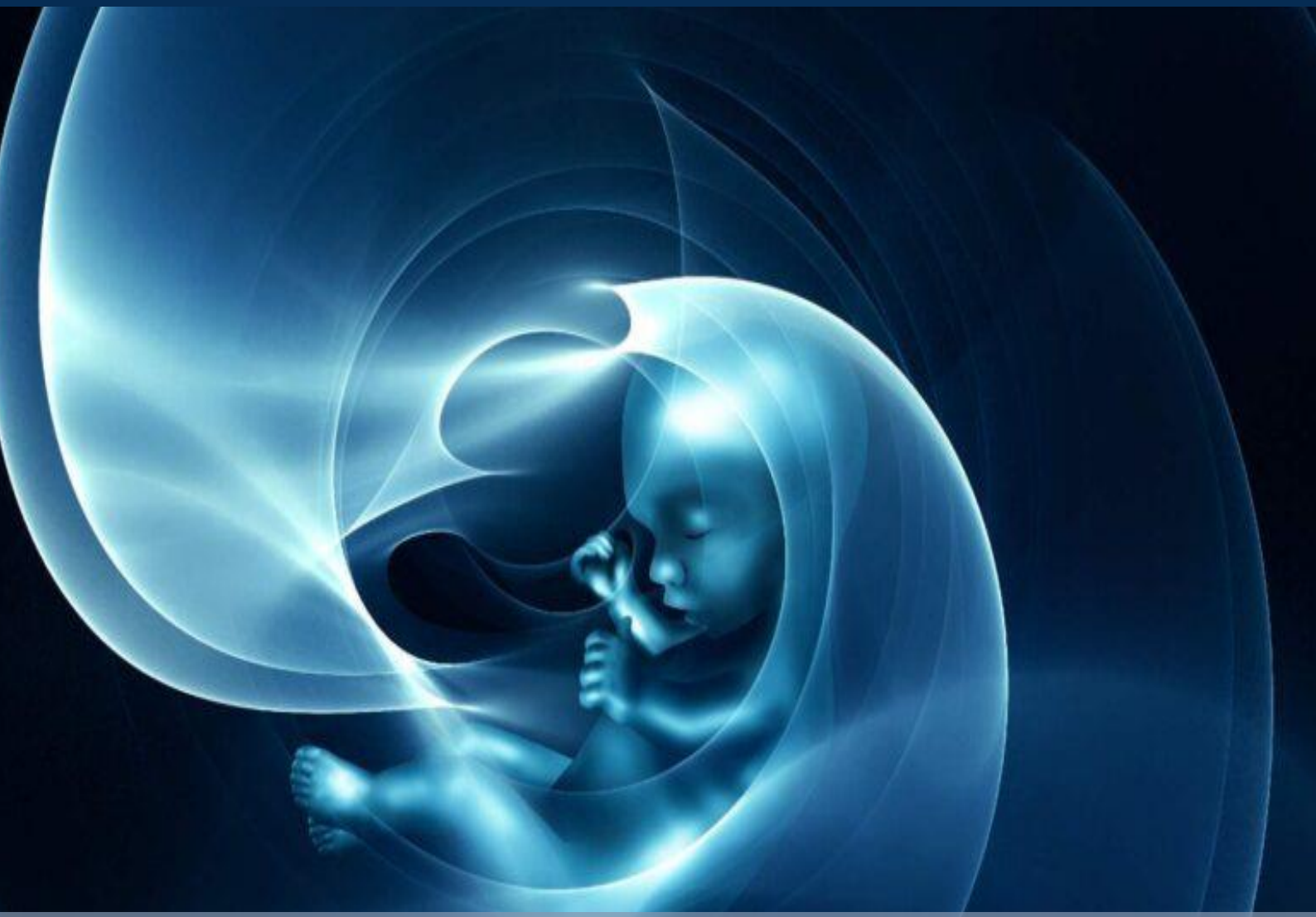
DYDROGESTERONE:

A Lifeline for Threatened Pregnancies



Module 3

Global Perspectives on Dydrogesterone Use and Future Directions

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Importance of Progesterone in Reproductive Health

Progesterone plays a crucial role in establishing an optimal endometrial environment for embryo implantation and is essential for the maintenance of pregnancy. Beyond its reproductive functions, progesterone is also thought to mediate an anti-inflammatory immune response to the allogenic fetus and induce relaxation of uterine smooth muscle. Due to these multifaceted roles, progestogens have been extensively employed to address progesterone deficiency associated with infertility and miscarriage. However, different progestogens exhibit variability in their potency, receptor-binding selectivity, bioavailability, and routes of administration. These factors significantly influence the selection of the most suitable agent for various clinical conditions.

Current Use and Challenges of Micronized Progesterone

Micronized progesterone has been in clinical use since the 1980s. However, its bioavailability is often low and inconsistent, necessitating high oral doses that can lead to side effects such as drowsiness, nausea, and headaches. For this reason, micronized progesterone is frequently administered vaginally. Yet, this route may not guarantee full absorption, may be compromised by vaginal bleeding, and can cause local irritation, which limits its efficacy and patient comfort.

Dydrogesterone: A Promising Alternative

Given these challenges, alternative progestogens have gained popularity for various obstetric indications. One such alternative is dydrogesterone, also known as 6-dehydro-retroprogesterone. This compound has a molecular structure that closely resembles that of natural progesterone and is administered orally. Dydrogesterone boasts an impressive oral bioavailability—approximately 5.6 times higher than that of natural progesterone—along with high selectivity for the progesterone receptor. Studies indicate that dydrogesterone requires a dosage that is 10–20 times lower than that of micronized progesterone to achieve similar pharmacological effects. Despite these advantages, there is currently limited data regarding the knowledge, perceptions, and routine clinical usage patterns of dydrogesterone among medical practitioners in India.

Efficacy and Safety Profile of Dydrogesterone

Dydrogesterone is a stereoisomer of progesterone, pharmacologically akin to endogenous progesterone. Its high oral bioavailability and specificity for progesterone receptors mean that it can exert its effects at significantly lower doses—10 to 20 times less than micronized progesterone. Additionally, dydrogesterone has fewer androgenic, glucocorticoid, mineralocorticoid, or estrogenic side effects compared to micronized progesterone. Over the past 60 years, dydrogesterone has demonstrated a favorable efficacy, safety, and tolerability profile across multiple obstetric and gynecological conditions.

Clinical Applications of Dydrogesterone

Dydrogesterone has been effectively utilized for treating progesterone-deficient obstetric conditions, including threatened abortion, recurrent pregnancy loss, and infertility due to luteal phase defects. It is also used in gynecological conditions such as endometriosis, dysfunctional uterine bleeding, secondary amenorrhea, irregular menstrual cycles, and premenstrual syndrome. It is notably the most frequently prescribed progestogen during pregnancy and for threatened abortion, where it has been found to carry the least risk of miscarriage compared to other progestogens.

Furthermore, dydrogesterone has shown efficacy comparable to that of micronized progesterone for luteal phase support during in vitro fertilization (IVF) cycles. Studies indicate that it may be associated with higher pregnancy and live birth rates than micronized progesterone in patients requiring luteal phase support during IVF. Despite the wealth of literature surrounding dydrogesterone, studies specifically examining its utilization patterns in Indian patients are notably sparse.

Pharmacological Characteristics of Progesterone and Dydrogesterone

While advancements have been made in improving the bioavailability of progesterone through micronization, the systemic bioavailability of both oral and vaginal micronized progesterone remains relatively poor, with values below 5% and ranging from 4% to 8%, respectively. In contrast, dydrogesterone exhibits superior oral bioavailability, coupled with its high specificity for progesterone receptors, allowing for effective endometrial transformation at doses significantly lower than those required for micronized progesterone. This low dosage not only

minimizes side effects but also reduces the risk of altered liver function, a concern with higher doses of oral progesterone.

Furthermore, early endocrinological studies in animal models indicated that dydrogesterone possesses potent progestogenic activity without any androgenic, glucocorticoid, or estrogenic effects. Recent in-vitro receptor binding studies confirm these early findings, demonstrating that dydrogesterone has negligible agonistic activity at androgen, glucocorticoid, and mineralocorticoid receptors, in contrast to progesterone, which shows relatively high agonistic activity at androgen receptors. Additionally, dydrogesterone has low antagonistic activity at glucocorticoid and mineralocorticoid receptors compared to progesterone. This selectivity minimizes activation of unintended receptors and reduces the risk of unwanted side effects.

Quantifying Dydrogesterone

A notable challenge in the clinical setting is the quantification of progestogens following administration. Due to structural differences from progesterone, neither dydrogesterone nor its metabolite, 20α-dihydrodydrogesterone, can be measured using standard diagnostic tests for progesterone levels. Instead, specialized instrumental chromatographic methods are necessary for accurate measurement of dydrogesterone levels.

Dydrogesterone for Luteal Phase Support in IVF-ART

Dydrogesterone has emerged as a viable alternative to progesterone for luteal phase support in assisted reproductive technology (ART), including in vitro fertilization (IVF). Numerous small-scale clinical studies and a meta-analysis have indicated that oral dydrogesterone is at least as effective as micronized vaginal progesterone in enhancing pregnancy rates after luteal phase support. A significant study, the Phase III Lotus I clinical trial, compared oral dydrogesterone (30 mg, administered as 10 mg three times daily) with micronized vaginal progesterone capsules (600 mg, administered as 200 mg three times daily) for luteal phase support in fresh IVF cycles. This double-blind, double-dummy study demonstrated that oral dydrogesterone was non-inferior to micronized vaginal progesterone capsules, with pregnancy rates at 12 weeks gestation of 37.6% and 33.1%, respectively.

Another study within the Phase III Lotus trial program, known as Lotus II, followed a similar design but compared oral dydrogesterone with 8% micronized vaginal progesterone gel. Results indicated non-inferiority of oral dydrogesterone to the gel, with pregnancy rates at 12 weeks gestation of 38.7% for dydrogesterone and 35.0% for the gel formulation. Moreover,

patient satisfaction regarding the tolerability of treatment was significantly higher in the oral dydrogesterone group compared to the micronized vaginal progesterone group, with no reported instances of vaginal pain or irritation in the dydrogesterone cohort. Conversely, such side effects were noted in 10.5% of patients using micronized vaginal progesterone.

Further clinical investigations have shown that perineal irritation, vaginal bleeding, vaginal discharge, and interference with coitus were significantly less prevalent in the oral dydrogesterone group compared to those receiving micronized vaginal progesterone gel. Overall, the evidence strongly supports the efficacy of oral dydrogesterone for luteal phase support in fresh IVF cycles, although more data is required regarding its use in artificial frozen-thawed cycles, which present different endocrinological challenges. The absence of endogenous corpora lutea in these cases means that endometrial changes necessary for implantation rely entirely on exogenous progestogen supplementation. Preliminary investigations into the use of oral dydrogesterone in artificial frozen-thawed cycles have yielded mixed results, emphasizing the need for further research to determine optimal dosing and efficacy in this context.

Overview of Dydrogesterone: Safety and Efficacy in Fertility Treatments

Introduction to Dydrogesterone and Luteal Phase Deficiency

Dydrogesterone has garnered significant attention as a treatment option for infertility related to luteal phase deficiency (LPD). A review of 12 studies assessing its safety highlighted its use in diverse assisted reproductive technology (ART) procedures, including in vitro fertilization (IVF), intrauterine insemination (IUI), intracytoplasmic sperm injection (ICSI), and frozen embryo transfer (FET). Luteal phase support (LPS) was initiated on the day of oocyte retrieval (OR), embryo transfer (ET), or 36 hours following the administration of recombinant human chorionic gonadotropin (rhCG) trigger, and continued until 8–12 gestational weeks if the β-human chorionic gonadotropin (β-hCG) test yielded a positive result.

Safety Profile of Dydrogesterone in LPD

The overall safety profile of dydrogesterone in the patient population showed no significant discrepancies when compared to micronized vaginal progesterone (MVP) capsules and gel regarding maternal complications, including spontaneous abortions, missed abortions, and ovarian hyperstimulation syndrome. In examining adverse events (AEs) related to vaginal administration, such as bleeding, discharge, and interference with coitus, these were infrequent and largely comparable between oral dydrogesterone and MVP formulations. Interestingly, a few studies indicated a higher incidence of vaginal AEs associated with MVP gel compared to oral dydrogesterone, while only one study noted increased bleeding with oral dydrogesterone in comparison to MVP pessaries.

Fetal and neonatal complications, including congenital anomalies, low birth weight, and neonatal death, remained low and comparable between the two treatment groups. Furthermore, there were no significant differences observed in common AEs, such as breast pain, breast fullness, headache, dizziness, abdominal pain, bloating, flatulence, constipation, and nausea/vomiting, between oral dydrogesterone and oral micronized progesterone sustained-release preparations, MVP capsules, gel, and pessaries. However, one particular study did report a notably higher frequency of headache, dizziness, abdominal pain, flatulence, nausea, and breast pain in the oral dydrogesterone group compared to those using MVP pessaries.

Dydrogesterone in Cases of Threatened Abortion and Recurrent Miscarriage

Two significant studies investigated the use of dydrogesterone among pregnant women in their first trimester who experienced threatened abortion or had a history of more than three first-trimester pregnancy losses requiring hormonal support. The findings indicated no substantial differences in fetal and neonatal complications, such as congenital malformations and low birth weight at term, when comparing oral dydrogesterone to placebo. Additionally, no noteworthy differences were found concerning maternal complications like antepartum hemorrhage, placenta previa, gestational hypertension, pre-eclampsia, or preterm labor between the oral dydrogesterone and placebo groups. Other routine AEs, including nausea, vomiting, headache, dizziness, abdominal pain, and bloating, also exhibited similar profiles across the groups.

Dydrogesterone has been employed for nearly six decades, with over 20 European countries endorsing its use for pregnancy-related conditions. A systematic literature review (SLR) aimed to collate recent evidence to reaffirm the safety and tolerability of dydrogesterone. A total of 32 studies, featuring large sample sizes and diverse progesterone-deficient conditions, were reviewed to synthesize comprehensive evidence regarding the safety and tolerability of this treatment.

Comparative Safety of Dydrogesterone with Other Progestogens

When compared as part of menopausal hormone therapy (MHT) regimens, dydrogesterone demonstrated an acceptable safety profile relative to oral micronized progesterone and other progestins. Notably, breast- and endometrium-related AEs were reported to be lower with dydrogesterone compared to placebo. Importantly, dydrogesterone presents a reduced risk of breast cancer in comparison to synthetic progestins such as medroxyprogesterone, levonorgestrel, and norethisterone, particularly with up to 260 weeks of use. Long-term use of dydrogesterone also poses a lower risk of breast cancer compared to other progestins. Additionally, it has been found to lower the risk of endometrial cancer relative to oral micronized progesterone during the same duration of use. The risk of venous thromboembolism (VTE) and cardiovascular events is also significantly low with dydrogesterone-containing MHT regimens.

In terms of luteal phase support, the safety profile of oral dydrogesterone is comparable to that of MVP gels, capsules, and pessaries. This finding is clinically relevant, as both patients and

healthcare providers often prefer oral formulations over vaginal options due to the latter's inconveniences during assisted reproductive technologies. While MVP gel has been associated with increased vaginal symptoms in some studies, dydrogesterone was reported to cause increased vaginal bleeding in one instance. Fetal and neonatal complications remained low when comparing oral dydrogesterone to MVP capsules and gel. Common AEs often associated with oral progesterone preparations, including headache, dizziness, abdominal pain, flatulence, and nausea, were reported more frequently in the oral dydrogesterone group compared to MVP gel and pessaries.

Conclusions on Dydrogesterone's Safety in Pregnancy-Related Conditions

In the context of pregnancy-related issues, such as threatened abortion and recurrent miscarriage, dydrogesterone does not present significant safety concerns regarding pregnancy complications or congenital anomalies attributable to its lack of androgenic effects on the developing fetus. Importantly, no causal relationship has been established between the administration of oral dydrogesterone during pregnancy and the occurrence of congenital anomalies.

Summary of Safety Data Related to Progestogen Use

Since its introduction in 1960, it is estimated that 113 million women and approximately 20 million fetuses have been exposed to dydrogesterone. Clinical studies have consistently demonstrated that oral dydrogesterone boasts a favorable benefit–risk profile comparable to that of micronized vaginal progesterone during luteal phase support. Assessments of maternal populations regarding liver function and the incidence of vascular, gastrointestinal, and nervous system disorders revealed comparable outcomes between the oral dydrogesterone and micronized vaginal progesterone capsule groups.

In the Lotus I study, the rate of serious treatment-emergent adverse events among mothers was similar across the groups, at 10.8% for oral dydrogesterone and 13.3% for micronized vaginal progesterone capsules. Among newborns, serious adverse event rates were low and comparable: 4.2% for oral dydrogesterone versus 5.7% for the micronized vaginal progesterone capsule group. Notably, the incidence of congenital, familial, and genetic disorders among newborns was also similar between the two groups in the Lotus I study.

In the Lotus II study, the incidence of serious treatment-emergent adverse events in mothers was again comparable, at 13.7% for oral dydrogesterone and 13.1% for micronized vaginal progesterone gel. The fetal and newborn populations mirrored these results, with similar rates

of serious treatment-emergent adverse events. Furthermore, the incidence of congenital, familial, and genetic disorders remained similar between the two treatment options.

A retrospective case-controlled study involving 202 children examined the use of oral dydrogesterone in early pregnancy to prevent miscarriage and found a potential association between congenital heart malformations and oral dydrogesterone treatment. However, the study design had significant methodological flaws, which precluded establishing a causal relationship. The Lotus II study, on the other hand, recorded a low incidence of congenital heart malformations, with six cases in the oral dydrogesterone group and ten cases in the micronized vaginal progesterone gel group. The Lotus I study similarly documented three congenital heart disease events in both treatment groups.

The 2017 European Society of Human Reproduction and Embryology guidelines recommend against vaginal progesterone use during early pregnancy for women with unexplained recurrent pregnancy loss, indicating no beneficial effect. Evidence suggests that oral dydrogesterone treatment, when initiated upon confirming fetal heart action, may be effective; however, further trials are warranted to solidify these claims.

In summary, oral dydrogesterone possesses a well-established safety profile, reinforced by the extensive findings from the Lotus I and II Phase III clinical trials, which identified no new safety concerns related to its use during early pregnancy for either mothers or developing fetuses. Importantly, no increased risk of congenital heart disease has been recognized in association with dydrogesterone administration.

Dydrogesterone Usage Pattern in India

A study by Khanna et al., conducted across India from December 2020 to February 2021, explored the knowledge, attitude, and practice (KAP) of Indian gynecologists regarding dydrogesterone use. The primary objective was to assess the clinical utility of dydrogesterone, particularly its benefits over micronized progesterone, in treating progesterone deficiency-related conditions, including threatened miscarriage, recurrent miscarriage, and luteal phase support during pregnancy.

This prospective, cross-sectional, observational survey included 1168 gynecologists across India. The participants completed a structured questionnaire comprising 16 multiple-choice questions. These questions focused on aspects such as indications for dydrogesterone use, dosage preferences, efficacy, and tolerability in everyday clinical practice.

Dydrogesterone Dosage

The preferred dosage of dydrogesterone across India was explored through this survey, with the majority of respondents (73%) favoring a 10 mg twice-daily regimen. The details of dosing preferences are as follows:

- **10 mg twice daily:** 823 gynecologists (73%) indicated this was their most commonly used dose.
- **10 mg once daily:** 171 gynecologists (15%) preferred to administer 10 mg of dydrogesterone only once daily.
- **10 mg three times daily:** 117 gynecologists (10%) preferred this more frequent dosage.
- **20 mg twice daily:** A small group of 33 gynecologists (3%) recommended a higher 20 mg dose taken twice daily.
- **Other dosing regimens:** 1% of respondents (6 gynecologists) reported using other unspecified dosing schedules.

These results suggest that dydrogesterone 10 mg twice daily is the dominant dose prescribed in routine clinical practice across India.

Average Dose of Dydrogesterone	No. of Doctors	Percentage (%)
10 mg once daily	171	15%
10 mg twice daily	823	73%
10 mg three times daily	117	10%
20 mg twice daily	33	3%
Other	6	1%

Indications for Use of Dydrogesterone

The survey explored the common clinical scenarios where dydrogesterone is prescribed. Notably, 87% of the gynecologists surveyed reported using dydrogesterone for conditions such as recurrent pregnancy loss, habitual abortion, threatened abortion, and luteal phase support. The duration of treatment for these indications also varied:

- **In cases of threatened abortion,** 42% of gynecologists recommended using dydrogesterone for up to 14 weeks. Another 33% preferred to continue the therapy until 18 weeks of gestation.
- **For recurrent miscarriage**, 36% of gynecologists prescribed dydrogesterone for a period of 10 to 14 weeks.

These findings highlight the widespread acceptance of dydrogesterone for preventing pregnancy complications related to progesterone deficiency.

Clinical Outcomes

The clinical outcomes associated with dydrogesterone usage were significant, with 30% of gynecologists reporting a clinical pregnancy rate greater than 40% at 12 weeks of dydrogesterone use. Additionally, 35% of the respondents observed an average live birth rate of 40% following dydrogesterone treatment. These statistics demonstrate that dydrogesterone is associated with positive clinical outcomes in the management of miscarriage and other pregnancy complications.

- **Clinical Pregnancy Rate:** 30% of gynecologists observed more than 40% pregnancy success at 12 weeks of dydrogesterone treatment.
- **Live Birth Rate:** 35% of respondents noted a live birth rate of approximately 40% after using dydrogesterone.

Advantages of Dydrogesterone Over Micronized Progesterone

The survey also compared dydrogesterone's advantages with those of natural micronized progesterone. Several factors were highlighted as reasons for favoring dydrogesterone:

- **Higher bioavailability:** Dydrogesterone is better absorbed than micronized progesterone, allowing for more predictable pharmacokinetics.
- **Improved patient compliance:** Due to its oral administration and favorable side effect profile, dydrogesterone was reported to have better patient adherence compared to other forms of progesterone.
- **Fewer side effects:** Dydrogesterone has a lower incidence of side effects such as drowsiness and nausea, which are commonly reported with micronized progesterone.
- **Better quality of life:** 72% of respondents felt that dydrogesterone contributed to an improved quality of life for patients compared to other progesterone formulations.

In contrast, 68% of gynecologists cited poor tolerability, compliance issues, and lower efficacy as the main limitations of micronized progesterone.

Co-administration of Dydrogesterone and Micronized Progesterone

Approximately 70% of gynecologists favored the combined use of dydrogesterone and micronized progesterone in various clinical scenarios. The co-administration was particularly common in cases of:

- **Recurrent miscarriage:** 54% of respondents reported using this combination.
- **Threatened abortion:** 41% favored this dual approach.
- **Luteal phase support:** 35% of gynecologists used both dydrogesterone and micronized progesterone in this context.

The use of combined therapies appears to be a prevalent strategy among Indian gynecologists for managing pregnancy complications.

Preference for Indigenously Developed Products

The survey also evaluated the preference for indigenously developed dydrogesterone products among Indian gynecologists. The results revealed a strong inclination toward locally produced medications:

- **38% of gynecologists** indicated that they "most preferred" indigenously developed products.
- **43%** had a general preference for locally made dydrogesterone formulations.
- **10%** were neutral, expressing no strong preference either way.
- **10%** felt that the origin of the product did not influence their choice.

In total, 81% of the gynecologists expressed a positive preference for indigenously developed dydrogesterone products.

Preference for Indigenously Developed Products	No. of Doctors	Percentage (%)
Most preferred	421	38%
Preferred	476	43%
Neutral	110	10%
Does not matter	108	10%
Total preference (most preferred + preferred)	**897**	**81%**

Factors for Selecting Dydrogesterone

In terms of factors that influenced the choice of dydrogesterone among Indian gynecologists, two key aspects stood out:

1. **Product Quality:** 46% of respondents identified the quality of the product as the most critical factor in selecting dydrogesterone.
2. **Patient-Related Outcomes:** 43% of the participants emphasized positive patient outcomes as a deciding factor in the selection process.

Cost was considered a less significant factor, with only 19% of respondents indicating that price influenced their decision.

Factors for Selection of Dydrogesterone	No. of Doctors	Percentage (%)
Quality of product	514	46%
Clinical data	229	20%
Patient-related outcomes	478	43%
Cost	211	19%
Other	31	3%

Conclusion

The survey highlights that dydrogesterone is highly valued by Indian gynecologists for its clinical effectiveness and favorable tolerability profile. The results confirm its utility, particularly in preventing miscarriage and supporting early pregnancy, with significant advantages over micronized progesterone. Dydrogesterone is well-accepted in clinical practice, with a majority of gynecologists preferring locally developed formulations.

Clinical Studies Evaluating Dydrogesterone in Fresh Cycle IVF

Numerous small-scale clinical studies have indicated that oral dydrogesterone is at least as effective as micronized vaginal progesterone in supporting pregnancy following fresh embryo transfer. These findings have reignited interest in oral dydrogesterone for luteal phase support (LPS) and paved the way for large Phase III prospective randomized controlled trials (RCTs), specifically the Lotus I and Lotus II studies, which ultimately led to the recent approval of oral dydrogesterone for LPS in IVF and assisted reproductive technology (ART).The Lotus I study was an international Phase III non-inferiority RCT that included 1,034 patients undergoing IVF with fresh embryo transfers. It demonstrated that a dosage of 30 mg of dydrogesterone (10 mg taken three times daily) resulted in comparable ongoing pregnancy rates—37.6% in the oral dydrogesterone group compared to 33.1% in the micronized vaginal progesterone group, which was administered at 600 mg (200 mg three times daily). Similarly, the Lotus II RCT compared oral dydrogesterone at the same dosage with an 8% micronized vaginal progesterone gel (90 mg once daily) and also showed non-inferiority, with ongoing pregnancy rates at 12 weeks of gestation being 38.7% for the oral dydrogesterone group and 35.0% for the micronized vaginal progesterone gel group. The main conclusion drawn from these two RCTs is that oral dydrogesterone is safe, well-tolerated, and as effective as vaginal progesterone.

Clinical Studies Evaluating Dydrogesterone in Frozen Embryo Transfer Cycles

Frozen-thawed embryo transfer (FET) has become an increasingly significant component of IVF treatment, with large clinical trials and meta-analyses showing similar live birth rates to those associated with fresh embryo transfers. Several endometrial preparation methods for FET have been developed, with hormone replacement therapy (HRT)-FET cycles being the most commonly used due to their reduced need for treatment monitoring and easier scheduling. In HRT-FET cycles, estrogen and progesterone are administered sequentially to mimic the endocrine conditions of a normal menstrual cycle. However, physiologically, LPS in HRT-FET differs significantly from LPS in fresh IVF cycles due to the absence of ovulation and endogenous corpora lutea, meaning that endometrial transformation into a receptive state for implantation relies entirely on exogenous progesterone supplementation.While there is

substantial evidence supporting the efficacy of oral dydrogesterone for LPS in fresh IVF cycles, very few small studies have evaluated its role in HRT-FET cycles using inconsistent dosing regimens. The only RCT conducted to date reported lower pregnancy rates in the oral dydrogesterone group compared to the micronized vaginal progesterone group when using doses of 20 mg and 800 mg, respectively. This highlights a significant gap in data regarding optimal dosing of oral dydrogesterone in FET-HRT cycles, underscoring the need for further research. Given the advancing understanding of how the absence of a corpus luteum affects FET-HRT cycles and the associated elevated risk for pregnancy complications, dydrogesterone's potential immunomodulatory effects present an intriguing area for future investigation. Developing a clinically applicable test for monitoring dydrogesterone levels or its metabolites will be crucial, as optimal luteal phase support likely requires individualized approaches.

Table 1. Overview of evidence of dydrogesterone use in HRT-FET cycles

Study	N	LPS in HRT-FET	Embryo stage	Outcome
Zarei et al. RCT	400	400 mg MVP 2x/d vs. 10 mg DYD 2x/d vs. 10 mg DYD 2x/d + 0.1 mg GnRHa vs. 10 mg DYD 2x/day + 1500 IU hCG	Cleavage stage	CPR 20, 9, 25, and 17% (p = 0.03) OPR 18, 9, 3, and 17% (p = 0.07) MR 18.1, 35.7, 14.8, and 19.1% (p = 0.84)
Alahmad et al. Retrospective	314	MVP 600 mg/day of 90 mg vs. DYD 10 mg 3x/day	2PN	Cumulative CPR Difference: 1.4%, 95% CI: (−9.4 to 12.6), p = 0.80 CPR of first FET Difference: −3.2%, 95%CI: (−12.8 to 7.4), p = 0.54

Guo et al. Retrospective	529	DYD 10 mg 4x/day vs. IM P4 60 mg/day	Cleavage stage/blastocyst	CPR IR MR EPR OPR DR no difference	significant
Rashidi et al. Pilot RCT	180	IM P4 50 mg 2x/d vs. DYD 20 mg 2x/d vs. MVP 400 mg 2x/d	95% cleavage stage5% blastcyst	CPR MR LBR no difference	significant

LPS, luteal phase support; HRT, hormone replacement therapy; FET, frozen embryo transfer; RCT, randomized controlled trial; MVP, micronized vaginal progesterone, DYD, dydrogesterone; GnRHa, gonadotrophin releasing hormone agonist; hCG, human chorionic gonadotrophin; IM P4, intramuscular progesterone; PN, pronuclei; CPR, clinical pregnancy rate; OPR, ongoing pregnancy rate; MR, miscarriage rate; IR, implantation rate; EPR, ectopic pregnancy rate; DR, delivery rate; LBR, life birth rate.

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