**Abstract title:**
FSH exposure between day 8 and day of hCG administration is an independent predictor of serum progesterone rise

**Study question:**
What is the effect of additional recFSH administration after one dose of corifollitropin alfa (CFA) on the progesterone rise on the day of final oocyte maturation?

**Summary answer:**
While little increase in progesterone levels is observed after seven days of CFA stimulation, post-CFA recFSH dosing is the strongest determinant of subsequent progesterone rise.

**What is known already:**
Late-follicular progesterone (LFP) increase is related to both ovarian response and the intensity of FSH exposure during controlled ovarian stimulation (COS). CFA-treated patients who reach the hCG triggering criteria without need for additional daily recFSH (<8 days) have a lower incidence of elevated progesterone >1.5ng/ml when compared to daily recFSH treated controls. This suggests that the pharmacokinetic profile of CFA, with its progressively declining FSH activity, also may reduce the progesterone rise. However, it remains unclear why favourable progesterone levels on the day of hCG administration are not observed in patients who need additional recFSH after CFA (>8 days).

**Study design, size, duration:**
A post-hoc subgroup data-analysis of three previously published trials; ENGAGE, ENSURE and PURSUE was performed. All were randomized double-blind trials comparing the efficacy of ovarian stimulation with 150μg (ENGAGE/PURSUE) or 100μg (ENSURE) CFA versus a recFSH control group. In both arms, recFSH doses were adjusted according to ovarian response. Cycles with a duration of ovarian stimulation >8 days, which includes all CFA cycles requiring additional recFSH (n=1234) and their daily recFSH controls (n=1026), were included.

**Participants/materials, setting, methods:**
The studies included women aged 18–42 years with a regular menstrual cycle (24–35 days), and an indication for ovarian stimulation for IVF/ICSI. All trials were multicentre and multinational involving centres in Europe, North America and Asia. Treatment cycles <8 days were excluded. Progesterone levels were obtained on days 1, 8 and the day of hCG administration. Linear regression analysis was performed to assess the factors contributing to the serum progesterone levels.

**Main results and the role of chance:**
Patient’s demographics and baseline characteristics were comparable between groups. Mean
progesterone levels on day 8 of stimulation were significantly lower in the CFA group when compared to the recFSH arm (0.6±0.3 ng/ml vs. 0.9±0.4 ng/ml; p<0.001), with a fourfold lower incidence of progesterone levels >1.5 ng/ml (2.2% vs. 8.7%; p<0.001). However, progesterone levels on day of hCG were comparable between groups (1.1±0.7 ng/ml vs. 1.2±0.6 ng/ml; p=0.18), owing to a significantly sharper increase in progesterone levels between day 8 and the day of hCG administration in CFA-stimulated cycles (0.5±0.5 ng/ml vs. 0.3±0.3 ng/ml; p<0.001). Multivariable linear regression analysis, controlling for age and progesterone on Day 8, showed that the post-CFA progesterone increase was independently associated with the number of days of recFSH stimulation from day 8 onwards (0.10 ng/ml per day; 95% CI 0.08-0.12; p<0.001), the daily dose of post-CFA recFSH (0.08 ng/ml per 50 IU; 95% CI 0.05-0.11; p<0.001) and the number of oocytes retrieved (0.02 ng/ml per oocyte; 95% CI 0.01-0.02; p<0.001).

**Limitations, reasons for caution:**
Although this post-hoc analysis is of importance to generate hypotheses on strategies to minimize progesterone rise, prospective randomized trials are needed to confirm whether reduced post-CFA recFSH dosing could prolong the favourable effect of CFA on progesterone levels without a clinically relevant impact on the ovarian response.

**Wider implications of the findings:**
This study found that CFA treatment has a lower incidence of elevated progesterone during the first week of treatment compared to a daily recFSH regimen. Moreover, it suggests that lower daily recFSH doses following CFA could significantly contribute to maintaining these favourable progesterone levels until the day of hCG.

**Trial registration number:**
Engage NCT00696800; Ensure NCT00702845; Pursue NCT01144416

**Keywords:**
FSH Exposure
Progesterone rise,