Oral dydrogesterone for luteal phase support in fresh in vitro fertilization cycles: a new standard?

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Oral dydrogesterone has been used for luteal phase support on an empirical basis since the early days of in vitro fertilization (IVF) treatment. Systematic comparisons of oral dydrogesterone with vaginal progesterone, so far considered to be the standard of care, started to appear in the middle 2000s. Recently, a large, randomized, double-blind, double-dummy phase III trial on the use of daily 30 mg oral dydrogesterone versus daily 600 mg micronized vaginal progesterone for LPS in IVF was published. This company-sponsored trial confirmed the efficacy findings from previous independent researchers and firmly established the noninferiority of daily 30 mg oral dydrogesterone for luteal phase support. Despite oral administration and first pass through the liver, dydrogesterone was as well tolerated as vaginal progesterone in safety analyses. Moreover, no new fetal safety concerns have arisen from that trial. Given the widespread preference of women for an oral compound, dydrogesterone may well become the new standard for luteal phase support in fresh embryo transfer IVF cycles. (Fertil Steril® 2018;109:756–62. ©2018 by American Society for Reproductive Medicine.)
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DYDROGESTERONE: BACKGROUND AND PHARMACOLOGY

Dydrogesterone is a potent orally active progesterone receptor agonist that was developed in the 1950s and that has been widely used since the 1960s for menstrual disorders such as premenstrual syndrome (1), cycle irregularity, endometriosis (2), threatened miscarriage (3), and habitual miscarriage (4), and for postmenopausal hormone therapy (5). Unlike other members of the progestin family, dydrogesterone and its main active metabolite, 20α-hydroxydydrogesterone, do not have any clinically relevant agonistic or antagonistic activity on the androgen, estrogen, and glucocorticoid receptors and only mild antimineralocorticoid properties (6–8). Safety concerns owing to receptor cross-activation have precluded the use of the majority of the progestins in fertility treatment and pregnancy. Only bioidentical progesterone, 17-hydroxyprogesteronecaproate and dydrogesterone are considered to be sufficiently safe for the developing fetus.

Interestingly, dydrogesterone has only little effect on gonadotropin release and therefore hardly interferes with follicular growth and corpus luteum formation and maintenance. At clinically used doses (5–30 mg) (6), ovulation is not suppressed in the human, although recently dydrogesterone (20 mg/d) has been used as an alternative to chlormadinone acetate for preventing premature LH surges in the context of controlled ovarian stimulation (COS) (9).

In contrast to natural progesterone, dydrogesterone has good oral bioavailabilty (∼28%). The half-life of dydrogesterone has been estimated to be 5–7 hours and the half-life of 20α-hydroxydydrogesterone to be 14–17 hours. Prereceptor regulation of action happens mostly by conversion of dydrogesterone to its biologically active 20α-hydroxymetabolite by aldoketo reductase 1C1 (10), an enzyme that also converts progesterone to its less potent metabolite 20α-hydroxyprogesterone.

Dydrogesterone is currently not available in the United States; it was withdrawn from the market for commercial reasons. Likewise, the product was withdrawn from the United Kingdom market in 2008 and from the Australian market in 2011 for commercial reasons. For the United States, dydrogesterone was registered in 1961

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and the license transferred over the years to several companies. In 1997, the current new drug application owner, Solvay, withdrew the product because the registered indications were no longer commercially viable and/or there were potentially conflicting interest regarding other products of which Solvay was the license holder. For the United Kingdom and Australia, low sales of a comparatively cheap drug and the lack of new and commercially interesting indications motivated the withdrawal from the markets.

However, dydrogesterone is currently licensed for use in more than 100 countries globally, with more than 20 European countries having at least one label for use of dydrogesterone in pregnancy. The most common brand names of medication containing dydrogesterone are Duphaston (10 mg tablets) and Femoston (combination of dydrogesterone and E_2 in one tablet in various doses), the latter being used for menopausal hormone treatment.

Dydrogesterone has long been used for exogenous support of endogenous progesterone production by the corpus luteum and placenta. Although definitive proof of luteal phase defect being an independent entity causing infertility has never been established (11), luteal phase defect is a well described iatrogenic phenomenon in the context of COS with multifollicular development and oocyte retrieval for in vitro fertilization (IVF) (12). Studies comparing progestogen usage versus nil or placebo in COS IVF treatment cycles have reported that the use of progestogen is associated with an improvement in ongoing pregnancy or live birth rate (13). Accordingly, luteal phase support (LPS) with the use of progestogens is routinely performed in IVF treatment cycles.

IS DYDROGESTERONE EFFECTIVE FOR LUTEAL PHASE SUPPORT IN FRESH IVF CYCLES?

After many years of empirical use of dydrogesterone for LPS in IVF treatment, the first systematic comparisons of oral dydrogesterone versus vaginal progesterone originated from India (14–17). Prompted by poor patient acceptance of vaginal progesterone, Chakravarty et al. (14) randomized 430 patients, 351 of which received luteal support with vaginal micronized progesterone (600 mg/d) and 79 with oral dydrogesterone (20 mg/d) after COS in a long GnRH-agonist protocol with 10,000 IU hCG triggering. Delivery rates were similar between the treatments (22.8% and 24.1% in the vaginal and oral group, respectively), which paved the way for further clinical investigations. By 2011, three randomized controlled trials (RCTs) (14, 17, 18) encompassing 2,348 patients in total, comparing oral dydrogesterone with micronized vaginal progesterone for LPS in fresh IVF cycles were included in a Cochrane review (19), which summarized that, "for the outcome clinical pregnancy, subgroup analysis of micronized progesterone versus synthetic progesterone showed a significant benefit from synthetic progesterone." No conclusion could be drawn on ongoing pregnancy rate nor live birth rate, because the larger studies (17, 18) did not report those outcomes. The conclusion of higher clinical pregnancy rate with the use of synthetic progesterone remained unaltered in an update of the Cochrane review in 2015 (13). However, a substantial risk of bias of the included studies was criticized (e.g., unclear method of random sequence generation and concealment of allocation). By 2015, eight RCTs (14–18,20–22) comparing oral dydrogesterone and either micronized vaginal progesterone (seven comparisons with a total n = 2,496) or vaginal gel (two comparisons with a total n = 1,735) were included in the latest systematic review and meta-analysis (23). Oral dydrogesterone was administered in daily doses of 20–40 mg, and 600–800 mg daily micronized progesterone or 8% vaginal gel (Crinone) was used in the control arms. It was found that the clinical pregnancy rate was higher in women treated with oral dydrogesterone compared with micronized vaginal progesterone (relative risk [RR] 1.19, 95% confidence interval [CI] 1.04–1.36; $I^2 = 6\%$), an effect not seen in the comparison with vaginal gel. Despite the relatively large total sample size in the meta-analysis, risk of bias in the individual studies, clinical heterogeneity between the studies (for example in doses compared), incomplete outcome reporting (only clinical pregnancy rate was reported in most trials), and insufficient safety surveillance in nearly all of the trials still limited the external validity and clinical utility of the meta-analysis.

Of note, the study by Patki et al. (17) comparing 30 mg/d oral dydrogesterone with 600 mg/d micronized vaginal progesterone in 675 randomized patients suggested superiority of oral dydrogesterone in terms of clinical pregnancy achievement (RR 1.39, 95% CI 1.13–1.72). Accordingly, that dose of dydrogesterone was chosen for further development, and in 2013 a company-sponsored phase III trial program was started, aiming to establish the efficacy and safety of daily 30 mg oral dydrogesterone compared with vaginal progesterone (Clinical Trial Registration Numbers NCT01850030 and NCT02491437) for LPS in IVF cycles with fresh embryo transfer. On completion, this program will have included more than 2,000 randomized study subjects in two large studies with complete assessment from start of treatment to childbirth and the child's health, respectively. Recently, the first of the two studies, LOTUS-I, was published (24). In this multinational, multicentric, randomized, double-blind, double-dummy clinical study, 1,031 patients undergoing IVF or intracytoplasmic sperm injection with fresh single or double embryo transfer after COS were randomized on the day of oocyte retrieval into one of the two treatment arms: The experimental group patients received oral dydrogesterone in 10 mg tablets (Abbott) with placebo intravaginal capsules (Catalent) three times daily, and the control group received micronized vaginal progesterone in 200 mg capsules (Utrogestan; Besins Healthcare) with oral placebo tablets (Abbott) starting on the evening of the day of oocyte retrieval and discontinuing on a negative serum hCG test or at 12 gestational weeks. The study was designed and powered to show noninferiority of oral dydrogesterone for ongoing pregnancy likelihood at 12 gestational weeks. The double-dummy design mandated that each study subject received both oral tablets and vaginal capsules. Accordingly, the patient preference of one of these two routes of administration could not be studied. However, the double-dummy design allows assessing adverse events without the risk of differences in "nocebo" between groups (a self-fulfilling prophecy on purported side-effects of a given drug or route of administration).