients.⁴⁻⁵ Yet, a considerable limitation of all the randomised trials up to date is the lack of a uniform definition to describe poor ovarian responders. Up to 2011, among 47 randomised trials in women with poor ovarian response, 41 different definitions for poor ovarian response were utilized⁶; surprisingly, no more than three trials used the same definition, whereas even trials from the same group of investigators used different definitions among different trials.⁶ Thus, it appears that any effort to identify the most optimal treatment for these women seems to be futile, simply due to the lack of a uniform definition to describe women failing to respond to stimulation.

Recently, the European Society of Human Reproduction and Embryology (ESHRE) developed a new definition in order to select patients suitable for inclusion in future clinical trials as poor ovarian responders, the so-called Bologna criteria.⁷ However, a limited number of studies has been published to date including patients with poor ovarian response according to the 'Bologna criteria', whereas no randomised trial is published or ongoing for this population.

Preliminary reports in 'Bologna poor responders' highlight the limited prospects for these women. Natural cycle IVF has been shown to result in disappointingly low live-birth rates, regardless of patients' age⁸; ovarian stimulation with widely accepted treatment modalities, for example, short agonist protocol, did not appear demonstrate substantial benefits,⁹ while unpublished data from our centre indicate an ongoing pregnancy rate of 8.3% in women less than 40 years old and 7% in women >40 years old. Finally, novel ovarian stimulation agents such as corifollitropin α did not appear to increase pregnancy rates, underscoring their poor prognosis for achieving pregnancy.⁹

Nonetheless, despite the disappointing results from the vast majority of the preliminary studies in this population, a recent pilot study by our group has shown that a specific protocol may indeed be a promising option for women of younger age fulfilling the 'Bologna criteria'.¹⁰ Corifollitropin α followed by highly purified menotropin (hpHMG) in an antagonist protocol

demonstrated an ongoing pregnancy rate of 28% in women <40 years, strongly suggesting the conduct of a future randomised trial testing this novel treatment protocol.¹⁰

SUMMARY: RATIONALE FOR COMPORT STUDY

The recently developed 'Bologna criteria' by The ESHRE working group on Poor Ovarian Response Definition represent the first realistic attempt by a scientific community (ESHRE) to standardise the definition of poor ovarian response in a simple and reproducible manner, and randomised trials are needed to test the pregnancy rates in this population. In combination with the existing literature, our previous work indicates that (1) women fulfilling these criteria have very low pregnancy rates, irrespective of age (2) current treatment protocols demonstrate ongoing pregnancy rates that do not exceed 8.5% and (3) corifollitropin α followed by hpHMG might increase ongoing pregnancy rates in young patients (<40 years old) fulfilling the criteria. These findings provide a strong rationale for a definitive large randomised controlled trial. The corifollitropin α followed by menotropin for poor ovarian responders' trial (COMPORT) study will provide conclusive evidence regarding the superiority or not of this novel protocol with corifollitropin α followed by hpHMG for the treatment of young poor ovarian responders fulfilling the Bologna criteria.

METHODS AND ANALYSIS

Study design

The COMPORT is a multicentre, open label, phase III multicentre superiority randomised trial using a parallel group, two-arm design with 1:1 allocation ratio with a primary endpoint ongoing pregnancy rates. Four participating centres in Europe will recruit women less than 40 years who fulfil the Bologna criteria for poor ovarian response. The COMPORT study will compare controlled ovarian hyperstimulation for intracytoplasmic sperm injection (ICSI) with corifollitropin α followed by hpHMG versus recombinant follicle-stimulating hormone (rFSH), in a gonadotropin-releasing hormone antagonist setting.

Study setting

The following three centres from three different countries will be participating in the study:

1. Centre for Reproductive Medicine, UZ Brussel, Belgium (co-ordinating centre)
2. Instituto Bernabeou, Alicante Spain
3. Genesis Medical Center, Athens Greece

Study population and eligibility criteria

Study inclusion criteria

Patients participating in the COMPORT study will be women less than 40 years who are considered as poor ovarian responders according to the 'Bologna criteria'.⁷

Corifollitropin α followed by menotropin for poor ovarian responders' trial**Table 1** Young poor ovarian responders according to the Bologna criteria

	Category 1	Category 2
Age	<40 years	<40 years
Previous cycle	≤ 3 oocytes in <i>at least 2 previous cycles</i> with ≥ 300 IU gonadotropins starting dose	≤ 3 oocytes in one of the previous cycles
AMH, AFC	Any value	AFC <7 follicles or AMH <1.1 ng/ml

AFC, antral follicle count; AMH; anti-müllerian hormone.

Patients should belong to one of the categories mentioned in [table 1](#).

In addition, women less than 40 years will be considered eligible if they had undergone previous ovarian surgery or chemotherapy (risk factors for poor ovarian response) and have an anti-müllerian hormone (AMH) <1.1 ng/ml or an antral follicle count (AFC) <7, as suggested by the Bologna criteria.

Study exclusion criteria

1. Uterine abnormalities
2. Recent history of any current untreated endocrine abnormality
3. Unilateral or bilateral hydrosalpinx (visible on transvaginal ultrasound (TVUS), unless clipped)
4. Contraindications for the use of gonadotropins
5. Recent history of severe disease requiring regular treatment

Recruitment and screening

A responsible investigator will be allocated in each of the recruiting sites in order to hold responsibility of local administration of the trial. The responsible investigator of each centre will identify potentially eligible patients upon fulfilment of the 'Bologna criteria' for poor ovarian response and age <40 years. All potentially eligible patients will be screened and documented as eligible; only if they fulfil the inclusion criteria, they will be included in the study. Each of the responsible investigators in the recruiting centres will obtain informed consents for participation in the study using local IRB-approved Informed Consent forms, which will be submitted to the co-ordinating centre on the completion of the study.

Consent will be obtained at the first consultation upon fulfilment of the criteria prior to random allocation to the treatment arms.

Assignment of interventions

Randomisation and allocation of patients to study groups

Patients will be randomised to either corifollitropin α followed by hpHMG (group A) or to rFSH (group B) only after patient eligibility is established and patient consent is obtained. Actual randomisation will occur after the assessment of eligibility and signing of the informed consents using a computer-generated randomisation list. Allocation concealment will be ensured by the use of sealed opaque envelopes in the co-ordinating

centre (no physician will have access in the randomisation list and envelopes will be opened by study nurses) and by central randomisation from the study nurses located in the co-ordinating centre for patients recruited from other centres ([table 2](#)).

Interventions

Investigational group (group A)

On day 2 of the menstrual cycle, a single SC injection of 150 μ g corifollitropin α will be administered (Stimulation Day 1). Starting on Stimulation Day 6, the patient will receive a daily SC injection of 0.25 mg ganirelix and including the day of human chorionic gonadotropin (hCG) administration to prevent premature LH surges. If at Stimulation Day 8–10 not at least one follicle ≥ 11 mm is visible on TVUS, then the cycle should be cancelled due to insufficient ovarian response; if one follicle ≥ 17 mm is observed, and tubal patency is confirmed, rescue intrauterine insemination will be performed. From Stimulation Day 8 onwards, the treatment is continued with a daily SC dose of hpHMG (300 IU/day) up to the day of hCG administration. Injections may be given by the subject herself, her partner or the medical staff ([figure 1](#)).

Reference group (group B)

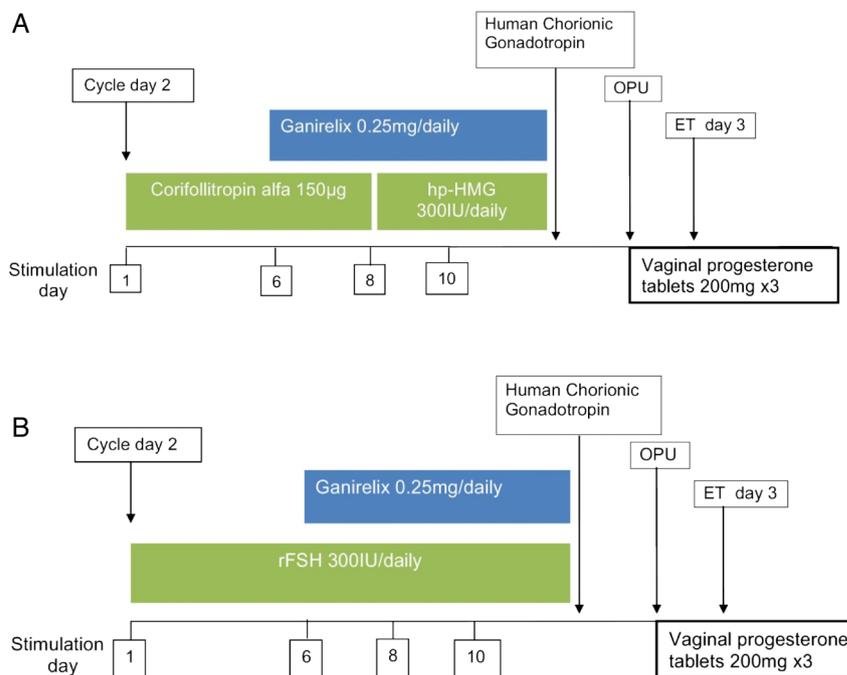
On day 2 of the menstrual cycle, a daily SC dose of rFSH (300 IU/day) is administered up to the day of hCG administration (Stimulation Day 1). Starting on Stimulation Day 6, the subject will receive a daily SC injection of 0.25 mg ganirelix up to and including the day of hCG administration to prevent premature LH surges. If at Stimulation Days 8–10 not at least one follicle ≥ 11 mm is visible on TVUS, the cycle should be cancelled due to insufficient ovarian response; if one follicle ≥ 17 mm is observed and tubal patency is confirmed, rescue intrauterine insemination will be performed. Injections may be given by the subject herself, her partner or the medical staff ([figure 1](#)).

Both groups

As soon as two follicles ≥ 17 mm are observed by TVUS, chorionic gonadotropin (uhCG, 10 000 or rechCG 250 μ g) has to be administered the same day or the day thereafter to induce final oocyte maturation. About 34–36 h thereafter, oocyte pick-up followed by ICSI will be performed. At day 3 after oocyte pick-up, a maximum of three embryos will be replaced. Luteal phase support

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Figure 1 Schematic presentation of the treatment arms. ET, embryo transfer; OPU, ovum pick-up.



with progesterone tablets (200 mg \times 3, intravaginally) will be initiated on the day of oocyte pick-up or the day thereafter and continued for at least 6 weeks or either up to menses or up to negative pregnancy test performed at least 14 days after oocyte pick up (figure 1).

Outcomes

Primary efficacy endpoint

The primary efficacy endpoint is the ongoing pregnancy rates, defined as the presence of intrauterine gestational sac with an embryonic pole demonstrating cardiac activity at 9–10 weeks of gestation.

Key secondary efficacy endpoints

The key secondary endpoints are

1. Clinical pregnancy rates (defined as the presence of intrauterine gestational sac at 7 weeks of gestation);
2. Biochemical pregnancy (defined as positive pregnancy test 2 weeks after embryo transfer);
3. Number of oocytes retrieved.

Other efficacy endpoints

1. Cycle cancellation due to poor-ovarian response;
2. Number of cycles reaching the stage of embryo transfer;
3. Number and quality of embryos;
4. Number of cycles with frozen supernumerary embryos;
5. Endocrine parameters (LH,FSH, E2, Progesterone) during ovarian stimulation.

Prespecified safety endpoints

The prespecified safety endpoint is the percentage of patients with cycle cancellation due to serious adverse

effects s(AE). Serious adverse effects of medication are defined in accordance to FDA guidelines. <http://www.fda.gov/safety/medwatch/howtoreport/ucm053087.htm>

Assessment of adverse events will be performed 20–25 days after the initiation of ovarian stimulation. All patients will be monitored for the occurrence of any adverse effect and cycle cancellation (during ovarian stimulation) due to a serious adverse effect from medication.

Participants follow-up

Patients will be followed in a uniform manner across recruiting centres with specific interventions at specific time points. Table 2 summarises the procedures during a trial's conduction with detailed description and exact time of assessment.

Participants may withdraw from the study at any time. Patients' follow-up will continue within the participating unit, and no data will be used after the decision of the patient to withdraw from the study. Withdrawals and reasons for withdrawal will be kept and reported.

Criteria for discontinuing or modifying allocated interventions

Participants may discontinue trial at their request or upon the occurrence of a serious adverse event. In case of monofollicular development, per protocol, participants will proceed in rescue insemination if tubal patency is confirmed. However, patients may proceed with stimulation upon their request. In such cases, the cycle will be considered as cancelled. In case of gonadotropins dose modification during treatment, the patient will be excluded from the study as a protocol violation.

Corifollitropin α followed by menotropin for poor ovarian responders' trial**Table 2** Trial conduct procedures with detailed description and time of assessment

Procedure	Detailed description	Assessment
Identification of patients	Direct referral from recruiting doctors within centre	First consultation
Assessment of eligibility	Review of eligibility criteria Study explanation	First consultation
Informed consent	Written informed consent from patients to be included in the study	Consultation with study nurses
Randomisation	Central randomisation by study nurses in the co-ordinating centre a. Patients from co-ordinating centre will be directed to study nurses where they will be allocated to treatment of control group following the selection of sealed-opaque sequentially numbered envelopes b. Patients from the other recruiting centres will be allocated to treatment and control groups following telephone contact with the co-ordinating centre from the recruiting physicians with the study nurse of the co-ordinating centre.	Consultation with study nurses
Treatment	Patients will receive allocated treatment	Within 2 months from randomisation
Follow-up during treatment		
Hormonal profile	► FSH, LH, E2, progesterone	Stimulation Days 1, 6, 8, 10 and day of hCG triggering
Ultrasound scans	► Assessment of number of growing follicles and endometrial thickness	Stimulation Days 6, 8, 10 and day of hCG triggering
Follow-up after treatment	► Cycle cancellation ► Number of oocytes retrieved ► Embryo transfer rate ► Positive hCG test ► Clinical pregnancy <i>Definition: Intrauterine gestational sac at 7 weeks of gestation</i> ► Ongoing pregnancy <i>Definition: Intrauterine gestational sac with an embryonic pole demonstrating cardiac activity at 9–10 weeks of gestation</i>	Stimulation day 8–10 Day of oocyte retrieval Day of embryo transfer 2 weeks after embryo transfer 7 weeks of gestation 9–10 weeks of gestation

FSH, follicle-stimulating hormone; hCG, human chorionic gonadotropin; LH, luteinising hormone.

Duration of the study

The study duration is estimated to be of 1 year duration with final date of completion of patients' recruitment on February–March 2014.

Statistical analysis

Analysis will be performed in an intent-to-treat fashion. All patients will be included in the final analysis as long as upon fulfilment of inclusion criteria they were randomly allocated to one of the treatment groups.

Sample size calculation

Sample size calculation was performed after considering results from a pilot study with corifollitropin α followed by hpHMG and results from a large series of young poor responders in our centre.

Based on the fact that our pilot study demonstrated an ongoing pregnancy rate per patient of 28% in young poor responders treated with corifollitropin α followed by hpHMG, whereas standard stimulation (including rFSH in an antagonist setting) in our centre has shown an ongoing pregnancy rate of 8.5%, we hypothesised that a randomised trial is essential to detect a difference

of 19.5% (from 8.5% to 28%) between treatment with rFSH in an antagonist setting versus corifollitropin α followed by HMG in an antagonist setting.

Consequently, we calculated that group sample sizes of 75 and 75 patients achieve 85% power to detect a difference of 19.5% in ongoing pregnancy rates between the null hypothesis that in both groups the pregnancy rates are 8.5% and the alternative hypothesis that the pregnancy rates in the corifollitropin α hp-HMG group is 28% using a two-sided Fisher's exact test with a significance level (α) of 0.05.

Statistical methods for analysis primary and secondary outcomes

Descriptive summary measures expressed as mean (SD) or median (IQR) will be used for continuous variables and number (per cent) for categorical variables, in order to provide a summary estimate of patient demographics and baseline characteristics. The analysis and reporting of the results of the clinical outcomes will follow the CONSORT guidelines (<http://www.consort-statement.org>).

For the primary outcome (ongoing pregnancy rates) and for the other secondary pregnancy outcomes

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(clinical pregnancy and biochemical pregnancy) results will be analysed by using a two-sided χ^2 test with a level of significance $p < 0.05$. Results will be summarised with a relative risk and 95% CI.

The mean number of oocytes retrieved will be compared between treatment groups by using parametric (independent t test) or non-parametric (Mann-Whitney test) tests depending on the normality of the distribution of the results with a level of significance $p < 0.05$.

Other secondary outcomes will be analysed with the use of χ^2 or Fisher exact test if categorical (cycle cancellation due to poor ovarian response, cycles with embryo transfer, number of cycles with frozen supernumerary embryos) or with the use of independent t test or Mann-Whitney test (number and quality of embryos and endocrine parameters (LH, FSH, E2, Progesterone)) during ovarian stimulation. All tests will be two-sided with a level of significance $p < 0.05$. All analyses will be performed in SPSS V.20 Statistical software.

Accounting for missing data

Efficacy analyses will be carried out per randomised patient. If a subject does not reach a certain stage in IVF treatment, zero values will be imputed (eg, pregnancy outcomes will be set to not pregnant).

Additional analyses will be performed for different stages (eg, pregnancy rates will be calculated only for those subjects who had oocyte retrieval or those who reached embryo transfer). As a consequence, patients who discontinue will be part of this analysis until they discontinue.

Missing numbers for subjects who reached a certain stage are not (frequently) expected. Participants who are lost to follow-up before a TVUS assessment will be counted as non-pregnant. For other parameters like oocytes, embryos etc, if missing values occur, then they will not be imputed.

Data management

The same extraction form for baseline characteristics, efficacy and safety endpoints will be distributed to each of the participating centres. The leading investigator in each of the recruiting centres will be responsible for the collection of individual patient data, for their accuracy and validity. The principal investigator of the study will have responsibility for the collection of data from each of the participating centres by the end of the study.

Data monitoring

Owing to the short duration of the study and the known minimal risks (extremely low chance of ovarian hyperstimulation in this group of patients and use of all medical products in accordance with the summary products characteristics), no need for data monitoring committee has been considered essential. There will be only one analysis by the end of the study. However, the principal investigator will be in contact with the leading investigators of each centre in order to review safety data and monitor the progress of the trial.

Feasibility of the study

Poor ovarian responders are women who had numerous unsuccessful IVF/ICSI trials, with an established poor prognosis, who are willing to participate in clinical trials. In our centre, approximately 20 poor ovarian responders are seen in outpatient clinic on weekly basis. Among them, around 40–50% (8–10 patients) are poor ovarian responders <40 years and are women suitable for inclusion in the study. The estimated participation rate is >80% (based on participation in ongoing pilot studies in this population in our centre). However, to secure recruitment and completion of the study within a time-frame of 6–12 months, two additional centres will enrol patients in the study (all of the recruiting centres have an annual number of fresh IVF/ICSI cycles between 1000 and ~2500 cycles) suggesting that recruitment is likely to be high. In order to ensure adequate participant enrolment, recruiting doctors from participating centres will prescreen all patients' files before their first consultation in order to confirm eligibility.

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Contributors NPP is the principal investigator, developed the concept, designed the study and wrote the protocol. MC, JL, KP, and HT were substantially involved in the design of the study and critically revised the manuscript. All the authors gave their final approval of the version to be published.

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Competing interests NPP has received honoraria for lectures from MSD.

Ethics approval The COMPOR protocol has been approved by the UZ Brussel Ethics Committee reference number: BUN 143201316398. Strict confidentiality of all personal and research data will be ensured. Principal investigators in all recruiting centres signed a clinical trial agreement document detailing their commitment towards complying with the relevant laws, regulations, codes of practice and obligations to publication. Site-specific institutional review board approval is required for each recruiting unit. COMPOR is registered in the European Union Drug Regulating Authorities Clinical Trials (EUDRACT), reference number 2013-000583-29 and in clinicaltrials.gov, registration number NCT01816321.

Provenance and peer review Not commissioned; externally peer reviewed.

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