# DYDROGESTERONE:

## A Lifeline for Threatened Pregnancies

## Module 2

### Dydrogesterone and Assisted Reproductive Technologies (ART)

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## Introduction

The menstrual cycle can be divided into two phases: the follicular and luteal phases, separated by ovulation and marked by the onset of menstrual bleeding. The follicular phase is characterized by the growth of the preovulatory follicle, which stimulates endometrial proliferation through estrogen. In contrast, the luteal phase is driven by the corpus luteum (CL), which secretes progesterone, inhibiting endometrial proliferation and preparing the endometrium for implantation. Both phases are essential for natural reproduction.

## Luteal Phase Physiology

During the follicular phase of the menstrual cycle, the dominant follicle matures and produces increasing levels of estradiol, which triggers a surge in luteinizing hormone (LH) from the anterior pituitary. This LH surge initiates several processes that lead to ovulation, including the release of the oocyte into the pelvis. Following ovulation, the empty follicle transforms into the corpus luteum (CL), which is essential for reproduction and maintaining normal menstrual cycles.

As the granulosa cells of the dominant follicle luteinize, they enlarge and develop vacuoles that contain the pigment lutein, giving the CL its characteristic yellow color. Before ovulation, these granulosa cells are separated from the bloodstream by a basal lamina, which regresses after ovulation, allowing the theca cells to migrate into the forming CL. The process of neovascularization, driven by vascular endothelial growth factor and fibroblast growth factor, ensures that the CL receives one of the highest blood flows per unit mass in the body, a feature that can be clinically significant when managing a hemorrhagic CL.

The CL produces several hormones, but progesterone is the most important, as it transforms the endometrium into a state ready for blastocyst implantation and early pregnancy maintenance. Progesterone production in the CL depends on the availability of cholesterol and low-level LH stimulation. The luteal cells differentiate into two types: small cells (likely from the theca cells) that contain LH and human chorionic gonadotropin (hCG) receptors, and large

cells (likely from granulosa cells) with greater steroidogenic capacity but without LH and hCG receptors. Communication between these cells through gap junctions ensures progesterone production in response to LH stimulation.

Multiple studies and clinical experiences with ART have demonstrated the crucial role of LH in stimulating progesterone production from the CL. In an experiment involving rhesus monkeys, it was shown that LH and progesterone levels drop rapidly when exogenous gonadotropin-releasing hormone (GnRH) pulses are stopped, but resume when GnRH is reintroduced. Similarly, in women undergoing in vitro fertilization (IVF) with suppressed LH production, progesterone production can be maintained with hCG supplementation.

Despite the essential role of LH in progesterone production, the lifespan of the CL appears to be programmed independently of LH secretion, typically lasting 11 to 17 days from ovulation to the onset of menstruation. If not rescued by hCG from an early pregnancy, the CL regresses into an avascular scar called the corpus albicans through a process known as luteolysis. Studies suggest that luteolysis is not solely dependent on LH, as progesterone production can resume after a temporary absence of LH stimulation.

The CL can be rescued from luteolysis by the rising levels of hCG produced by the trophoblast in early pregnancy. HCG production begins 7 to 8 days after fertilization, and while the survival of the CL is necessary for early pregnancy, the CL is also crucial for sustaining early pregnancy. Studies have shown that luteectomy (removal of the CL) before 7 weeks of gestation leads to pregnancy loss, while luteectomy after 9 weeks does not affect pregnancy, highlighting the transition of progesterone production from the CL to the placental trophoblast.

These findings emphasize the critical role of progesterone in establishing and maintaining pregnancy. There is a threshold level of progesterone below which pregnancy is impaired or cannot be maintained, making it essential for clinicians to recognize abnormal luteal phase function and consider appropriate therapies in both ART and natural cycles.

## Luteal Phase Deficiency

Luteal phase deficiency (LPD) occurs when there is insufficient progesterone to support the normal development of a secretory endometrium, which is necessary for proper embryo implantation and growth. The condition was first identified in 1949 by Georgiana Seegar Jones

as a potential cause of infertility. In her seminal study of 206 ovulatory women with primary or secondary infertility, some displayed a blunted rise in basal body temperature, reduced 48-hour urinary pregnanediol excretion, or inadequate secretory changes in endometrial biopsies—characteristics labeled as LPD. Despite decades of research, the understanding of LPD remains incomplete, and its pathogenesis and diagnosis are still subjects of ongoing debate.

Clinically, LPD can manifest as a shortened luteal phase of less than 9 days, from ovulation to the onset of menstruation. It may also present as spotting several days before menstruation, without any structural or infectious causes. LPD has been linked to irregular menstrual bleeding, infertility, and recurrent pregnancy loss.

## Treatment of Luteal Phase Deficiency

Due to the limited understanding of LPD's pathophysiology and the lack of a reliable diagnostic method, treating suspected LPD empirically is not fully evidence-based. Clinical trials face a dilemma—how to assess treatment for a condition that cannot be accurately diagnosed. Most studies have relied on surrogate markers such as endometrial biopsy results and progesterone levels to evaluate treatment outcomes. However, these markers have not been consistently linked to improved fertility outcomes. Although these challenges make it difficult to study treatment regimens, many clinicians continue to treat suspected LPD cases based on clinical judgment, considering the potential benefits outweigh the risks.

Progesterone supplementation is a common treatment for LPD, although no published evidence supports improved pregnancy outcomes in natural cycles. Progesterone is typically provided as micronized progesterone or synthetic progestins. Due to early concerns about teratogenic effects associated with synthetic progestins (later disproven), natural micronized progesterone is often preferred. This can be administered orally, sublingually, rectally, as an oil-based vaginal suppository, an aqueous vaginal cream, or via intramuscular injection.

A retrospective study comparing clomiphene citrate (CC) to vaginal progesterone suppositories in patients with suspected LPD (based on endometrial biopsy) reported a 100% pregnancy rate in those treated with progesterone and an 81% pregnancy rate in those treated with CC after one year. Compared to a historical control group with a pregnancy rate of 93%, these findings suggest that LPD treatment may be effective.

## Luteal Function and Luteal Phase Deficiency (LPD) in Assisted Reproductive Technology (ART)

Normal luteal function, characterized by adequate progesterone production by the corpus luteum, is essential for pregnancy maintenance until placental function begins around seven weeks of gestation. Any disruption in progesterone secretion during the luteal phase may result in luteal phase deficiency (LPD), a condition where insufficient progesterone impairs embryo implantation. This deficiency is associated with infertility and pregnancy loss.

In controlled ovarian stimulation (COS) cycles, LPD is a frequent complication, lowering pregnancy rates in in vitro fertilization (IVF) cycles. Luteal-phase support (LPS) is, therefore, a critical intervention for almost all stimulated ART cycles. The use of gonadotropin-releasing hormone (GnRH) agonists or antagonists for ovarian stimulation often leads to luteal dysfunction, impairing embryo implantation due to high estradiol and progesterone levels, which inhibit luteinizing hormone (LH) secretion from the pituitary gland.

Additionally, granulosa cell disruption during oocyte retrieval and prolonged pituitary suppression caused by GnRH agonists and antagonists contribute to LPD. In frozen-thawed cycles, where there is no corpus luteum, endometrial preparation is entirely dependent on exogenous estrogen and progesterone.

## Luteal Phase Support in ART Treatments

In ART cycles, treatments such as IVF, intracytoplasmic sperm injection (ICSI), and frozen embryo transfer (FET) often result in LPD. In nonovulatory cycles, where natural cyclicity is absent or suppressed, progesterone supplementation is essential for endometrial preparation and embryo implantation. By mimicking the luteal phase with progesterone exposure, successful implantation can be achieved.

The luteal phase following controlled ovarian hyperstimulation (COH) and oocyte aspiration has long been recognized as dysfunctional, with multiple explanations proposed. Earlier theories suggested that LPD resulted from granulosa cell destruction during oocyte aspiration, but this was challenged by studies showing no change in progesterone levels after single follicle aspiration in natural cycles. Another theory implicated HCG administration in inhibiting

endogenous LH secretion, but normal luteal phase length and pregnancy rates in women receiving HCG triggers in natural cycles contradicted this.

The current most widely accepted theory posits that supraphysiologic steroid hormone levels, secreted by multiple corpora lutea (CL) in the early luteal phase of an IVF cycle, inhibit LH secretion via negative feedback on the hypothalamic-pituitary axis.

## Progesterone in Luteal Phase Support

Exogenous progesterone supplementation is the cornerstone of LPS, although the optimal route of administration remains controversial. Progesterone stabilizes the uterus by maintaining quiescence, stabilizing lysosomal membranes, inhibiting prostaglandin synthesis, and reducing intracellular calcium levels. It also plays an essential role as an immunomodulator, improving endometrial receptivity and facilitating implantation through increased endometrial vascularity and decidual transformation.

Evidence suggests that a "luteal gap" in progesterone secretion, particularly in the second part of the luteal phase, leads to inadequate endometrial luteinization. Exogenous progesterone can close this gap, making it a preferred choice for LPS. Successful implantation relies on the precise timing of endometrial receptivity, which progesterone effectively induces.

Progesterone for LPS is available in both synthetic (17-alpha-hydroxy derivatives) and natural (micronized) forms and can be administered via various routes, including intramuscular (IM), oral, intravaginal, subcutaneous (SC), and transdermal methods. The choice of administration route depends on patient preference and clinical protocols, with ongoing debate regarding the most effective and convenient method.

## Luteal Phase Support in In Vitro Fertilization (IVF)

Luteal phase support (LPS) plays a critical role in assisted reproductive technology (ART) cycles, particularly in in vitro fertilization (IVF). The luteal phase is the period after ovulation, during which progesterone levels must be maintained to support the endometrium and promote implantation. Various treatment modalities have been explored to support the luteal phase, including progesterone, human chorionic gonadotropin (HCG), and gonadotropin-releasing hormone (GnRH) agonists.

## Changing Trends in Luteal Phase Support

In a recent survey of 408 ART centers across 82 countries conducted by Vaisbuch and colleagues, all of the centers used some form of progesterone for luteal phase support, with none using HCG as the sole agent. This marks a significant shift from previous practice, as a similar survey conducted just three years earlier found that approximately 5% of IVF clinics were still using HCG as the only agent for luteal support. Although HCG was historically used for this purpose and remains effective, it has largely fallen out of favor due to the increased risk of ovarian hyperstimulation syndrome (OHSS). Because of the diminished use of HCG in current practice, this article will focus primarily on the use of progesterone for luteal phase support.

## Progesterone Supplementation in IVF

Progesterone is available in several forms for luteal phase supplementation, including intramuscular (IM), vaginal, oral, and, more recently, subcutaneous preparations. A large survey conducted in 2014, which encompassed 284,600 IVF cycles across 82 centers, reported that 77% of these cycles used vaginal progesterone exclusively, while an additional 17% combined vaginal progesterone with either oral or intramuscular formulations. Only 5% of the cycles relied solely on intramuscular progesterone, and 0.5% used oral progesterone exclusively. Despite these global trends, regional variations exist, particularly in North America, where 57% of cycles utilize intramuscular progesterone for luteal phase support.

## Oral Progesterone

In the 1980s, oral micronized progesterone was commonly used for luteal support. However, it has since been shown to be a less effective option due to poor and inconsistent bioavailability. Oral micronized progesterone undergoes first-pass metabolism in the liver, which reduces its bioavailability to only 10% compared to intramuscular formulations. This leads to erratic serum progesterone levels, requiring more frequent dosing to maintain adequate luteal support. For instance, serum progesterone levels peak 2 to 4 hours after oral ingestion but drop significantly within 6 to 7 hours, making consistent dosing difficult.

Clinical trials have highlighted the limitations of oral micronized progesterone. One randomized, controlled trial demonstrated that oral progesterone resulted in significantly lower implantation rates compared to intramuscular progesterone (18.1% vs. 40.9%, $p = 0.004$).

Another study comparing oral to vaginal micronized progesterone similarly found lower implantation rates with the oral route (10.7% vs. 30.7%, $p \leq 0.01$).

## Intramuscular Progesterone

Intramuscular progesterone was first introduced for luteal phase support during IVF in 1985. Although it has proven effective, it is associated with several drawbacks, including injection site pain, skin irritation, inflammatory reactions, and rare instances of abscess formation. Early randomized controlled trials indicated that intramuscular progesterone was superior to vaginal progesterone in terms of pregnancy outcomes. However, more recent studies and meta-analyses have shown no significant differences between the two forms in terms of pregnancy and ongoing pregnancy rates. A 2009 meta-analysis and a 2011 Cochrane review concluded that while intramuscular progesterone showed a slight advantage in ongoing pregnancy rates, overall pregnancy and live birth rates were equivalent between intramuscular and vaginal progesterone.

## Vaginal Progesterone

Vaginal progesterone has become the mainstay for luteal phase support in IVF due to its ease of administration and comparable efficacy to intramuscular formulations. Vaginal progesterone is available in various forms, including tablets, suppositories, and 8% gels. The benefit of vaginal progesterone lies in its "first-pass" uterine effect, wherein high concentrations of the drug are delivered directly to the endometrial tissue, bypassing systemic circulation.

Several randomized controlled trials have demonstrated that vaginal progesterone is just as effective as other routes of administration. For example, a large multicenter trial compared progesterone tablets (Endometrin 100 mg twice daily or thrice daily) with 8% vaginal progesterone gel (Crinone 8%) and found similar live birth rates between the two groups (35% for Endometrin twice daily, 38% for Endometrin three times daily, and 38% for Crinone gel).

While vaginal progesterone is generally well tolerated, it is associated with some drawbacks, such as higher cost, difficulty of administration, and vaginal discharge.

## Subcutaneous Progesterone

A newer formulation, subcutaneous progesterone (Prolutex), has recently been introduced as a water-soluble injectable progesterone complex. Initial pharmacokinetic studies indicate that

subcutaneous progesterone produces sufficient serum levels to support luteal phase supplementation. Two randomized, noninferiority trials have compared subcutaneous progesterone to vaginal preparations. In one study, subcutaneous progesterone was compared with vaginal progesterone gel (Crinone) with no significant difference in ongoing pregnancy rates (27.7% vs. 30.5%). Another trial comparing subcutaneous progesterone to vaginal progesterone tablets (Endometrin) also found similar ongoing pregnancy rates (40.8% vs. 43.3%). Common side effects of subcutaneous progesterone include injection site pain, bruising, inflammation, and edema.

## Timing and Duration of Progesterone Administration

Despite the extensive use of progesterone for luteal phase support in IVF, there is no clear consensus on when to begin supplementation. Typically, the first dose of progesterone is administered between the day of egg retrieval and two days after, with no significant difference in pregnancy outcomes. Studies on the timing of embryo transfer in relation to progesterone exposure have shown that the optimal window for progesterone administration ranges from 2 to 6 days before embryo transfer. Most IVF clinics (80.1%) begin progesterone on the day of egg retrieval.

There is also no consensus on the duration of progesterone supplementation. Although a recent meta-analysis of six studies involving 1,201 participants found no significant difference in live birth, ongoing pregnancy, or miscarriage rates when progesterone was discontinued after a positive pregnancy test, the majority of clinics (72%) continue progesterone until 8 weeks of pregnancy.

## Adjuvants to Progesterone

In addition to progesterone, some clinicians recommend adjuvant therapies to improve pregnancy rates. The corpus luteum (CL) produces not only progesterone but also estradiol and other nonsteroidal hormones, leading some to suggest that estradiol supplementation may benefit luteal phase support. However, a 2008 meta-analysis of four randomized studies found no significant difference in clinical pregnancy or live birth rates with the addition of estradiol to progesterone. The 2011 Cochrane review similarly found no benefit of estradiol supplementation, although a subgroup analysis suggested that transdermal estradiol might offer a slight advantage.

Another potential adjuvant is a single dose of GnRH agonist administered 5 to 6 days after oocyte retrieval. This approach is hypothesized to support the CL by stimulating luteinizing hormone (LH) secretion from the pituitary gland. A 2010 meta-analysis of five randomized trials showed an increase in pregnancy rates with GnRH agonist use (42.4% vs. 35.7%). Subgroup analysis indicated a more pronounced benefit in cycles using a GnRH antagonist protocol.

## Luteal Phase Progesterone in Frozen Embryo Transfer (FET) and Donor Cycles

In frozen embryo transfer (FET) and donor oocyte cycles, the corpus luteum is absent, and therefore, exogenous progesterone and estradiol are required to prepare the endometrium for implantation. Intramuscular progesterone is commonly used in the United States, while vaginal progesterone is preferred in Europe. Several small, prospective randomized trials have found no difference in pregnancy outcomes between intramuscular and vaginal progesterone for FET and donor oocyte cycles, although some studies have reported a slightly lower live birth rate with vaginal progesterone in these populations.

The timing of progesterone administration is critical in FET cycles, where cleavage-stage embryos are transferred after 3 to 4 days of progesterone exposure, and blastocysts after 5 to 6 days. Studies have shown that even small deviations in the timing of progesterone administration can negatively affect pregnancy outcomes. Therefore, it is essential that luteal phase support be carefully timed and individualized for optimal results.

## Dydrogesterone: A New Oral Agent

To overcome the limitations of oral micronized progesterone, dydrogesterone, an oral progestin with improved bioavailability, has been studied as an alternative. In a randomized controlled trial, pregnancy rates were higher among women undergoing IVF who received oral dydrogesterone for luteal support compared to vaginal micronized progesterone (41.0% vs. 29.4%, $p \leq 0.01$). Another study comparing dydrogesterone to vaginal progesterone gel (Crinone 8%) found equivalent pregnancy rates (28.7% vs. 28.6%). A 2011 Cochrane review supported the use of synthetic progesterones over micronized progesterone, favoring synthetic formulations for clinical pregnancy (odds ratio [OR]: 0.79, 95% CI 0.65–0.96).

## Effectiveness of Dydrogesterone for Luteal Phase Support in Fresh IVF Cycles

Dydrogesterone has been used empirically for luteal phase support (LPS) in in vitro fertilization (IVF) treatments for many years. The first systematic comparisons of oral dydrogesterone and vaginal progesterone for LPS in IVF treatments were initiated in India. The shift in focus towards oral dydrogesterone was prompted by poor patient compliance with vaginal progesterone. In one of the early studies, Chakravarty et al. randomized 430 patients undergoing controlled ovarian stimulation (COS) with a long gonadotropin-releasing hormone (GnRH)-agonist protocol and human chorionic gonadotropin (hCG) trigger. Of these, 351 patients received luteal support with 600 mg/day of vaginal micronized progesterone, while 79 patients were treated with 20 mg/day of oral dydrogesterone. The delivery rates between the two groups were comparable, with 22.8% for the vaginal group and 24.1% for the oral group. This study opened the door for further clinical investigation of dydrogesterone as a viable alternative to vaginal progesterone for luteal phase support.

## Early Clinical Trials and Cochrane Review

By 2011, three randomized controlled trials (RCTs) comparing oral dydrogesterone and vaginal micronized progesterone for luteal phase support in fresh IVF cycles had been conducted, with a total of 2,348 patients. These trials were included in a Cochrane review, which concluded that synthetic progesterone (including dydrogesterone) had a significant advantage in terms of clinical pregnancy outcomes compared to micronized progesterone. However, the review was unable to draw any conclusions on the ongoing pregnancy rate or live birth rate due to the lack of reported data in larger studies. Despite this, the initial Cochrane review supported the use of synthetic progesterone for achieving higher clinical pregnancy rates.

In an updated 2015 Cochrane review, the conclusion regarding the higher clinical pregnancy rate with synthetic progesterone remained unchanged. However, the review also highlighted the substantial risk of bias in the included studies, such as unclear methods for random sequence generation and allocation concealment. These limitations called for more rigorous trials to confirm the findings.

## Meta-Analysis and Risk of Bias

By 2015, eight randomized controlled trials comparing oral dydrogesterone with vaginal progesterone (seven trials using micronized progesterone and two using vaginal gel) were included in a systematic review and meta-analysis. These trials had a combined sample size of 2,496 patients in the micronized progesterone comparisons and 1,735 patients in the vaginal gel comparisons. Oral dydrogesterone was administered in daily doses ranging from 20 mg to 40 mg, while the control arms used 600–800 mg/day of micronized progesterone or 8% vaginal gel (Crinone).

The meta-analysis found that women treated with oral dydrogesterone had a higher clinical pregnancy rate compared to those using micronized vaginal progesterone, with a relative risk (RR) of 1.19 (95% confidence interval [CI] 1.04–1.36, I2 = 6%). However, this effect was not observed in the comparison between dydrogesterone and vaginal gel. Despite the large total sample size, the meta-analysis had significant limitations, including a risk of bias in individual studies, clinical heterogeneity in the doses compared, incomplete outcome reporting, and insufficient safety surveillance in nearly all trials. As a result, the external validity and clinical utility of the meta-analysis remained limited.

## Patki Study and the Development of Dydrogesterone for IVF

A notable study by Patki et al. compared 30 mg/day of oral dydrogesterone with 600 mg/day of micronized vaginal progesterone in 675 randomized patients. This trial suggested the superiority of oral dydrogesterone in achieving clinical pregnancies, with a relative risk of 1.39 (95% CI 1.13–1.72). Based on these results, the 30 mg/day dose of dydrogesterone was chosen for further investigation. In 2013, a company-sponsored phase III trial program began, aiming to establish the efficacy and safety of daily oral dydrogesterone at 30 mg for luteal phase support in IVF cycles with fresh embryo transfers.

This program includes more than 2,000 randomized patients across two large studies, which will assess treatment outcomes from the initiation of luteal phase support to childbirth and the child’s subsequent health. The first of these studies, known as LOTUS-I, was recently published.

## LOTUS-I Trial: Dydrogesterone vs. Vaginal Progesterone

The LOTUS-I trial is a multinational, multicenter, randomized, double-blind, double-dummy clinical study designed to evaluate the noninferiority of oral dydrogesterone compared to vaginal micronized progesterone for luteal phase support in IVF cycles. A total of 1,031 patients undergoing IVF or intracytoplasmic sperm injection (ICSI) with fresh single or double embryo transfer were randomized on the day of oocyte retrieval into two treatment arms.

In the experimental group, patients received oral dydrogesterone (10 mg tablets) with placebo intravaginal capsules three times daily. The control group received micronized vaginal progesterone (200 mg capsules) with oral placebo tablets. Both treatments began on the evening of oocyte retrieval and were discontinued upon a negative serum hCG test or at 12 weeks of gestation.

The study was powered to demonstrate the noninferiority of oral dydrogesterone for ongoing pregnancy rates at 12 weeks of gestation. Due to the double-dummy design, patients in both groups received both oral tablets and vaginal capsules, making it impossible to assess patient preference for one administration route over the other. However, this design helped minimize the risk of "nocebo" effects, where negative expectations of side effects might have influenced patient-reported outcomes.

The mean age of women in the LOTUS-I study was 32.5 years, with a mean body mass index (BMI) of 23 kg/m². Approximately 43% of participants underwent single-embryo transfer. The trial successfully established that oral dydrogesterone is noninferior to vaginal micronized progesterone. Ongoing pregnancy rates were 37.6% in the oral dydrogesterone group and 33.1% in the vaginal progesterone group, with a difference of +4.7% in favor of dydrogesterone (95% CI −1.2% to +10.6%).

Similarly, live birth rates were slightly higher in the dydrogesterone group, at 34.6%, compared to 29.8% in the vaginal progesterone group (difference +4.9%, 95% CI −0.8% to +10.7%). However, the sample size was insufficient to detect statistical superiority for a difference in pregnancy rates of 5% or less.

### Implications of LOTUS-I Results and Comparison to Other Preparations

While the LOTUS-I trial firmly established that oral dydrogesterone is noninferior to vaginal progesterone for luteal phase support, its results have raised questions about the efficacy of vaginal progesterone. The 95% confidence interval for the difference in ongoing pregnancy

rates at 12 weeks included effect sizes not favorable to vaginal progesterone, which could be considered unacceptable by many clinicians.

Utrogestan is a soft gelatin capsule containing 100 mg of micronized progesterone suspended in refined sunflower oil, soy lecithin, glycerol, titanium dioxide, and purified water. In the U.S., the two available preparations for vaginal progesterone in IVF luteal phase support are Endometrin and Crinone. Endometrin is an effervescent tablet containing 100 mg of micronized progesterone in lactose monohydrate, polyvinylpyrrolidone, adipic acid, sodium bicarbonate, sodium lauryl sulfate, magnesium stearate, pregelatinized maize starch, and colloidal silicon dioxide. Crinone is a vaginal gel formulation, designed to adhere to the vaginal wall, containing 90 mg of micronized progesterone in a gel base of glycerol, paraffin, hydrogenated palm oil glyceride, and other excipients.

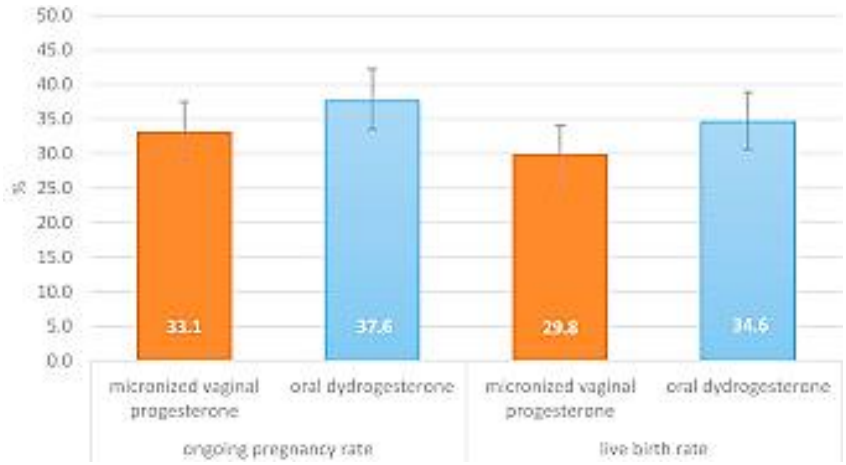


**Figure 1. Ongoing pregnancy rates and live birth rates (with 95% confidence intervals) in the in the two groups (total n = 974) of the LOTUS I trial.**

## Comparisons and Future Research

Despite differences in formulation and dosage, no significant differences in pregnancy rates have been observed between various vaginal progesterone preparations. Beyond the evidence from studies comparing oral dydrogesterone with micronized vaginal progesterone, dydrogesterone has also been tested in two investigator-initiated randomized trials against progesterone gel (Crinone 8%). These trials found no difference in ongoing pregnancy rates (RR 0.97, 95% CI 0.83–1.13), although the dose of oral dydrogesterone used in both trials was only 20 mg/day.

To date, no randomized trials have directly compared Endometrin with oral dydrogesterone, nor has any study compared intramuscular progesterone with oral dydrogesterone. In the United States, intramuscular progesterone continues to be used frequently due to concerns over

the efficacy of vaginal progesterone. However, intramuscular administration is associated with significant side effects, underscoring the need for a randomized trial comparing oral dydrogesterone with intramuscular progesterone for luteal phase support in fresh IVF cycles.

In conclusion, the available evidence supports the use of oral dydrogesterone as an effective alternative to vaginal progesterone for luteal phase support in fresh IVF cycles. While the LOTUS-I trial established noninferiority, further research is needed to clarify its superiority and address concerns about the side effects and patient preferences for different administration routes.

## Patient Preference for Oral vs. Vaginal Administration of Progesterone

Studies consistently show that patients tend to prefer oral administration over vaginal routes, as seen with medications like misoprostol. This preference may be even more pronounced in luteal phase support (LPS), where treatment can last at least 10 days and may continue into early pregnancy. Patients often find once-daily vaginal progesterone application easier and more convenient compared to multiple daily doses, as it is less messy. However, it's worth noting that in a recent phase III trial comparing vaginal progesterone gel with daily subcutaneous injections, no clear preference for one method emerged. Interestingly, despite the general discomfort associated with injections, fewer patients (10.4%) experienced vaginal irritation and related side effects with subcutaneous progesterone compared to the 50.8% of patients who reported irritation with vaginal gel.

In a study by Chakravarty et al., patient satisfaction with the tolerability of oral dydrogesterone (2 × 10 mg) was significantly higher than with vaginal micronized progesterone (3 × 200 mg). Additionally, a randomized controlled trial (RCT) involving 831 IVF patients found that oral dydrogesterone users were more satisfied and significantly less dissatisfied with their medication compared to those using vaginal progesterone gel. However, a recent study from Iran on 240 patients showed no significant difference in overall satisfaction or dissatisfaction between the two routes of administration.

These findings suggest that patient preference for administration routes is influenced by personal habits and cultural factors. Some patients may feel that more invasive routes, such as injections, indicate a stronger medication, which could impact their perception of treatment efficacy. Therefore, individual preferences, potential side effects, and patient beliefs should be considered to ensure treatment compliance and adherence.

## Physician Preference for Oral vs. Vaginal Administration of Progesterone

Luteal phase support with progesterone typically begins between oocyte retrieval and embryo transfer. When the embryo transfer catheter passes through the cervical canal, there is a possibility of introducing not only the progesterone itself but also the excipients from tablets, suppositories, or gel into the uterine cavity. Additionally, the high concentrations of progesterone in the vagina may affect the local microbiome, which has recently become an area of interest in IVF research.

Although there is no documented negative impact of drug excipients or high progesterone doses on the endometrium, embryo, or microbiome, physicians often ensure the outer cervical os is clean before performing embryo transfer. While no formal study has been conducted to evaluate physician preferences, it is speculated that many doctors may favor a cleaner vaginal environment—thereby preferring oral or injectable progesterone—during embryo transfer or transvaginal scans at later stages of treatment.

## Safety and Tolerability of Oral Dydrogesterone

Bioidentical oral progesterone can lead to the formation of sedative metabolites due to its first-pass metabolism in the liver. These metabolites can cause side effects such as fatigue, headaches, and increased urinary frequency. Additionally, concerns have been raised about the risk of intrahepatic cholestasis with oral progesterone. As a result, vaginal preparations for luteal phase support (LPS) in IVF were developed. However, vaginal progesterone can also cause issues such as discharge and irritation.

Chakravarty et al. conducted an objective comparison of oral dydrogesterone (20 mg/day) with vaginal micronized progesterone (600 mg/day). Liver function tests were performed before treatment and on the day of the pregnancy test (after approximately 14 days of intake). Both groups showed similar liver function outcomes, with no significant differences in abnormal test results. Additionally, vaginal discharge or irritation was reported in 10.5% of patients using micronized progesterone, while no such side effects were noted in the dydrogesterone group.

Tomic et al. also found that patients using vaginal progesterone gel experienced significantly higher rates of perineal irritation, vaginal bleeding, discharge, and interference with sexual activity compared to those using oral dydrogesterone. However, there were no significant differences between the two groups in terms of dizziness, headaches, nausea, breast tension, or bloating.

The most comprehensive data on the safety and tolerability of oral dydrogesterone comes from the LOTUS-I trial, which involved blinding of both doctors and patients. Participants were randomized to receive either oral dydrogesterone or vaginal micronized progesterone, alongside a placebo dummy treatment. Adverse events were monitored throughout the pregnancy, with treatment-related events leading to study termination reported in 12.4% of dydrogesterone users and 16.0% of vaginal progesterone users. Liver enzyme levels were normal in nearly all participants across both groups. While some adverse events were observed, they were infrequent, and no significant differences were found between the groups. Additionally, no new safety or tolerability concerns emerged from the study.

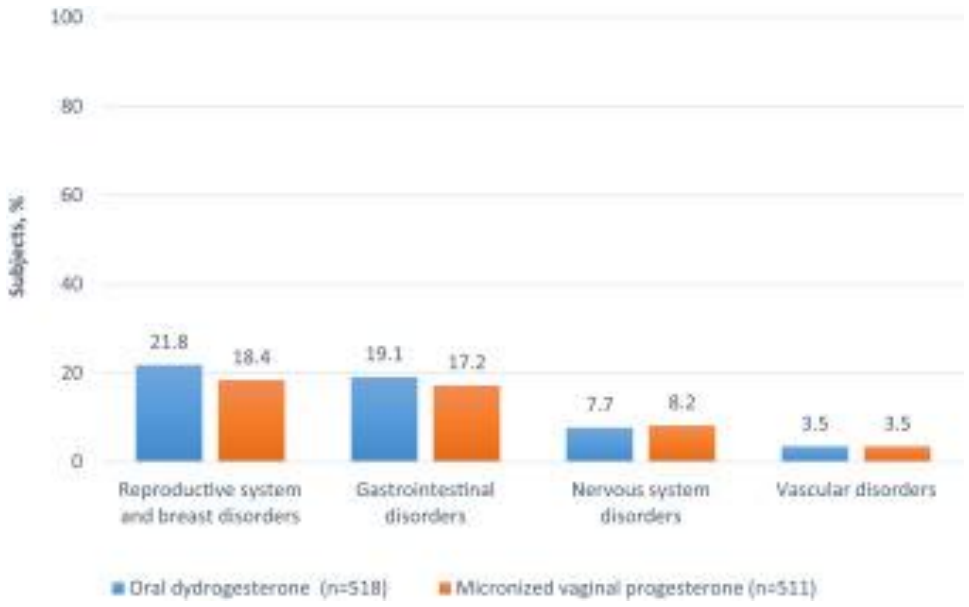


**Figure 2. Proportion of female subjects reporting treatment emerging adverse events according to organ system in the two groups of the LOTUS I trial.**

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.

## Fetal Safety of Dydrogesterone

Dydrogesterone has been in use since the 1960s and is widely approved for use during pregnancy to prevent recurrent miscarriage or threatened abortion. Based on global sales data, an estimated 8 million fetuses have been exposed to dydrogesterone in utero, with no substantial risk to fetal health identified over the decades of its use. While rare risks could theoretically be detected through large observational studies, the data thus far suggest no significant teratogenic risk.

An analysis of pharmacovigilance data from 1977 to 2005 identified 28 cases of congenital defects potentially linked to dydrogesterone exposure. However, the number of reported cases is minimal when compared to the millions of pregnancies exposed, and no specific pattern of abnormalities has emerged.

In the LOTUS-I trial, which compared oral dydrogesterone with vaginal progesterone, no significant differences in the rates of congenital, familial, or genetic disorders were found between the two groups. Additionally, no pattern of congenital defects was observed with the use of dydrogesterone. Further data from randomized controlled trials on dydrogesterone for miscarriage prevention also indicated no safety concerns for the fetus.

In 2015, a case-control study from Palestine suggested a potential association between dydrogesterone use in the first trimester and congenital heart defects in offspring. The study found that 38% of mothers of children with heart defects reported dydrogesterone use, compared to 18% in the control group. However, the study had significant methodological flaws, including failure to control for confounding factors such as previous miscarriages, reliance on maternal recall, and pooling different heart defects into a single group. As a result, no causal link between dydrogesterone and congenital heart defects can be inferred.

Given the estimated 1% incidence of congenital heart defects in the general population, verifying or refuting the hypothesis of an increased risk with dydrogesterone would require a large-scale study involving more than 10,000 patients. Since such a trial is unlikely to be conducted soon, physicians must rely on existing pharmacovigilance data, which show no substantial fetal risk associated with dydrogesterone.

## Live birth rates and safety profile using dydrogesterone for luteal phase support in assisted reproductive techniques

**Abstract**

Introduction: Assisted reproductive techniques (ARTs) result in a deficient luteal phase, requiring the administration of intramuscular, intravaginal or oral exogenous progesterone. Dydrogesterone, an oral retroprogesterone with good bioavailability, has been used in assisted reproductive cycles with outcomes that are comparable to those of vaginal or intramuscular progesterone. However, there are limited reviews on its use for luteal phase support in ARTs, in terms of pregnancy outcomes and associated fetal anomalies. This study aimed to review the live birth rates and associated fetal anomalies of women who were given dydrogesterone for luteal phase support in assisted reproductive cycles at a tertiary hospital in Singapore.

**Methods:** This retrospective descriptive study included 1,050 women who underwent in vitro fertilisation/intracytoplasmic sperm injection at the Centre for Assisted Reproduction of Singapore General Hospital between 2000 and 2011. The women were given dydrogesterone for luteal phase support. The main outcome measures were rates of pregnancy, live birth, miscarriage and fetal anomalies.

**Results:** The pregnancy and live birth rates were 34.7% and 27.7%, respectively. Among those who achieved pregnancy, 17.0% miscarried, 0.8% had ectopic pregnancies and 0.3% had molar pregnancies. Fetal anomalies were detected in 1.9% of pregnancies, all of which were terminated by choice.

**Conclusion: Since the outcomes of dydrogesterone are comparable to those of intramuscular and vaginal progesterone**, it is a reasonable option to provide luteal phase support for women who are uncomfortable with injections or vaginal insertions. Randomised controlled studies are needed to determine the optimal dosage of dydrogesterone for luteal phase support in ARTs.

## Oral dydrogesterone vs. vaginal progesterone capsules for luteal-phase support in women undergoing embryo transfer: a systematic review and meta-analysis


### Abstract

Objective: To identify, appraise, and summarize the evidence from randomized controlled trials (RCTs) comparing oral dydrogesterone to vaginal progesterone capsules for luteal-phase support (LPS) in women offered fresh or frozen embryo transfers following in vitro fertilization.

Methods: Two independent authors screened the literature for papers based on titles and abstracts, then selected the studies, extracted data, and assessed the risk of bias. Dydrogesterone and progesterone were compared based on risk ratios (RR) and the precision of the estimates was assessed through the 95% confidence interval (CI).

Results: An electronic search performed on June 7, 2017 retrieved 376 records, nine of which were papers deemed eligible and included in this systematic review and quantitative analysis. Good quality evidence indicates that oral dydrogesterone provided at least similar results than vaginal progesterone capsules on live birth/ongoing pregnancy (RR=1.08, 95%CI=0.92-1.26, I2=29%, 8 RCTs, 3,386 women) and clinical pregnancy rates (RR 1.10, 95% CI 0.95 to 1.27; I2=43%; 9 RCTs; 4,061 women). Additionally, moderate quality evidence suggests there is no relevant difference on miscarriage rates (RR=0.92, 95%CI=0.68-1.26, I2=6%, 8 RCTs, 988 clinical pregnancies; the quality of the evidence was downgraded because of imprecision).

Conclusions: Good quality evidence from RCTs suggest that oral dydrogesterone provides at least similar reproductive outcomes than vaginal progesterone capsules when used for LPS in women undergoing embryo transfers. Dydrogesterone is a reasonable option and the choice of either of the medications should be based on cost and side effects.

## Dydrogesterone as an oral alternative to vaginal progesterone for IVF luteal phase support: A systematic review and individual participant data meta-analysis


### Abstract

The aim of this systematic review and meta-analysis was to conduct a comprehensive assessment of the evidence on the efficacy and safety of oral dydrogesterone versus micronized vaginal progesterone (MVP) for luteal phase support. Embase and MEDLINE were searched for studies that evaluated the effect of luteal phase support with daily administration of oral dydrogesterone (20 to 40 mg) versus MVP capsules (600 to 800 mg) or gel (90 mg) on pregnancy or live birth rates in women undergoing fresh-cycle IVF (protocol registered at PROSPERO [CRD42018105949]). Individual participant data (IPD) were extracted for the primary analysis where available and aggregate data were extracted for the secondary analysis. Nine studies were eligible for inclusion; two studies had suitable IPD (full analysis sample: n = 1957). In the meta-analysis of IPD, oral dydrogesterone was associated with a significantly higher chance of ongoing pregnancy at 12 weeks of gestation (odds ratio [OR], 1.32; 95% confidence interval [CI], 1.08 to 1.61; P = 0.0075) and live birth (OR, 1.28; 95% CI, 1.04 to 1.57; P = 0.0214) compared to MVP. A meta-analysis combining IPD and aggregate data for all nine studies also demonstrated a statistically significant difference between oral dydrogesterone and MVP (pregnancy: OR, 1.16; 95% CI, 1.01 to 1.34; P = 0.04; live birth: OR, 1.19; 95% CI, 1.03 to 1.38; P = 0.02). Safety parameters were similar between the two groups. Collectively, this study indicates that a higher pregnancy rate and live birth rate may be obtained in women receiving oral dydrogesterone versus MVP for luteal phase support.

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