The effect of oral dydrogesterone (DYD) on the hypothalamic-pituitary-ovarian (HPO) axis (gonadotropin and sex-steroid levels) and ovulation inhibition: a double-blind, phase I, randomized-controlled, parallel-group trial

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**Study question:** What is the effect of oral dydrogesterone (three cycles daily 20mg/30mg) on pituitary, ovarian and adrenal hormones, ovulation inhibition and endometrium in healthy ovulatory women?

**Summary answer:** Daily oral dydrogesterone, 20mg or 30mg, suppresses LH and inhibits ovulation in 33% and 73% of subjects, respectively, while not reducing E2 and other hormones.

**What is known already:** Dydrogesterone, a steroid oestrogen of progestosterone, has high oral bioavailability and has demonstrated clinical utility in several indications, including endometriosis and assisted reproduction technologies. Progestosterone primed ovarian stimulation (PPOS) provides a cost effective and convenient alternative to the GnRH antagonist protocol to suppress a premature LH surge during ovarian stimulation in preparation for frozen embryo transfers (IVF). In PPOS, studies have shown that dydrogesterone provides a comparable number of mature oocytes as a standard GnRH antagonist. The effects of various formulations and routes of administration of different progestins on the sex hormones and the HPO have not been determined across the indications.

**Study design, size, duration:** A single-centre, double-blind, randomised, multiple-dose, parallel-group study of two doses of oral dydrogesterone over three 28-day treatment cycles: dydrogesterone 30mg, 10mg in the morning, afternoon and evening; dydrogesterone 20mg, afternoon dose replaced with placebo. The primary efficacy outcome was the number of subjects with “no ovulation at all” (Hoogland and Skouby score [HSS] 1-4) or “ovulation without pregnancy risk” (HSS 5-6 with negative Landgren criterion) recorded in all treatment cycles.

**Participants/materials, setting, methods:** The study population was 44 healthy, pre-menopausal women aged 18–35 years, with proven pre-treatment ovulation. The inclusion/exclusion criteria were defined to reflect the intended target population and the general contraindications for hormonal preparations. The primary objective was to compare the effect of the two self-administered doses of dydrogesterone on ovarian follicular growth leading to ovulation and E2 suppression. Secondary objectives included effect on other HPO hormones, the endometrium, PK characteristics and safety.

**Main results and the role of chance:** The number of responders to ovulation inhibition was dose-dependent: DYD 30mg, 72.7%, 95% CI: 49.78–89.27%; DYD 20mg, 33.3%, 95% CI: 14.59–56.97%. Based on HSS and Landgren criteria, there was 42.4% and 15.15% ovulation with pregnancy risk with the 20mg and 30mg doses, respectively. Neither dose had any clinically relevant influence on the average E2 concentration or FSH, androstenedione, dehydroepiandrosterone sulphate, testosterone and sex hormone binding globulin levels, while both doses suppressed the pre-ovulatory LH surge. Endometrial proliferation was mildly suppressed to a comparable extent with both daily doses. Hyperechogenic endometrium pattern was observed in 50% and 72% of treatment cycles in ovulating women in the 20mg and 30mg groups, respectively. Treatment with DYD did not significantly delay follicular growth or postpone ovulation in ovulating women. The more pronounced progesterone suppression with the higher 30mg dose may be due to the higher number of subjects without ovulation and thus without a post-ovulatory progesterone rise in that group. Return of ovulation after treatment cessation occurred in 91% women in the 42-day post-treatment period. The most frequently reported TEAE was ‘ovarian cyst’; all cases were of mild intensity and resolved at the end of the trial. No severe TEAE was reported.

**Limitations, reasons for caution:** Only two doses were studied in healthy, ovulatory women. DYD is used in various clinical contexts with concomitant other medications, such as gonadotropins for ovarian stimulation, or under luteotropic circumstances with human chorionic gonadotropin activity from exogenous or endogenous sources. Only limited morning PK sampling was performed.

**Wider implications of the findings:** Oral dydrogesterone used for endometriosis symptom reduction may be associated with a low risk of long-term adverse events from hypoestrogenism and suppression of androgens. Oral dydrogesterone displays relevant and short-term effects on LH levels, supporting its use in PPOS protocols. At therapeutic doses, dydrogesterone does not completely inhibit ovulation.

**Trial registration number:** EudraCT-No.: 2021-004747-24