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.)
Key Words: Luteal phase support, progesterone, retroprogesterone, dydrogesterone, vaginal progesterone, progestogen

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

Received February 26, 2018; revised March 19, 2018; accepted March 20, 2018.
G.G. reports personal fees and nonfinancial support from Merck-Serono, Ferring, IBSA, TEVA, Gedeon Richter, Finox, MSD, Abbott, Reprodwissen, NMC Healthcare, ZIVA, Biosilu, and Glycotope outside the submitted work. C.B. reports personal fees from Merck-Serono, Ferring, IBSA, Finox, MSD, Abbott outside the submitted work. H.T. reports grants from Merck, MSD, Goodlife, Cook, Roche, Besins, Ferring, Mithra (now Allergan), and Research Fund of Flanders (FWO) and consultant fees from Finox, Abbott, Obseva, and Ovascience outside the submitted work.
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Fertility and Sterility® Vol. 109, No. 5, May 2018 0015-0282/$36.00

https://doi.org/10.1016/j.fertnstert.2018.03.034

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?

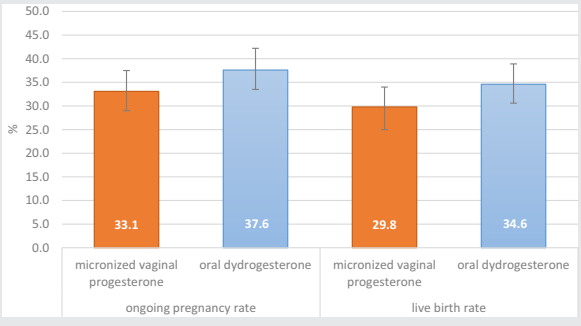
After many years of empirical use of dydrogesterone for LPS in IVF treatment, the first systematic comparisons of oral dydrogesterone versus vaginal progesterone originated from India (14–17). Prompted by poor patient acceptance of vaginal progesterone, Chakravarty et al. (14) randomized 430 patients, 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).

The mean female age in the LOTUS I study was 32.5 years, mean body mass index was 23 kg/m^2, and ~43% of patients underwent single-embryo transfer. The LOTUS I trial firmly established that oral dydrogesterone is noninferior to micronized vaginal progesterone. The ongoing pregnancy rates were 37.6% and 33.1% in the oral and vaginal group treatment groups, respectively (difference +4.7% with dydrogesterone; 95% CI −1.2% to +10.6%). Similar results were observed for the live birth rate: 34.6% and 29.8% in the oral and vaginal treatment groups, respectively (difference +4.9% with dydrogesterone; 95% CI −0.8 to +10.7%). Of note, this single trial did not establish superiority at a statistical significant level owing to the design and sample size, which was still too small for a pregnancy rate difference of the magnitude of ≤5% to be detected with confidence. Conversely, noninferiority of 3 × 200 mg micronized vaginal progesterone against 3 × 10 mg oral dydrogesterone for LPS in a fresh IVF cycle has come under scrutiny with the LOTUS I trial results, because the 95% confidence interval of the difference in ongoing pregnancy at 12 weeks includes effect sizes (−1.2 to +10.6%) not in favor of vaginal progesterone, which most clinicians would not consider to be acceptable (Fig. 1).

The comparator drug in the LOTUS I trial, Utrogestan, is not available in the United States. Utrogestan is a soft gelatin capsule consisting of 100 mg micronized progesterone in refined sunflower oil (previously peanut oil), soya lecithin, glycerol, titanium dioxide, and purified water. The two available preparations in the United States for vaginal administration of progesterone in the context of LPS in IVF are Endometrin and Crinone. Endometrin is an effervescent tablet consisting of, in essence, progesterone in starch (100 mg micronized progesterone in lactose monohydrate, polyvinylpyrrolidone (Povidone K29/32), adipic acid, sodium bicarbonate, sodium lauryl sulfate, magnesium stearate, pregelatinized maize starch, and colloidial silicone dioxide). Crinone is micronized progesterone administered as a gel, which is supposed to better adhere to the vaginal wall. One administration of Crinone 8% consists of 90 mg micronized progesterone in a gel of glycerol, paraffin-light liquid, hydrogenated palm oil glyceride, carbomer 974 P, polycarbophil, sorbic acid, sodium hydroxide, and purified water. Despite the use of different doses and administration regimen, differences in pregnancy rate between these vaginal preparations have never been documented (13). Beyond the evidence on oral dydrogesterone versus micronized vaginal progesterone cited above, dydrogesterone has been tested in two investigator-initiated randomized trials against progesterone in gel (Crinone 8%) (23). No difference in ongoing pregnancy rates was found (RR 0.97, 95% CI 0.83–1.13), but the dose of oral dydrogesterone was only 20 mg/d in both trials (23). No randomized trial has compared vaginal Endometrin versus oral dydrogesterone. Likewise, no randomized trial has compared intramuscular progesterone versus oral dydrogesterone (13). Of note, intramuscular progesterone is still frequently used in the United States owing to concerns about the efficacy of vaginal progesterone. Because intramuscular progesterone is associated with significant side-effects, a randomized trial comparing oral dydrogesterone with intramuscular progesterone is warranted.

FIGURE 1



Ongoing pregnancy rates and live birth rates (with 95% confidence intervals) in the in the two groups (total n = 974) of the LOTUS I trial. (adapted from Tournaye et al. 2017 (24))

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IS ORAL ADMINISTRATION PREFERRED BY THE PATIENT OVER VAGINAL ADMINISTRATION?

Studies on the administration of, for example, vaginal versus oral misoprostol have consistently reported the oral route to be preferred by the majority of patients (25–28). Preference for oral administration may be even higher in the context of LPS, with a minimum intake duration of 10 days and often treatment extension into early pregnancy. Furthermore, patients exposed to once daily or three times daily administration of a vaginal progesterone prefer once daily application, because this was considered to be easier, more convenient, and less messy (29). It is also noteworthy that in a recent phase III trial program comparing vaginal progesterone gel once daily with subcutaneous progesterone injection once daily for LPS (30), no difference in patient preference for one of the two administration routes could be seen, despite the fact that injectable drugs are usually less tolerated, especially when self-injected. In that trial, the incidence of vaginal irritation, inflammation, dryness, pruritus, discharge, or pain was 50.8% in patients on daily vaginal gel administration compared with 10.4% in patients on subcutaneous progesterone.

Chakravarty et al. (14) reported, based on questionnaires handed out in the context of one of their randomized studies, that satisfaction of patients with the tolerability of oral dydrogesterone for LPS (2 × 10 mg) was significantly higher compared with micronized vaginal progesterone (3 × 200 mg). In another RCT on 831 patients undergoing IVF (21), patients were found to be significantly more often satisfied with oral dydrogesterone (2 × 10 mg) and more often significantly dissatisfied with once daily vaginal progesterone gel when ranking the drugs on scale from 1 to 5. No such difference was seen, however, in a recent study from Iran on 240 patients (22), in which total satisfaction and total dissatisfaction was equally distributed between 2 × 10 mg oral dydrogesterone and 2 × 400 mg vaginal micronized progesterone for LPS.

The above results illustrate that the preference for a route of administration in an individual patient is likely a function of personal habits and cultural circumstances. It has been suggested that patients may believe that they are receiving a "stronger" medicine when the administration is by injection or other uncomfortable route of administration and that such expectations may even influence the response to a drug. Although the latter is unlikely in the context of LPS, implicit judgments on a medication by an individual patient (efficacy beliefs), concerns about potential adverse reactions, and personal preferences should be taken into account to achieve good compliance and treatment adherence.

IS ORAL ADMINISTRATION PREFERRED BY THE PHYSICIAN OVER VAGINAL ADMINISTRATION?

Luteal phase support with the use of progesterone is usually started within the time interval between oocyte pick-up and embryo transfer. When the embryo transfer catheter passes through the cervical canal, there is a risk of introducing not only progesterone itself, but also excipients of tablets, suppositories, or gel into the uterine cavity. Furthermore, the supraphysiologic progesterone concentrations in the vagina may alter the local microbiome, which has become a recent focus of interest in the context of IVF (31). Although a negative effect of drug excipients or high doses of progesterone on the endometrium, embryo, or the microbiome have never been documented, doctors usually take great care in cleaning the outer cervical os before the embryo transfer. A formal physician preference study has not been done, but an educated guess is that most doctors prefer a cleaner vagina (and therefore oral or injectable administration) when doing the embryo transfer or when performing a transvaginal scan at later stage.

IS ORAL DYDROGESTERONE SAFE AND WELL TOLERATED BY THE PATIENT?

Bioidentical orally administered progesterone has been associated with the formation of sedative metabolites due to a first pass effect in the liver. These metabolites act centrally, and side-effects of oral progesterone, such as fatigue, headache, and urinary frequency, in addition to safety concerns regarding intrahepatic cholestasis with oral progesterone intake, have prompted the development of vaginal preparations for LPS in IVF (32, 33). The most important tolerability issue with vaginal progesterone is, however, discharge and irritation.

An objective assessment of the tolerability of dydrogesterone (20 mg/d) compared with vaginal micronized progesterone (600 mg/d) was done by Chakravarty et al. (14). Liver function tests were performed at baseline (before administration) and on the day of pregnancy test (e.g., after ~14 days of intake). The percentage of patients with abnormal liver function tests and the mean serum glutamate-pyruvate transaminase, bilirubin, and alkaline phosphatase levels were highly similar between the groups. In 10.5% of patients given micronized progesterone, vaginal discharge or irritation was confirmed, whereas 0% of dydrogesterone patients had those side-effects.

Tomic et al. (21) reported that perineal irritation, vaginal bleeding, vaginal discharge, and interference with sexual activity was significantly higher in patients receiving vaginal progesterone gel compared with oral dydrogesterone. No difference was seen for dizziness, headache, nausea, breast tension, or bloating.

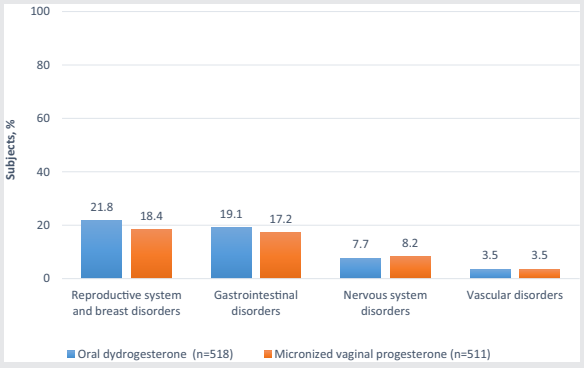
The most comprehensive and robust insight into the maternal safety and tolerability of oral dydrogesterone comes from the LOTUS I trial (24), in which doctors and patients were blinded and each patient was randomized to oral dydrogesterone or micronized vaginal progesterone and received a dummy medication with placebo. In addition, the patients were monitored for adverse events during later stages of pregnancy. Treatment emerging adverse events leading to study termination were reported in 12.4% of subjects in the dydrogesterone group and in 16.0% of subjects in the micronized vaginal progesterone group. Liver enzyme analysis was normal in nearly all patients in both groups. Because most adverse events leading to study termination or discontinuation of the study drug were infrequent, events were grouped by organ system (e.g., gastrointestinal, nervous system, reproductive organ system, vascular system). No differences were identified (Fig. 2), and no new safety or tolerability issues were found in this large study.

In summary, the use of oral dydrogesterone avoids the frequently reported and negatively perceived side effects of vaginal preparations, whereas no systemic tolerability difference from micronized vaginal progesterone has been identified in a large, double-blind, double-dummy randomized trial.

IS DYDROGESTERONE SAFE FOR THE FETUS?

Dydrogesterone has been on the market since the 1960s and is labeled for use in pregnancy (e.g., for recurrent miscarriage or threatening abortion) in numerous countries worldwide. From

FIGURE 2



Proportion of female subjects reporting treatment emerging adverse events according to organ system in the two groups of the LOTUS I trial. (adapted from Tournaye et al. 2017 (24))

Griesinger. Luteal phase support with oral dydrogesterone. Fertil Steril 2018.

sales figures, it has been estimated that more than 8 million fetuses must have had in utero exposure to dydrogesterone during more than half a century of use on a global scale (34). In view of this extensive use, a substantial fetal risk of dydrogesterone can be ruled out, although a low-level risk could be detected only via sophisticated and large observational studies.

A review and in-depth analysis of available pharmacovigilance data identified 28 cases of congenital defects with a potential link to dydrogesterone exposure in pregnancy recorded within the time span from 1977 to 2005 (35). Malformation rates associated with a drug can not be calculated from pharmacovigilance data, but the low number of reported cases (some of which occurred within controlled studies) in relation to the (estimated) number of pregnancies exposed makes a relevant teratogenic risk of dydrogesterone highly unlikely. Moreover, the types of defects potentially associated with dydrogesterone in the pharmacovigilance data were very diverse, with no evidence of a pattern of abnormalities (35).

In the LOTUS I trial (24), child health was recorded at birth for the total maternal population and 6 months after birth in a subset of 216 patients who had been treated in Russia (36). Overall, 213 and 158 children were recorded in the oral dydrogesterone and vaginal progesterone group, respectively. The incidences of congenital, familial, and genetic disorders were <2% in both treatment groups. No difference in the incidence of congenital malformations was found, and no distinct pattern of defects with the use dydrogesterone or progesterone was observed (24).

Further safety data stem from RCTs on dydrogesterone use in threatened miscarriage (37–41) and recurrent miscarriage (42). None of those studies revealed a safety concern with dydrogesterone use.

In 2015, a retrospective case-control study compared exposure to dydrogesterone in pregnancy in 202 children born with congenital heart disease and a control group of 200 healthy children born from 2010 to 2013 in the Gaza strip of Palestine (43). Dydrogesterone exposure was defined as any reported use (by recall) in the first trimester of pregnancy. A higher rate of dydrogesterone intake was found in mothers of children with a heart defect (38%) compared with control children (18%), and the authors concluded that there was a positive association between dydrogesterone use during early pregnancy and congenital heart disease in the offspring (adjusted odds ratio 2.71, 95% CI 1.54–4.24; $P<.001$). However, this study violated numerous basic principles of epidemiologic research. First, all comparisons should have been made within the same study base, that is, women who have had an indication for dydrogesterone and who did or did not receive that drug. Second, because dydrogesterone is often prescribed for miscarriage prevention, all women should have had a similar risk background; the difference in maternal population leads to the issue of confounding: There is evidence from the literature that previous miscarriages are an important and strong risk factor for congenital heart defects (44–46). Third, the authors did not confirm exposure (at least retrospectively based on medical records) but instead relied on recollection of the mothers. However, mothers are likely to recollect any event in pregnancy better if their child has an abnormality. Finally, different heart defects were pooled into one group and socioeconomic status was ignored, as were comorbidities. In summary, a causal relationship of dydrogesterone and heart defects can not be inferred from this study.

Congenital heart defects are common, with an estimated incidence of 1%. A study verifying or refuting the hypothesis of a threefold increased risk of a heart defect in offspring exposed to dydrogesterone would require >3,000 infants to be studied in a 1:1 randomized trial. With a live birth rate of 30% in patients undergoing IVF, a two-armed study on women receiving dydrogesterone or a control drug for LPS in IVF treatment would therefore require a total sample size of ≥10,000 patients (alpha error <5%, beta error <20%). It is unlikely that a study of such dimension will soon be performed, and physicians therefore will have to rely on the available pharmacovigilance data. Of note, larger-size randomized studies assessing the risk of bioidentical progesterone have not been conducted, despite the fact that a theoretic risk of bioidentical progesterone in supraphysiologic doses can not be ruled out.

WHAT IS THE FINANCIAL COST OF DYDROGESTERONE?

The financial cost of dydrogesterone varies between markets. In Germany, for example, 1 day of treatment with 30 mg dydrogesterone costs, at the time of writing, ~1.2 USD, the same daily dose would cost approximately 1.5 USD in Russia, 1.9 USD in India, 2.4 USD in Saudi Arabia, and 3.1 USD in China. A simple determination of medication price is, however, inadequate for determining the actual cost of a medicine for treating a certain disorder, which must consider efficacy, safety, and aspects of patient preference. Furthermore, the cost-effectiveness of a drug should be compared with the cost-effectiveness of a comparator drug to determine how much more or less cost comes with clinical benefit. Such analyses are complex in infertility treatment and would be redundant in ideal scenarios, i.e., in which drugs were more efficacious while not increasing burden and risk and having a lower direct financial cost.

For efficacy and safety aspects of dydrogesterone for LPS, valid data can be retrieved from the LOTUS I trial (24). Physicians can use the efficacy and adverse event data from the LOTUS trial to model cost-effectiveness of dydrogesterone in their specific health care settings. This has recently been done for two countries, Russia and China, in a deterministic economic model using live birth as the primary efficacy outcome, as well as direct cost of dydrogesterone (Duphaston) versus micronized vaginal progesterone (Utrogest) in addition to infertility treatment costs (47, 48). In both settings, a lower cost per live birth was observed with the use of dydrogesterone.

CONCLUSION

After many years of empirical use of dydrogesterone for LPS in IVF treatment, evidence-based medicine has been catching up on this topic with a number of investigator-initiated trials and, most recently, the publication of a large randomized,

double-blind, double-dummy phase III trial of 30 mg dydrogesterone for LPS in IVF. This phase III trial confirms the efficacy findings from previous independent research and thus firmly establishes the noninferiority in efficacy of daily 30 mg oral dydrogesterone versus daily 600 mg micronized vaginal progesterone. 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 LPS in fresh embryo transfer IVF cycles.

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