Appendix II

Characteristics of included studies

Study
*Bringer et al.*, 1985

Methods
Randomised trial. Method of randomisation not described.
Cross-over study, pre- and post- crossover data combined.
Nine patients randomised.

Participants
Clomiphene citrate resistant infertile women.
Patients with high androgen levels and high LH. Presence of polycystic ovaries at laparoscopy. Nothing mentioned about the age and BMI of women and no information on infertility work-up. The study was performed at the Hospital Lapeyronie in Montpellier, France. Timing and duration of study was not stated.

Interventions
Pulsatile GnRH versus hMG.
IV pulsatile GnRH was started on cycle day 2 or 5 after spontaneous or induced menses, using a portable pump at 8-20 mcg/pulse every 90 to 128 minutes. HMG was administered intramuscularly at cycle days 2 and 5 (75 or 150 IU). Based on ultrasound and E2 evaluation, doses were individualized. HMG was stopped and hCG (5,000 IU) injected when at least 1 but not more than 3 follicles >18 mm had developed.

Outcomes
Pregnancy rate (per woman), ovulation rate (per cycle) and OHSS (per cycle).

Study
*Remorgida et al.*, 1991

Methods
Randomised trial. Method of randomisation not described.
Crossover study, only the pre-crossover data are included.
8 patients randomised.

Participants
Clomiphene citrate resistant women with oligomenorrhoea and infertility for at least 3 years. All patients had at least 3 prior attempts of pulsatile GnRH therapy before, without ovulation as outcome. Mean age (+/- SEM) was 27.6 years (1.15). Patients had an infertility work-up consisting of laparoscopy, hysterosalpingography, and semen analysis. Mean BMI (+/- SEM) was 24.4 kg/m2 (1.09) and mean LH/FSH ratio (+/- SEM) was 3.5 (0.16) respectively. The study was performed at the University of Genoa, Italy. Timing and duration of study not stated.
Interventions
Pulsatile GnRH and FSH versus FSH.
IV pulsatile GnRH was started on (progestin-induced) cycle day 2, using a portable pump at 20 mcg/pulse every 59 minutes. On cycle days 5, 7, and 9 patients received two ampules of FSH (75 IU/ampule).
Patients treated with FSH alone took FSH on cycle days 3, 5, and 7 (two ampules 75IU/ampule).
In both groups, based on ultrasound and E2 evaluation, the FSH therapy was individualized (0-4 ampules). FSH and/or GnRH-pump was stopped and hCG (5,000 IU) injected when at least 1 but not more than 3 follicles >18 mm had developed.

Outcomes
Pregnancy rate (per woman), ovulation rate (per woman) and multifollicular development (per woman).

Study
Scheele et al., 1993

Methods
Randomised trial. Method of randomisation not described.
Cross-over study, pre- and post-crossover data combined.
12 patients randomised.

Participants
Women with oligo- or amenorrhoea and raised LH/FSH ratio. Not selected for clomiphene citrate resistance. Mean age (+/- SEM) was 30 years (4). Infertility work-up was not specified. Mean BMI (+/- SEM) was 26.3 kg/m2 (7.2) and mean LH/FSH ratio (+/- SEM) was 1.7 (1.2) respectively. The study was performed at the Free University of Amsterdam, The Netherlands. Timing and duration of trial not stated.

Interventions
Pulsatile GnRH following pretreatment with GnRHagonist pulsatile versus GnRH only.
IV pulsatile GnRH was started on (progestin-induced) cycle day 2, using a portable pump at 10 mcg/pulse every 90 minutes. Discontinuation of treatment when: no ovulation after 5 weeks, menses or positive pregnancy test. GnRHa (Buserelin) was self-administered intra-nasally (4 times daily, 300 mcg) during 3 weeks. The day after discontinuation, pulsatile LHRH was started.

Outcomes
Ongoing pregnancy (per woman), clinical pregnancy (per woman), ovulation rate (per cycle), miscarriage rate (per pregnancy), multifollicular development (per cycle).
Study
Timmerman et al., 2000

Methods
Randomised trial. Randomisation with sealed envelopes (oral communication). 30 patients were randomised. 2 patients dropped out before treatment. Data analysis of 28 patients.

Participants
Women with oligo-or amenorrhoea and LH level >6.5 IU/L and/or LH-FSH ratio >1.5. Women were not treated with clomiphene citrate previously. Median age was 26 in the GnRH group and 27 in the clomiphene citrate group. Only information about semen analysis was available in the study. The study was performed at the Catharina Hospital, Eindhoven, The Netherlands. Timing and duration of study was not stated.

Interventions
Pulsatile GnRH following pretreatment with GnRHagonist versus clomiphene citrate. Patients in the GnRHa group received for at least 3 weeks, 400 mcg nafarelin/day. Immediately after discontinuing GnRHa, IV pulsatile GnRH was started at 10 mcg/pulse at pulse intervals of 90 minutes. The clomiphene citrate group received 50 mg clomiphene citrate on cycle days 3-7 after spontaneous or induced menses. GnRH was increased to a maximum of 20 mcg and clomiphene citrate to a maximum of 150 mg after anovulation.

Outcomes
Pregnancy rate (per woman), ovulation rate (per cycle), multifollicular development (per cycle), pregnancy tests were performed 16 days after ovulation by determination of B-hCG in the urine and serum. ovulation was assumed by disappearance of the dominant follicle on vaginal ultrasound and a subsequent increase in serum Progesteron (>10 nmol/l).