**Abstract**

**Study question:** Does ultra-long downregulation with a GnRH agonist (triptorelin depot) in previously operated patients with endometriosis improve the rate of clinical pregnancy with positive fetal heart beat (CPHB) in the subsequent initiated fresh ART cycle?

**Summary answer:** Ultra-long downregulation with a GnRH agonist prior to ART did not improve the rate of CPHB in the subsequent fresh ART cycle in previously completely operated patients but the trial was underpowered due to early termination.

**What is known already:** Administration of GnRH agonists for a period of 3-6 months prior to ART in women with endometriosis may increase the odds of clinical pregnancy. However, the quality of the studies on which this statement is based is questionable, so these findings need confirmation.

**Study design, size, duration:** A controlled, randomized, open label trial was performed between 1 June 2013 and 31 December 2016 (start and end of recruitment, respectively). Patients with prior complete laparoscopic treatment of any type or stage of endometriosis and an indication for ART were randomized (by a computer-generated allocation sequence) into two groups: the control group underwent ART stimulation in a classical long agonist protocol using preparation with oral contraceptives, the ultra-long group first underwent at least 3 months downregulation followed by a long agonist protocol for ART stimulation. The sample size was calculated to detect a superiority of the ultra-long downregulation protocol, based on the hypothesis that baseline CPHB rate in the control group of 20% would increase to 40% in the ultra-long group. For a power of 20% at a significance level of 5%, based on two-sided testing, including 5% of patients lost to follow-up, the necessary sample size was 172 patients (86 per group).

**Participants/materials, setting, methods:** This trial was conducted at the Leuven University Fertility Center, a tertiary care center for endometriosis and infertility, and a total of 42 patients were randomized (21 in the control group and 21 in the ultra-long group).

**Main results and the role of chance:** Baseline characteristics were similar in both groups. The primary outcome studied-CPHB after the initiated ART treatment-did not differ and was 25% (5/20) in the control group, and 20% (4/20) in the ultra-long group (P > 0.999; relative risk (RR) 1.25, 95% CI 0.41-3.88). Cumulative (fresh + associated frozen) CPHB rates were also similar in the control versus ultra-long group (8/20, 40% vs 6/20, 30%, P = 0.7411; RR = 1.33, 95% CI 0.57-3.19). When other secondary outcomes were compared with the ultra-long group, patients from the control group had a shorter duration of stimulation (mean 11.8 days (SD ± 2.4) versus 13.2 days (SD ± 1.5), P = 0.0373), a lower total dose of gonadotrophins used (mean 1793 IU/d (SD ± 787) vs 2329 (SD ± 680), P = 0.0154), and a higher serum estradiol concentration (ng/ml) at the end of ovarian stimulation on the day of ovulation triggering or cycle cancellation (mean1971 (SD ± 1495) vs 929 (± 548); P = 0.0326), suggesting a better ovarian response in the control group.

**Limitations, reasons for caution:** Due to a strong patient preference, nearly exclusively against ultra-long downregulation (even though patients were thoroughly informed of the potential benefits), the targeted sample size could not be achieved and the trial was stopped prematurely.

**Wider implications of the findings:** Conditional power analysis revealed that the probability of confirming the study hypothesis if the study were completed would be low. We hypothesize that in patients with prior complete surgical treatment of endometriosis, the ultra-long protocol does not enhance ART-CPHB rates. Patient's concerns and preferences regarding possible side-effects, and delay of ART treatment start with the ultra-long protocol should be taken into account when considering this type of treatment in women with endometriosis.