Downloaded from UvA-DARE, the institutional repository of the University of Amsterdam (UvA)
http://dare.uva.nl/document/75612

File ID	75612
Filename	Appendix I

SOURCE (OR PART OF THE FOLLOWING SOURCE):

Type	Dissertation
Title	Polycystic ovary syndrome. A therapeutic challenge
Author	N. Bayram
Faculty	Faculty of Medicine
Year	2004
Pages	135
ISBN	9090184260

FULL BIBLIOGRAPHIC DETAILS:
http://dare.uva.nl/record/202975

Copyright

It is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), other then for strictly personal, individual use.

UvA-DARE is a service provided by the library of the University of Amsterdam (http://dare.uva.nl)

Study
Balasch et al., 2001

Methods
Randomised cross-over study, method of randomisation not stated. Duration and timing not stated. Single center study.
Sample size with power calculation was performed on basis of expected difference in monofollicular development. Allocation concealment unclear. 29 patients randomised. One pre- and one post-crossover cycle/patient. No intention-to-treat analysis performed. Source of funding not stated.

Participants
Women with oligo/amenorrhoea with ultrasonographic evidence of polycystic ovaries. Women had either failed to ovulate after clomiphene citrate treatment or had not conceived after a minimum of three ovulatory cycles at doses 200 mg/day for 5 days. Mean (SE) basal LH/FSH ratio 2.3 (0.35). Mean (SE) basal androstenedione and free testosterone concentrations were 298 (24) ng/dl (normal values 60-200 ng/dl) and 5.8% (0.7) (normal values (0.3-3.8%). Mean age (SE) of the patients was 31.1 (0.6) years. Body mass index (SE) was 26.8 (0.7). Duration of infertility (SE) was 4.1 (0.5) years. Number of subjects with primary infertility was not given. Normal male partner semen parameters, normal hysterosalpingogram or laproscopy. No history of pelvic surgery and/or pelvic inflammatory disease recorded prior to ovulation induction.

Interventions
Chronic low dose step up versus a modified step down regimen with rFSH (Gonal-F®). Treatment was started at day 3 of an induced or spontaneous menses. Chronic low dose step-up protocol: the starting dose of 75 IU rFSH (sc)/day was maintained up to 14 days, unless follicle maturity was reached. If no ovarian response was noted after this period (no follicle > 10 mm) the dose was increased with 37,5 IU/day weekly. Modified step down protocol: the starting dose was 300 IU on cycle day 3 and no treatment was given on the next 3 days. On treatment day 5 rFSH was given 75 IU/day. This dose was maintained for two days. The subsequent treatment protocol followed the low dose step up approach. 10.000 IU HCG (Profasi) was given when a follicle >17 mm developed. Cycles were cancelled when four or more follicles with >14 mm were present.

Outcomes
Pre-crossover data available for ovulation and pregnancy rate only. For other outcomes pre- and post- crossover data were combined:
Total rFSH dose required, duration of stimulation, total number of follicles >10 mm subdivided in number of follicles >14 and >17 mm on day of hCG, oestradiol concentration on day of hCG and number of cycle cancellations.

Notes
No definition of ovulation and pregnancy reported.

Study
Christin-Maitre et al., 2003

Methods
Randomised multicentric study covering 11 centers. Randomisation by numbered sealed envelopes that had to be used in numerical order. 83 patients randomised. Duration and timing not stated. No sample size with power calculation was performed. Patients were treated with the same protocol for three consecutive cycles unless pregnancy was achieved. Source of funding not stated. No intention-to-treat analysis performed.

Participants
Women with oligo/amenorrhoea or anovulatory cycles with polycystic ovaries. Women had either failed to ovulate after clomiphene citrate after three cycles or had failed to conceive after six cycles at doses 100 mg/day for 5 days. Mean age (SD) was 28.8 (3.0) and 28.7 (3.4) years in the step up and step down group. Mean BMI (SD) was 23.6 (4.2) and 23.5 (4.7), duration of infertility (SD) was 2.8 (1.6) and 3.0 (1.8) years in the groups. 75% and 76.9 % of the women suffered from primary infertility. All patients had to have a normal serum prolactin (<20ng/ml), FSH levels <10 IU/l with a testosterone levels <1ng/ml. Serum LH was not used as a diagnosis criteria. A normal hysterosalpingogram or laparoscopy in the past 3 years. Normal male partner semen parameters.

Interventions
Chronic low dose step up versus step down regimen with rFSH (Puregon®). Ovulation induction was started at day 3 to 5 of an induced or spontaneous menses. Chronic low dose step up regimen: the starting dose of 50 IU rFSH (sc)/day was maintained up to 14 days, unless follicle maturity was reached. If no ovarian response was noted after this period (no follicle > 9 mm) the dose was increased with 25 IU/day at weekly intervals up to 100 IU during the first cycle.
Step down regimen: the starting dose was 100 IU on cycle day 3 to 5 until a follicular development (>9mm) could be detected. The dose was decreased to 75 IU for 3 days and secondly to 50 IU until the day prior to hCG administration. In the absence of follicular development after 5 days of treatment, the initial dose of rFSH was increased to 150 IU. When follicular development occured (>9mm) the FSH dose was decreased to 125 IU for 3 days, 100 IU for 3 days and 75 IU until the day prior to hCG administration. In both protocols 5.000 IU hCG was given when the leading follicle reached >18mm. Cycles were cancelled when four or more follicles with >16 mm was present and or if the serum estradiol level was ≥ 1000 pg/ml. Ovulation induction was withheld in the absence of follicular development after 21 days of stimulation or in case of cyst development.

Outcomes
Cumulative ovulation rate, cumulative clinical pregnancy rate, total FSH required, duration of treatment, rate of monofollicular, bifollicular and multifollicular development, estradiol level at hCG gift, rate of hyperstimulation. Ovulation was assessed by a progesterone level > 8ng/ml (30 nmol/l) 7-10 days after hCG administration and/or pregnancy at the end of the treatment cycle.

Notes No definition of ovulation and pregnancy reported.

Study
Coelingh Bennink et al., 1998

Methods
Randomised, assessor blind, prospective, multicenter trial. Method of randomisation: women received a subject number from a randomisation list corresponding with patient boxes in which the medication was kept. Randomisation ratio between rFSH and uFSH 3:2. Duration, timing and location of the trial: Between june 1992 and March 1994, in 12 centers throughout Europe. No sample size with power calculation was performed. 178 patients randomised. 3 cycles/patient. Parallel design, an intention- to- treat analysis was performed.

Participants
Clomiphene citrate-resistant, normogonadotropic, chronic anovulatory (not defined) (WHO group II) patients. Aspect of the ovaries is not described. Serum levels of FSH, prolactin and TSH had to be normal in the early follicular phase. Serum concentrations of testosterone, androstenedione, dehydroepiandrosterone and 17-OH-progestorne had to be below 7, 20, 25 and 20 nmol/L, respectively.
Mean age (SD) of the patients was 28.9 (4.2) for the rFSH group and 29.4 (3.9) for the uFSH group. Body mass index (SD) of the patients was 24.5(3.4) and 24.3 (3.1) respectively.
Duration of infertility (SD) was 3.9 (2.4) and 4.5 (2.7) respectively.
Number of subjects with primary infertility was 58 (55.2%) for the rFSH and 51(76.1%) for the uFSH group.
Number of infertility work up consisted endocrinology (FSH, prolactin, TSH, testesteron, androstenedion, dehydroepiandrosterone, 17-OH-progesterone) and in the group of patients who failed to conceive, a HSG and a semen analysis.

Interventions
Recombinant FSH (Puregon®) versus uFSH (Metrodin®). Treatment was started within 5 days after a spontaneous or induced menses. Starting dose was 75 IU/d, IM, up to 14 days in the first treatment cycle. Weekly dose increasement by half an ampule if no follicle of ≥ 12 mm or a significant rise in serum E2 levels was seen. Maximum dose was 225 IU. Treatment was discontinued after 6 weeks. hCG administration was canceled if more than three follicles of ≥ 15 mm were present. In the second and third cycle increasement could be made after 1 week of treatment, if needed.
HCG, 10.000 IU, (Pregnyl) was given when a follicle of ≥ 18 mm or 2-3 follicles of ≥ 15 mm was developed.

Outcomes
Cumulative ovulation rate, cumulative pregnancy rate (per patient), ongoing pregnancy, miscarriage rate (per patient), ovarian hyperstimulation syndrome (OHSS), multiple pregnancy, total FSH dose, duration of stimulation, treatment period needed to achieve ovulation, the threshold dose, number of follicles of ≥ 12mm, ≥ 15mm, ≥ 18mm on the day of hCG gift. Serum FSH, LH and E2 on the day of hCG gift and cancellation rate.

Notes
Outcome definitions; ovulation: mid luteal serum progesterone concentration of 25 nmol/L or higher on at least one occasion.
Clinical pregnancy: abortion before 12 weeks after hCG administration.
Ongoing pregnancy: a vital pregnancy at least 12 weeks after hCG administration.

Study
Hedon et al., 1998

Methods
Randomised, comparative, open label and multicentre trial.
Method of randomisation: computer-generated random assignment schedule for each centre. Duration, timing and location of the trial: Between January and October 1996 in six French reproductive medicine centers. No sample size with power calculation was performed.
103 patients randomised, 1 cycle/patient.
Randomisation ratio between various dose regimens was 1:1. Parallel design. No intention-to-treat analysis was performed.

Participants
Clomiphene citrate-resistant WHO Group II anovulatory women. Clomiphene citrate resistancy is not defined. Anovulation was defined by cycle length ≥ 41 days with amenorrhoea and a medical history of anovulation. When cycle lenght < 41 days anovulation was confirmed with progesteron < 1.5 ng/ml. Women with a BMI ≥ 35 were excluded. Women must have had two patent tubes and a normal uterine cavity documented by recent hysterosalpingography or hysterosalpingoscopy. Aspect ovaries described. Mean age (SD) of the patients was 29.4(4.3) for the CLD and 29.7(4.0) for the conventional group. Body mass index (SD) was 22.6(4.7) and 22.7(3.7), duration of infertility (SD) was 3.4(1.9) and 2.9(1.5) respectively. Primary infertility was 73.6% and 74% respectively. Infertility work up consisted endocrinology (LH, FSH, Progesteron), hysterosalpingography or hysterosalpingoscopy and semen analysis.

Interventions
Chronic low dose step up versus conventional regimen with recombinant FSH (Gonal-F®). Treatment was started between day 3 and day 5 of a induced or spontaneous menses. Starting dose was 75 IU rFSH (sc)/d. Chronic low dose step up regimen: the starting dose was maintained up to 14 days, unless follicle maturity was reached. If no ovarian response was noted after this period the dose was increased with 37.5 IU/d weekly .
Conventional regimen: the starting dose was increased 75 IU every 5 days from day 7 of stimulation, depending on ovarian response.
Treatment was discontinued after 35 days of treatment or if the patient was at risk for OHSS. HCG (5.000 IU, Profasi) was given when a follicle of 16 mm developed.

Outcomes
Ovulation, clinical pregnancy, live birth per woman, miscarriage, multiple pregnancy, OHSS, total FSH dose, duration of stimulation, oestradiol concentration on day of

HCG, no of follicles > 10 mm, ≥ 16 on day of HCG gift, mono- or bifollicular development > 16 mm.

Notes
No definition of ovulation and pregnancy reported.

Study
Loumaye et al., 1996

Methods
Randomised, comparative, open label and multinational trial.
Method of randomisation: truly randomised using sealed opaque envelopes. Duration, timing and location of the trial: Between 1992 and 1994, multinational, European study. Sample size with 90% power to detect a difference of 20% in cummulative ovulation rate, two-sided test with an alpha of 0.05. 222 patients randomised. 3 cycles/patient.
Ratio between recombinant and urinary FSH was 1:1. Parallel design, no intention- to-treat analysis was performed.

Participants
Clomiphene citrate-resistant (no definition) WHO Group II anovulatory (no definition) women. Aspect ovaries not described. Mean age, BMI, duration and type of infertility unknown.

Interventions
Recombinant FSH (Gonal-F®) versus urinary FSH (Metrodin®). Treatment was started within 5 days after a spontaneous or induced menses.

Outcomes
Cumulative ovulation rate, cumulative pregnancy rate (per patient), miscarriage rate (per patient), ovarian hyperstimulation syndrome (OHSS) and multiple pregnancy.

Notes
Outcome definitions; ovulation: progesteron concentration of at least 30 nmol/l in the mid luteal phase. Clinical pregnancy: urine positive for hCG.

Study
Yarali et al., 1999

Methods
Randomised trial. Method of randomisation: women received a subject number corresponding with patient drug codes. The trial was carried out at the Hacettepe University Hospital, Ankara, Turkey. Timing and duration of trial not stated. No sample size with power calculation was performed. 51 patients randomised. 3 cycles/patient. Parallel design. No intention-to-treat analysis was performed. Randomisation ratio between uFSH and rFSH was 2:1.

Participants
Infertile women with WHO II group anovulation (not defined), resistant to clomiphene citrate, i.e. failure to ovulate with incremental doses of CC up to 150mg/d for 5 days in three previous cycles or failed to conceive with the ovulatory dose of CC during six previous cycles. Aspect ovaries not described. Mean age (SD) of the patients was 27.8(4.8) for the uFSH and 30.0(5.8) for the rFSH group.
Body mass index (SD) was 27.1(5.5) and 27.1(3.7), duration of infertility (SD) was 7.0 (5.6) and 9.0 (4.2) respectively.
LH:FSH ratio (SD) was 2.4 (1.3) for the uFSH and 3.4 (5.5) for the rFSH group. Testesteron level (ng/mL) (SD) was 0.9 (0.4) and 0.97 (0.9) respectively. Infertility work up consisted endocrinology (FSH, prolactin, TSH), HSG or laparoscopy/hysteroscopy and semen analysis.

Interventions
Urinary FSH (Metrodin®) versus rFSH (Gonal F®).
Treatment was started between day 3 and day 5 of a spontaneous or induced menses. Chronic Low dose step up regimen was used.
Starting dose was 75 IU uFSH (im)/d or rFSH (sc)/d up to 14 days, unless follicle maturity was reached. If no ovarian response was noted after this period a weekly increasement by half an ampule to a maximum of 225 IU/d was performed. Treatment was discontinued after 35 days of treatment. In addition if there were > 4 follicles of ≥ 15 mm in diameter, the cycle was cancelled. HCG (10.000 IU, Profasi) was given when a follicle of 17 mm developed.

Outcomes
Cumulative ovulation rate, cumulative pregrancy rate, miscarriage rate
multiple pregnancies, ovarian hyperstimulation syndrome (OHSS), total gonadotrophin dose, duration of stimulation, single follicle development rate, no of follicles of 10-14mm and > 14 mm on day of HCG administration.

Notes
Outcome definitions; ovulation: progestorone level >5ng/mL in the midluteal phase. Clinical pregnancy: at least one gestational sac on transvaginal ultrasound examination. A serum pregnancy test was performed 13-15 days after the administration of hCG.