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Review Article

Dydrogesterone update: insights on its therapeutic applications

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ABSTRACT

Progesterone deficiency is commonly implicated as an important etiology in pregnancy complications like threatened miscarriage, luteal phase defect (LPD), recurrent pregnancy loss (RPL), etc. LPD characterized by inadequate progesterone secretion during the luteal phase of the menstrual cycle, is associated with implantation failure and early pregnancy loss. Hormonal imbalances are a common element in the etiology of threatened abortion (TA) and RPL. Dydrogesterone, a synthetic progestin, has emerged as a viable treatment option in many reproduction-related disorders, including LPD, TA, RPL, and LPD associated with assisted reproductive technologies (ART). Dydrogesterone has been shown to be effective in preventing miscarriages by maintaining the corpus luteum and promoting endometrial receptivity. This up-to-date article highlights the clinical implications of dydrogesterone pertaining to its use in LPD, TA, and RPL.

Keywords: Dydrogesterone, LPD, RPL, TA, Progesterone, ART

INTRODUCTION

In India, the vast majority of couples aspire to have a family, but many of them face obstacles when trying to conceive. This difficulty in conceiving has resulted in a decrease in pregnancy rates by 30% in first month and about 5% by the end of the first year.¹ Also, safe pregnancy is a significant concern, leading to a noticeable drop in the number of live births in the country. Progesterone is essential for the maintenance of healthy pregnancy as it is primarily concerned with preparing the uterus for the embryo implantation. Low progesterone levels increase the risk of pregnancy complications ectopic pregnancy, or may even cause miscarriage or stillbirth.² Along with other factors, like reduced ovarian reserve, pregnancy at an advanced age, obesity, diabetes, hypertension, hormonal imbalance, LPD, and HIV positive, progesterone deficiency is widely implicated as a significant cause of TA, RPL, and reduced success rates in ARTs. Pituitary negative feedback loop induced by increased estradiol

naturally promotes low progesterone levels during luteal phase and luteolysis.³ Therefore, luteal phase insufficiency is a serious issue with ART that necessitates progesterone supplementation to improve pregnancy outcomes.

LUTEAL PHASE DEFECT

In menstrual cycle, luteal phase is crucial in preparing the body for a potential pregnancy. It unfolds as a complex sequence of events orchestrated by a delicate interplay of hormones and physiological changes.⁴ Its culmination in establishing the corpus luteum and the subsequent rise in progesterone levels transforms the uterus into an optimal environment for embryo implantation. This period of preparation and anticipation lays the foundation for early pregnancy development, making the luteal phase a critical juncture in the menstrual cycle. Progesterone, the hormone predominantly produced during this phase, is pivotal in preparing the uterine lining for embryo attachment and nurturing the early stages of pregnancy.

Disruptions in this phase or functioning of the corpus luteum can lead to a condition known as LPD. It was first described in 1949 by Georgiana Seegar Jones and LPD continues to be a significant concern, with the prevalence of LPD being reported in 3.7-20% infertile women.⁵ LPD is mainly characterized by inadequate progesterone production associated with compromised endometrial receptivity, hampered embryo implantation, unexplained infertility, and an increased risk of early pregnancy loss. Ovarian stimulation cycles using gonadotropin-releasing hormone agonist or antagonist protocols have been associated with a defective luteal phase that can disturb embryo implantation. The approach to management of LPD involves treatment of the underlying pathology such as thyroid dysfunction, hyperprolactinemia or PCOS. Luteal-phase support is a well-known intervention for almost all stimulated assisted reproductive technology cycles.⁶ To improve successful embryo implantation and maintenance of pregnancy, luteal phase support (LPS) in the form of progesterone supplements (progestins), human chorionic gonadotropin (HCG), or gonadotrophin-releasing hormone (GnRH) agonists/ antagonists have been shown to boost the activities of corpus luteum. Polycystic ovarian syndrome (PCOS) and LPD, although they are distinct conditions, have similar pathophysiological characteristics and can coexist. Both PCOS and LPD are caused by abnormalities in the angiogenesis of the corpus luteum, hyperinsulinemia, and excess anti-mullerian hormone (AMH). An impaired corpus luteum may cause infertility in PCOS ovulatory cycles.⁷ Thyroid disorders, mainly hypothyroidism, may interfere with reproductive hormones, potentially affecting ovulation and the luteal phase. LPD and thyroid disorders together can contribute to infertility; hyperprolactinemia can also have an impact on reproductive health because it suppresses the release of gonadotropin-releasing hormone from the hypothalamus, which in turn can lead to decreased progesterone secretion, ultimately causing disruptions in the menstrual cycle and ovulation.

THREATENED ABORTION AND RECURRENT PREGNANCY LOSS

Vaginal bleeding in the first half of pregnancy is a common problem encountered in obstetrics practice. Vaginal bleeding before 20 weeks of gestation accompanied by a positive urine and/or blood pregnancy test with a closed cervical OS, with or without abdominal pain, without passage of products of conception, and without evidence of a foetal or embryonic demise is considered a TA. During the first two trimesters, around 25% of pregnant women experience some degree of vaginal bleeding and about 50% of these progress to loss of pregnancy.⁸ The bleeding during a TA is typically mild to moderate. Abdominal pain can manifest as suprapubic pain, pelvic pressure, intermittent cramps/lower back pain.

The definition of RPL has long been debated and differs among international societies. As per the European Society for Human Reproduction and Embryology (ESHRE) and

the Royal College of Obstetricians and Gynaecologists (RCOG), American Society for Reproductive Medicine (ASRM), RPL refers to three consecutive pregnancy losses, including non-visualized ones. According to the American Society for Reproductive Medicine (ASRM), it is characterised two or more clinical pregnancy losses, not necessarily consecutive that are documented by ultrasonography or histopathologic examination.⁹ There are 10-20% of women who experience a miscarriage during their reproductive period; out of that, 2% of women have two consecutive abortions, and 0.5-1% of them have three consecutive abortions.⁹ RPL is a multifactorial condition due to genetic, anatomic, endocrine, antiphospholipid antibody syndrome, immunologic, and environmental factors. Primary RPL, which refers to multiple pregnancy loss in a woman with no previous viable infants, is more eminent than secondary RPL, which refers to multiple pregnancy loss in a woman who already had a pregnancy beyond 20 gestational weeks.

PROGESTINS IN PREGNANCY COMPLICATIONS

Progesterone deficiency is prevalent in conditions such as luteal phase deficiency, TA, and RPL, necessitating the use of progesterone supplementation. Various progestins are utilized to enhance outcomes in high-risk pregnancy situations and increase live birth rates. These include oral natural micronized progesterone (NMP), vaginal micronized progesterone (VMP), oral dydrogesterone, hydroxyprogesterone caproate injection, etc. Natural progesterone, derived from plant sources or synthesized to mimic endogenous progesterone, bolsters progesterone levels in the body. Micronized progesterone formulated for administration via the vaginal route, offers localized delivery and improved bioavailability, making it a preferred option in specific scenarios. On the other hand, dydrogesterone is a synthetic progestin that offers the convenience of oral administration with much higher bioavailability compared to NMP. It exhibits progesterone-like activity, thereby aiding in maintenance of pregnancy and mitigating associated risks. Moreover, its administration is associated with reduced adverse effects commonly observed with other progestins, thereby enhancing tolerability and patient adherence to therapy.

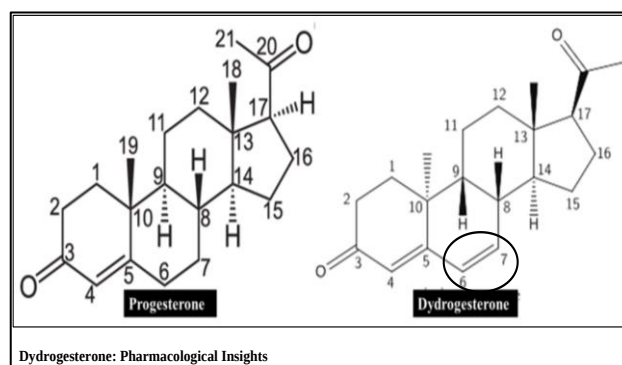


Figure 1: Chemical structure of progesterone and dydrogesterone.

Dydrogesterone (6-dehydro-retroprogesterone) is a retroprogesterone that was developed in the 1950s and commercially introduced in the 1960s for the treatment of progesterone deficiency and associated conditions such as premenstrual syndrome, endometriosis, TA, and for postmenopausal hormone replacement therapy. It is highly similar to endogenous progesterone in structure, function, and biological characteristics. Dydrogesterone is a stereoisomer of progesterone with a methyl group at carbon 10 in the α -orientation rather than the β -orientation and hydrogen at carbon 9 in the β -orientation rather than the α -orientation. Additionally, there is another double bond between carbons 6 and 7 in dydrogesterone. These unique molecular features create a 'bent' conformation with enhanced rigidity compared with progesterone, which accounts for dydrogesterone's high selectivity for progesterone receptors. It has relatively low antagonistic activity at glucocorticoid and mineralocorticoid receptors compared with progesterone. Dydrogesterone is a selective progesterone receptor agonist with 5.6 times higher bioavailability than progesterone.¹⁰

Oral dydrogesterone doses of 10 mg and 20 mg for 12-14 days, in combination with estrogen, were effective in inducing secretory transformation of the endometrium.¹¹ Dydrogesterone also has high specificity for progesterone receptors and causes endometrial transformation at 10- to 20-fold lower doses than micronized progesterone.¹² It facilitates implantation via the improvement of endometrial receptivity by increasing the endometrial nutrient stores and enhanced blood supply. It has been demonstrated to induce decidual transformation through increased endometrial vascularity.⁶ Dydrogesterone helps the uterus quiescent by stabilizing lysosomal membranes, inhibiting prostaglandin synthesis, and reducing intracellular calcium concentration.⁶ It also causes uterine relaxation by causing nitric oxide synthesis.¹³ Dydrogesterone causes atrophy of ectopic endometrium without suppressing the normal endometrium and simultaneously inhibits the development of new endometriotic lesions.¹⁴

Sustained release (SR) formulation of dydrogesterone is a new emergent that offers a valuable option for individuals requiring hormone therapy for preventing TA, RPL and endometriosis. The SR preparation of dydrogesterone has been proven to be bioequivalent to the immediate release formulation of dydrogesterone. The SR tablets of 20 mg and 30 mg ensure a more consistent and stable level of dydrogesterone in the bloodstream over an extended period. This can lead to better symptom control and efficacy in managing conditions such as hormone imbalance or LPD in ART. The SR formulation would provide a "therapeutic compliance" as it will decrease dosing frequency and thus improve patient convenience. Patients utilizing sustained-release dydrogesterone would have better treatment adherence due to simpler dosage regimens and fewer adverse effects, thus providing better clinical results.

DYDROGESTERONE AS LUTEAL PHASE SUPPORT IN ART

During pregnancy, the immune system undergoes adjustments to create a tolerant environment for the developing fetus. Dydrogesterone, plays a crucial role in this process due to its novel mechanism of immune modulation. Dydrogesterone, along with hormones like HCG and cortisol, work to inhibit tissue rejection and protect the conceptus through its immunomodulatory actions.¹⁵ Dydrogesterone positively regulates the expression of 'progesterone induced blocking factor' (PIBF), 'natural killer (NK) cells,' HOX-10, and trophoblast human leukocyte antigens (HLA) genes, leading to a favorable shift towards a T helper 2 immune response.¹³ PIBF, in particular, is essential for regulating NK cell cytotoxicity by inhibiting the release of perforin from the cytoplasmic granules of NK cells. During a healthy human pregnancy, serum concentrations of PIBF increase with gestational age, and lower-than-normal levels of PIBF in the serum may indicate a risk of spontaneous pregnancy termination.¹⁵ Dydrogesterone supplementation can help maintain adequate levels of PIBF supporting a successful pregnancy outcome.

DYDROGESTERONE AS LPS IN ART

LPD has emerged as a raising concern associated with compromised endometrial receptivity, hampered embryo implantation, and leading to an increased risk of pregnancy complications. In ARTs, offering support during the luteal phase can enhance the possibility of a successful outcome and reduce the risk of cycle cancellation. Oral dydrogesterone has demonstrated significant efficacy as LPS in women undergoing fresh IVF resulting in successful embryo implantation (Table 1). The meta-analysis included eight articles, the efficacy of oral dydrogesterone (DYD, n=3051) with vaginal progesterone (VP, n=690)/intramuscular progesterone (IMP, n=1484) for LPS in women undergoing frozen embryo transfer. The study demonstrated that oral DYD is a better option with fewer side effects and significantly higher patient satisfaction than VP and IMP.¹ Another single-centre retrospective cohort study compared five different hormonal LPS regimens that are: oral dydrogesterone (30 mg/day), VMP gel (90 mg/day), dydrogesterone (20 mg/day) plus micronized progesterone gel (MPG 90 mg/day) (Dydrogesterone + micronized progesterone gel), micronized progesterone capsules (600 mg/day), and subcutaneous injection of progesterone 25 mg/day (subcutan-P4) in frozen embryo transfer cycles.

The study concluded that DYD is well-tolerated and probably contributes to the immunomodulation of the receptive endometrium. It can, therefore, be applied for LPS in FET cycles. In addition, DYD in LPS in artificial frozen-thawed embryo transfer cycles was associated with higher clinical pregnancy rate (CPR) and live birth rate (LBR) than using MPG alone.¹⁶

A randomized open-label trial conducted in 162 participants by Ikechebelu et al found that dydrogesterone was better tolerated and significantly less expensive than MVP pessary. Dydrogesterone is less expensive and appears to be more user-friendly in cases of LPS in *in-vitro* fertilization cycles (IVF).¹⁷ A systematic review and meta-analysis comparing oral dydrogesterone to micronized vaginal progesterone for LPS in women undergoing IVF found that oral dydrogesterone was associated with significantly higher rates of ongoing pregnancy and live births. Safety profiles between the two treatments were similar, suggesting that oral dydrogesterone may offer superior efficacy in achieving successful pregnancies

during IVF cycles.¹⁸ A large, randomized, double-blind, phase III trial evaluated the use of 30 mg oral dydrogesterone versus 600 mg micronized vaginal progesterone daily for LPS in IVF. Despite undergoing oral administration and undergoing first-pass metabolism in the liver, Dydrogesterone exhibited comparable tolerability to vaginal progesterone in safety evaluations. Furthermore, no additional foetal safety issues emerged from the trial. Considering the prevalent preference among women for an orally administered medication, dydrogesterone holds promise to potentially establish itself as the preferred choice for LPS in fresh embryo transfer during IVF cycles.¹⁹

Table 1: Summary of clinical trials of oral Dydrogesterone in ART.

Study design	Study population	Study size (N)	Treatment	Study outcome
RCTs (meta-analysis)⁶	Women undergoing frozen embryo transfer for LPS.	5225 (3051/690/1484)	Oral dydrogesterone (DYD= 10-40 mg) with vaginal progesterone (VP=400 mg BD/ 8% gel BD) or IM progesterone (IMP=50-100 mg)	Fewer side effects, higher patient satisfaction with oral DYD and a better option than VP and IM progesterone.
Single center retrospective observational study²⁶	Women undergoing artificial frozen thawed embryo transfer cycles for luteal phase support.	391 (52/281/17/37/4)	1) Oral Dydrogesterone (DYD=30 mg/day), 2) Vaginal micronized progesterone gel (MPG=90 mg/day), 3) Dydrogesterone (20 mg/day) plus micronized progesterone gel (DYD+MPG=90 mg/day) 4) Micronized progesterone capsules (MPC=600 mg/day) (5) Subcutaneous injection of progesterone (SC-P=25 mg/day)	DYD is well-tolerated with higher clinical pregnancy rates and live birth rates. Clinical pregnancy rates (%) DYD=42.3% MPG=17.8% DYD+MPG=58.8% MPC=8.1% SC-P=25% Live birth rates (%) DYD=26.9% MPG=11.7% DYD+MPG=29.4% MPC=5.4% SC-P=25%
Randomised open-label study¹⁵	LPS for women undergoing IVF embryo transfer treatment with stimulated cycles or donated oocyte.	162 (81/81)	Oral dydrogesterone (10 mg TID) and micronized vaginal progesterone pessary (MVP=400 mg BD)	Dydrogesterone was better tolerated, more user-friendly and less expensive with better safety profile than MVP. DYD vs MVP: Positive pregnancy (35.8% vs. 32.7%). Clinical pregnancy (32.1% vs. 28.8%), Ongoing pregnancy rates (26.4% vs. 23.1%)
Meta-analysis study²⁵	For LPS.	1957	Oral dydrogesterone 20 to 40 mg vs MVP gel 90 mg or capsules 600 to 800 mg.	Higher pregnancy rate (38.1% vs 34.1%) and live birth rate (34.5% vs 31.2%) in women receiving oral dydrogesterone vs MVP for LPS.
A large, randomized, double-blind, double-dummy phase III trial²⁷	In women for LPS in fresh embryo transfer IVF cycles.	1029 (518/511)	Oral dydrogesterone (30 mg) versus daily 600 mg micronized vaginal progesterone	Dydrogesterone was well tolerated with no new foetal safety concerns.

DYDROGESTERONE IN THREATENED ABORTION

TA may complicate pregnancy cases, that can progress to spontaneous, incomplete or complete abortion. To address this issue, dydrogesterone has been used extensively in the treatment of threatened miscarriage with promising outcomes. Studies have found that dydrogesterone is particularly effective in preventing miscarriage in women who experience vaginal bleeding during pregnancy (Table 2). An analysis of 617 case report forms of patients presenting with symptoms like vaginal bleeding/spotting before 20 weeks of gestation and needed surgical intervention. Treatment with dydrogesterone was found to be well-tolerated with minimal adverse events. The study also concluded that dydrogesterone is effective and safe in reducing incidence of pregnancy loss in women with TA.²⁰ A prospective cohort study was conducted in 1,285 patients with threatened miscarriage due to insufficient corpus luteum. Compared with progesterone, dydrogesterone improved delivery outcome and demonstrated higher safety in treatment of threatened miscarriage.²¹

A total of 10,424 participants across 59 randomised controlled trials (RCTs), were included to determine the efficacy and safety of progestogens in the treatment of threatened miscarriage. The results of the study showed that when ranked from best/safest therapy, oral DYD was first (surface under the cumulative ranking area {SUCRA} 100.0%), vaginal progesterone was second (SUCRA 67.9%), placebo and intramuscular progesterone that had the same SUCRA rank indicating a similar possibility of miscarriage were both third (SUCRA 35.2% and 31.2%, respectively). Oral micronized progesterone was fourth (SUCRA 15.7%). It was found that oral DYD is effective and safe in the treatment of TA.²² Eight randomized controlled trials, including 845 women who faced threatened miscarriage, demonstrated that dydrogesterone is effective in reducing the incidence of miscarriage as compared to natural vaginal progesterone.²³ A study was

conducted to compare oral dydrogesterone and micronized progesterone in threatened miscarriage in terms of pain in the lower abdomen and bleeding per vaginum. The study found that the group who received dydrogesterone was associated with 95% of normal-weight babies and also reduced pain in the lower abdomen and bleeding more in comparison to micronized progesterone (80%) in threatened miscarriage.²⁴

Another prospective interventional study included 16 pregnant women presented with symptoms of TA to assess the immunomodulatory role of dydrogesterone. The study demonstrated that dydrogesterone is useful in the treatment of TA via modulating cytokine profile and causing a shift in Th1/Th2 ratio for Th2 predominance and, more specifically, via decreasing level of Th1 markers such as IF- γ .²⁵

A randomized controlled trial study included 140 patients aged 20 to 45 years. Patients with signs of TA before 20 weeks of gestation, having single intrauterine pregnancy based on ultrasound findings, and presenting with vaginal bleeding, received micronized progesterone and dydrogesterone treatments. Micronized progesterone and dydrogesterone treatments showed similar efficacy in the treatment of threatened miscarriage. However, the rate of side effects was significantly higher in women treated with micronized progesterone. The rate of drowsiness (61.43% vs. 31.43%) and giddiness (22.86% vs. 8.57%) was significantly ($p < 0.05$) higher in micronized progesterone group as compared to dydrogesterone group.²⁶ In a randomized selection, 99 patients with TA due to luteal phase deficiency received oral dydrogesterone tablets or intramuscular progesterone injections. The success rate in preventing miscarriage for the dydrogesterone group (90.0%) was significantly higher compared to the intramuscular progesterone injections (81.6%) group. Additionally, therapy with dydrogesterone successfully increased serum sex hormone levels, enhanced cytokine levels, and accelerated the resolution of clinical symptoms in TA caused by LPD.²⁷

Table 2: Summary of treatment with oral dydrogesterone in TA.

Number of patients	Study population	Intervention	Treatment duration	Clinical outcome
617 (Case reports)²⁰	Women with TA in the first trimester of pregnancy	Dydrogesterone 20-40 mg, followed by a maintenance of 10 mg/BID	20 weeks	In women with TA, dydrogesterone is effective and safe in decreasing the incidence of pregnancy loss.
1,285²¹	Patients with threatened miscarriage due to corpus luteum insufficiency	Dydrogesterone 40 mg, followed by 10 mg/time, 3 times/day Progesterone 0.1 g/time, 2 times/day	2 weeks	Dydrogesterone can improve the delivery outcome and demonstrates a higher safety in treatment of threatened miscarriage.
10,424 (59 RCTs)²²	Threatened miscarriage	Vaginal progesterone, oral dydrogesterone, oral micronized progesterone, IM	-	Oral dydrogesterone is effective and safe in the treatment of TA.

Continued.

Number of patients	Study population	Intervention	Treatment duration	Clinical outcome
		progesterone, and placebo.		
845 (8 RCTs) ²³	Women with threatened miscarriage	Dydrogesterone, natural progesterone, vaginal progesterone	Up to 20 th week of pregnancy	Dydrogesterone, was associated with a lower risk of miscarriage.
126 ²⁴	Threatened miscarriage	Dydrogesterone 10 mg twice daily micronized progesterone 200 mg twice daily	12 weeks	Dydrogesterone reduced pain in lower abdomen and bleeding per vagina to a greater extent in comparison to micronized progesterone.
32 ²⁵	Women presented with symptoms of TA or normal pregnancy	Dydrogesterone 40 mg followed by 10 mg every eight hours until symptoms subside placebo	Treatment until at least one week after symptoms subside	Dydrogesterone was associated with increased rates of successful term pregnancies.
140 ²⁶	Patients with signs of TA before 20 weeks of gestation, having single intrauterine pregnancy based on ultrasound findings, presenting with vaginal bleeding	Dydrogesterone 10 mg twice a day and micronized progesterone 200 mg twice a day	2 weeks	Dydrogesterone showed similar efficacy and fewer side effects than micronized progesterone.
99 ²⁷	Patients with TA caused by LPD.	Oral dydrogesterone tablets + intramuscular injection of progesterone	-	Success rate in preventing miscarriage with dydrogesterone group (90.0%) and intramuscular progesterone injections (81.6%).

DYDROGESTERONE IN RECURRENT PREGNANCY LOSS

Various factors are responsible for RPL, including lifestyle influences, insufficient progesterone level or abnormalities in the progesterone receptor, and affinity, leading to increased pregnancy loss. Treating RPL patients with dydrogesterone can create a suitable endometrial environment for implantation. It is also essential for maintaining pregnancy and achieving a higher pregnancy success rate. A retrospective cohort study by Bashiri et al was conducted in 866 patients with RPL. The study concluded an increased live birth rate was found in women treated with dydrogesterone regardless of other treatments. In addition, there may be immunological imbalances in these patients, and the immunomodulation of dydrogesterone may improve their pregnancy outcomes.²⁸ Another prospective study conducted at Nalanda medical college in Patna demonstrated that dydrogesterone administration resulted in significantly lower miscarriage rates (4%, one patient) compared to micronized progesterone (12.5%, 3 patients) with early pregnancy loss and TAs, highlighting dydrogesterone's efficacy in supporting successful pregnancies. These findings suggest that dydrogesterone, with its favorable tolerability and bioavailability, is a preferred option for adjuvant progesterone supplementation in high-risk pregnancies.²⁹ A meta-analysis of 13 studies included a total of 2,454 recurrent spontaneous abortion (RSA) patients treated with

dydrogesterone. In summary, dydrogesterone had an apparent therapeutic effect on patients with unexplained RSA. It effectively improved levels of hCG and progesterone through immune regulation and the expression of IL-4, IL-10, and IFN- γ cellular immune factors. Dydrogesterone, a synthetic progesterone drug is safe, effective and had a significant clinical effect on RSA.³⁰

SAFETY ANALYSIS OF DYDROGESTERONE

Dydrogesterone is an approved progesterone supplement for several indications, with a favorable efficacy and safety profile compared to other progestogens. It is more advantageous due to its selective action on the progesterone receptors and minimal androgenic effects. Various studies have evaluated its safety profile, which generally suggests that it is well-tolerated with a low incidence of adverse effects. Reports by compared treatment showed a significantly higher patient satisfaction score in women on oral DYD than on vaginal progesterone.¹ Oral dydrogesterone has a well-established safety profile; the results of the large and robust phase III clinical trials (Lotus I and Lotus II) demonstrated no new safety concerns related to oral dydrogesterone use during early pregnancy for either the mother or the developing foetus and identified no increased risk of congenital heart disease.¹¹ Dydrogesterone appears more user-friendly and

less expensive in cases of luteal-phase support IVF cycles.¹⁷

In a safety analysis involving 617 pregnant women, adverse events were reported in 3.72% patients treated with dydrogesterone. The most common ADR reported were bloating (1.4%), nausea (0.6%), constipation (0.6%), and giddiness (0.3%). On the global assessment of tolerability scale, the tolerability of dydrogesterone was assessed by the physicians as excellent in 99% of the patients.²⁰ In pregnancy-related conditions, such as TA and recurrent miscarriage, dydrogesterone poses no significant safety concerns in terms of pregnancy complications or congenital anomalies which could be attributed to a lack of androgenic effects on the fetus. No causal link between the use of oral dydrogesterone during pregnancy and congenital anomalies has been established. For correcting menstrual irregularities, the safety of dydrogesterone was well established and was supported by the post-marketing safety data.³¹

For 60 years, dydrogesterone has been an essential part of women's lives, right from adolescence to post-menopause. The evidence presented revalidates the well-established safety of dydrogesterone when it is mainly used as LPS in ART procedures, as hormonal support for preventing TA and recurrent miscarriages, for correcting menstrual irregularities, and in menopause hormone therapy (MHT) regimens.³¹

CONCLUSION

The widespread availability and accessibility of dydrogesterone has significantly impacted the management and treatment of high-risk pregnancies, offering several advantages that have revolutionized prenatal care. The structural distinction of dydrogesterone enhances its oral bioavailability compared to natural progesterone and enables effective oral administration that results in practical and clinical advantages. Several clinical trials underscore the effectiveness and long-term safety of dydrogesterone in threatened or recurrent miscarriage and LPS during assisted reproduction. The reliable and consistent delivery of dydrogesterone through SR formulation has the potential to offer better therapeutic outcomes and improved maternal as well as fetal health. As research continues to advance, dydrogesterone is poised to remain a cornerstone in the management of reproductive health, safeguarding healthier pregnancies.

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