CLINICAL SUMMARY

Title	Oral dydrogesterone for luteal phase support in fresh in vitro fertilization cycles: a new standard?
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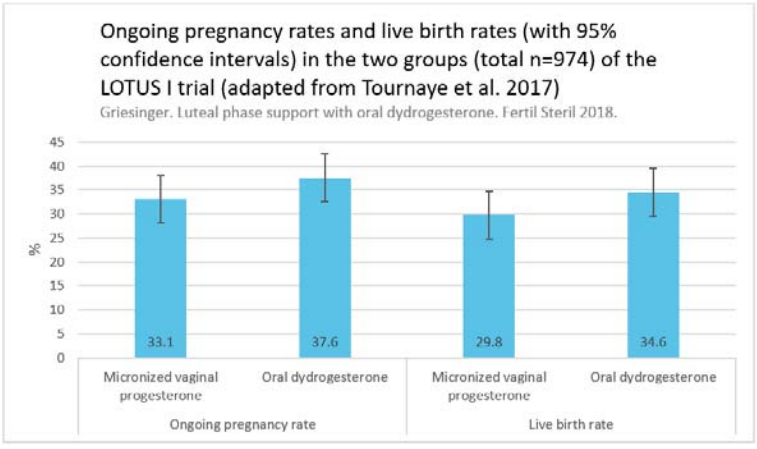
Dydrogesterone: Background and pharmacology

- Dydrogesterone is a potent orally active progesterone receptor agonist. dydrogesterone and its main active metabolite, 20a-hydroxydydrogesterone, do not have any clinically relevant agonistic or antagonistic activity on the androgen, estrogen, and glucocorticoid receptors and only mild antimineralocorticoid properties.
- Dydrogesterone has only little effect on gonadotropin release and therefore hardly interferes with follicular growth and corpus luteum formation and maintenance.
- In contrast to natural progesterone, dydrogesterone has good oral bioavailability (~28%).

Is dydrogesterone effective for luteal phase support in fresh IVF cycles

- By 2015, eight RCTs 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.
- Oral dydrogesterone was administered in daily doses of 20–40 mg, and 600–800 mg daily micronized progesterone or 8% vaginal gel 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.
- Of note the Patki study in 2007 showed superiority in clinical pregnancy achieved of 30mg/day dydrogesterone versus 600mg/day micronised vaginal progesterone and this paved the way for the dosage used in the LOTUS studies.
- The LOTUS I study showed comparable efficacy and safety versus micronised vaginal progesterone.



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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 most patients.
- Chakravarty et al. reported, that satisfaction of patients with the tolerability of oral dydrogesterone for Luteal Phase Support (LPS) (2x10 mg) was significantly higher compared with micronized vaginal progesterone (3x200 mg).
- In another RCT on 831 patients undergoing IVF, patients were found to be significantly more often satisfied with oral dydrogesterone (2x10 mg) and more often significantly dissatisfied with once daily vaginal progesterone gel when ranking the drugs on scale from 1 to 5.

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.
- 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.

Is oral dydrogesterone safe and well tolerated by the patient?

- 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.
- 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.
- The LOTUS I study results are show in the below figure.

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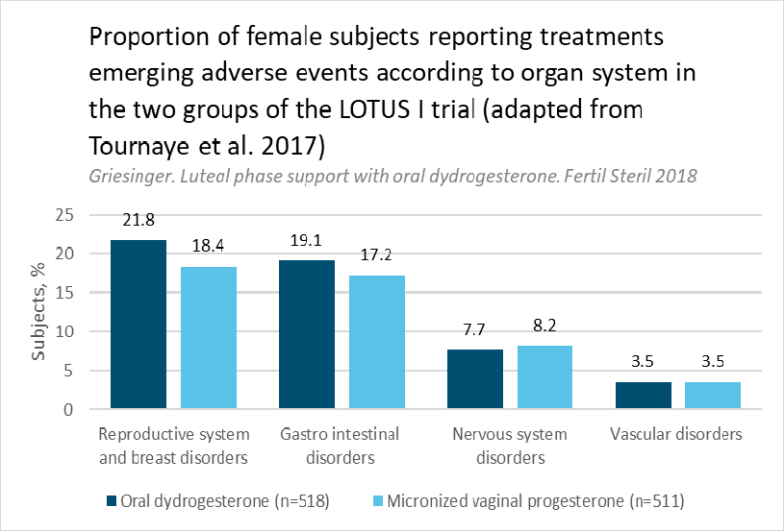

- The use of oral dydrogesterone avoids the frequently reported and negatively perceived side effects of vaginal preparations, whereas no systemic tolerability difference from micronized vaginal progesterone has been identified in a large, double-blind, double-dummy randomized trial.

Is dydrogesterone safe for the foetus?

- It has been estimated that more than 8 million foetuses must have had in utero exposure to dydrogesterone during more than half a century of use on a global scale.
- As such a substantial foetal 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.
- Malformation rates associated with a drug cannot 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.
- In the LOTUS I trial, 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.

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- 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. 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.
    1. 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.
    2. 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.
    3. The authors did not confirm exposure 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.
    4. 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 cannot be inferred from this study.

What is the financial cost of dydrogesterone?

- The financial cost of dydrogesterone varies between markets.

  The efficacy and adverse event data from the LOTUS trial can be used to model cost-effectiveness of dydrogesterone. This has been used in 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.

- In both settings, a lower cost per live birth was observed with the use of dydrogesterone.

Conclusions

- After many years of empirical use of dydrogesterone for LPS in IVF treatment, phase III trial data 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.

- 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.