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Review Article

Recent trends on dydrogesterone in gynaecology, obstetrics, and infertility: insights from Indian experts

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ABSTRACT

Infertility affects millions globally, with significant prevalence in India due to conditions like endometriosis and polycystic ovarian syndrome (PCOS). Dydrogesterone, a synthetic progesterone, has demonstrated efficacy in managing endometriosis, recurrent pregnancy loss (RPL), and infertility. Endometriosis, affecting 10% of reproductive-aged women, often leads to infertility and recurrent pain despite surgical interventions. Dydrogesterone 20 mg effectively reduces chronic pelvic pain and improves quality of life in these patients. In infertility management, dydrogesterone enhances luteal phase support (LPS), leading to higher pregnancy rates and better reproductive outcomes compared to other progesterone forms. It is particularly beneficial in in vitro fertilization (IVF) and intrauterine insemination (IUI) cycles, showing improved patient compliance and reduced side effects. For RPL, dydrogesterone stabilizes the endometrial environment, supporting implantation and early embryonic development. Its use in PCOS aids in menstrual regulation and pregnancy preparation without inhibiting ovulation. Expert opinions from Indian gynaecologists highlight the need for tailored dydrogesterone protocols to address the unique challenges in Indian healthcare. This document gathers insights from these experts, emphasizing the therapeutic potential of dydrogesterone in gynaecology, obstetrics, and infertility management.

Keywords: Dydrogesterone, Infertility, Endometriosis, RPL, PCOS, Gynaecology and obstetrics

INTRODUCTION

Infertility is a significant global health issue, affecting an estimated 60-80 million couples globally each year. According to a report by the World Health Organization (WHO), one in every four couples in developing countries is affected by infertility. In India alone, approximately 15-20 million couples, or about 25% of the total, experience infertility annually.[1]

One of the leading causes of infertility among women is endometriosis, a condition where tissue similar to the lining inside the uterus grows outside it, causing pain and complications in the reproductive system.[2] Endometriosis is known to affect 10 percent of women of reproductive age which translates to approximately 247 million females affected globally and 42 million women in India.[3] Among women struggling with infertility, between 25% and 50% are found to have endometriosis. Similarly, 30% to 50% of women diagnosed with endometriosis experience infertility.[4] Although research indicates that women with endometriosis may have a higher risk of miscarriage, especially recurrent pregnancy loss (RPL), defined as two or more clinical pregnancy losses.[5,6]A recent study by Boje et al found that 2.1% of women with endometriosis experience RPL, compared to 1.5% of women without endometriosis.[5] Polycystic ovary syndrome (PCOS) is another common female endocrine disorder and a leading cause of infertility, with a global prevalence ranging from 6-26% and 3.7-22.5% in India.[7]

Current treatment options for endometriosis, RPL, PCOS, and infertility include medical therapy, surgical intervention, or a combination of both approaches. Management strategies for these conditions are closely interconnected due to their overlapping pathophysiology.[4,5] Endometriosis necessitates a lifelong personalized management plan to optimize medical treatment and minimize repeated surgeries. Treatment is tailored to each woman based on her symptoms, age, and fertility goals.[8]

Dydrogesterone has a multi-faceted approach that concurrently addresses endometriosis, PCOS, mitigates RPL, and ultimately improves fertility outcomes. Hormonal treatment with dydrogesterone targets the pathological mechanisms of endometriosis by modulating the inflammatory environment and suppressing ectopic endometrial tissue proliferation. Additionally, dydrogesterone holds therapeutic potential for RPL by stabilizing the endometrial environment, thereby enhancing conditions for implantation and early embryonic development. This stabilization is achieved through its progestogenic activity, which supports the luteal phase and maintains an optimal endometrial receptivity essential for successful implantation and pregnancy maintenance.[9,10]

NEED FOR EXPERT OPINION

Endometriosis presents an escalating challenge for the medical community, as current treatments manage symptoms but fail to provide a permanent solution. There is a pressing need for therapies that address the underlying causes of the disease.[11] Dydrogesterone has established applications in obstetrics, gynaecology, and infertility. However, uncertainties surround the current use patterns and the specific benefits of the 20 mg sustained release (SR) formulation. To address this gap, expert opinion is crucial. This approach will shed light on the current landscape of dydrogesterone prescription across these specialties. Furthermore, experts can elucidate the distinct advantages of the 20 mg SR formulation compared to existing options. By exploring its potential for new indications and administration routes, this expert opinion can pave the way for future research and broaden the therapeutic applications of dydrogesterone, particularly the 20 mg SR formulation, in Indian healthcare.

METHODOLOGY

The panel included 9 experts, mainly gynaecologists, from India, who participated in an in-person expert group meeting conducted in November 2023 to discuss the role of dydrogesterone in gynaecology, obstetrics, and infertility management. Objectives and topics related to endometriosis, RPL, infertility and the role of dydrogesterone in their management were discussed, and the experts shared their views, which led to a group discussion. A leading gynaecologist moderated the expert group meeting and examined the existing literature and current practice with panel members to draft the expert's opinion. The document aimed to gather insights from Indian gynaecologists ensuring relevance to address specific challenges in the Indian healthcare landscape. Seeking input from these specialists is vital to tailor approaches suited to the Indian context.

EXPERT OPINIONS ON DYDROGESTERONE

Dydrogesterone in endometriosis

Evidence

Post-surgical outcomes for endometriosis indicate that while most women experience pain relief, there remains a significant likelihood of pain recurrence. Up to 80% of women report a return of pain within two years following surgery, with recurrence being more likely in severe cases. Hormonal treatments can inhibit the growth of endometrial tissue and prevent the formation of new adhesions; however, they do not eliminate pre-existing endometriosis tissue.[8] Despite surgical intervention being regarded as the primary treatment for many years, it is now recognized that repeated surgeries do not guarantee sustained improvement in fertility or pain reduction. While endometrioma resection demonstrably improves natural conception rates, its impact on assisted reproductive technology (ART) outcomes remains controversial. Dydrogesterone has been shown to relieve symptoms of endometriosis and regress lesions.[12] The ORCHIDEA study found that both Dydrogesterone 10 mg 2-3 times daily between days 5-25 of the menstrual cycle (prolonged cyclical regimen) and continuous dydrogesterone (continuous regimen) treatments significantly reduced chronic pelvic pain (mean changes of-3.3±2.2 and -3.0±2.2, respectively) in patients with endometriosis. Both regimens also improved dysmenorrhea, quality of life, and sexual well-being.[13] In a retrospective observational study of 235 premenopausal women with chronic endometriosis (CE) and endometrial polyps, the combination of dydrogesterone and antibiotics had a cure rate of 85.2%, compared to 74.3% with antibiotics alone, yielding an overall cure rate of 80.0% (188/235) ($p<0.05$).[14]

Expert opinion

Dydrogesterone is effective for endometriosis patients, particularly those with recurrent RPL and progesterone resistance. In such cases, it can be administered four times daily with extended-or sustained-release doses. Treatment should be from day 15 to 25 of the cycle, especially if planning pregnancy.

Patient profile: Patients with abnormal uterine bleeding or endometriosis especially those planning for pregnancy.

Target symptom: Specifically for pain management, not for menstrual cycle regulation.

Dosage and application: Normally, 10 mg twice a day in second half of the cycle. In cases of progesterone resistance, administer up to four times daily with extended- or sustained-release doses.

Duration: For 15 days, followed by withdrawal of drug.

Dydrogesterone in infertility

Evidence

Following the successful trials demonstrating its efficacy in *in-vitro* fertilization (IVF) luteal phase support (LPS), dydrogesterone has gained significant traction as a versatile therapeutic option in India. Its applications now span a broad spectrum within the fields of infertility, gynaecology, and pregnancy management. Dydrogesterone has potential to improve patient compliance, minimize side effects, and control costs. The introduction of extended-release formulations presents a promising avenue for further enhancing treatment effectiveness.

Dydrogesterone is a synthetic progesterone that's used to treat infertility caused by luteal phase insufficiency. Clinical studies show that dydrogesterone can improve pregnancy rates, extend LPS, and improve reproductive outcomes.[15] A meta-analysis shows that oral dydrogesterone significantly improves the chances of ongoing pregnancy at 12 weeks (OR 1.32, p=0.0075) and live birth (OR 1.28, p=0.0214) compared to micronized vaginal progesterone (MVP) for LPS.[16]

A randomized controlled trial found that oral dydrogesterone combined with vaginal progesterone for luteal support in intrauterine insemination (IUI) cycles resulted in significantly higher mean serum progesterone levels (p=0.001) and greater patient satisfaction compared to vaginal progesterone alone. The study concluded that oral dydrogesterone is as effective as vaginal progesterone for LPS in women undergoing IUI cycles.[17] Recent studies, including the 2017 and 2018 lotus I and II trials, have shown that oral dydrogesterone (DYD) is superior to micronized progesterone capsules (MPC) and gel (MPG) for LPS in fresh IVF cycles. A retrospective study of women undergoing frozen embryo transfers (FETs), revealed higher clinical pregnancy rates with oral DYD (OR=2.87, 95% CI 1.38-6.00, p=0.005) and DYD+MPG (OR=5.19, 95% CI 1.76-15.36, p=0.003) compared to MPG alone.[18]

Dydrogesterone optimizes luteal phase function by closely mimicking natural progesterone, enhancing endometrial receptivity for embryo implantation and early pregnancy development in patients undergoing FET.[15,19] A study analysing 304 FET cycles from 241 couples found that 11.8% (n=36) had serum progesterone (P4) levels below 10 ng/ml on the day of transfer. The study concluded that women with low P4 levels on the day of blastocyst transfer can be effectively rescued with DYD. Administering DYD 10 mg three times a day to women with P4 serum levels <10 ng/ml resulted in pregnancy rates beyond 12 weeks that were comparable to those with P4 levels >10 ng/ml.[20]

Table 1: Recommendations for dydrogesterone use in infertility based on recent guidelines.

Guideline	Recommendation
ISAR (2022)[21]	Micronized progesterone and dydrogesterone are recommended to be suitable options for LPS (Level A/ class I)
	Dydrogesterone (30 mg) is recommended be a viable alternative to MVP gel in fresh ART cycles due to its comparable efficacy and tolerability, as per the ESHRE. (Level A/ class I).
	In LPS, oral dydrogesterone has advantages over other progesterone routes due to its lower cost, easy administration, and better patient compliance in patients undergoing IUI. (Level B/ Class I).
	Oral dydrogesterone ranging from 20 mg to 40 mg daily for LPS in women undergoing fresh embryo transfers following IVF can be beneficial and probably recommended. (Level A/ Class I).
	Progesterone supplementation, with either oral dydrogesterone or MVP, is beneficial and can be recommended in HRT frozen embryo transfer cycles. (Level A/ class I).
	Oral dydrogesterone should be a preferred choice for LPS in HRT frozen embryo transfer cycles over the vaginal route, due to the higher tolerance, better compliance and negligible side-effects. (Level B/ class I).
ESHRE (2017)[22]	Vaginal progesterone does not improve live birth rates in women with unexplained RPL. (SoR: Conditional, QoE: Moderate). Justification: There is some evidence that oral dydrogesterone initiated when fetal heart action can be confirmed may be effective, but more trials are needed.

ART: Assisted Reproductive Technology; ESHRE: European Society of Human Reproduction and Embryology; HRT: Hormone Replacement Therapy; IUI: Intrauterine Insemination; IVF: In Vitro Fertilization; LPS: Luteal Phase Support; MVP: Micronized Vaginal Progesterone; RPL: Recurrent Pregnancy Loss; SoR: Strength of Recommendation; QoE: Quality of Evidence.

Expert opinion

Dydrogesterone standard protocols: IUI: 10 mg twice a day, IVF: 400 mg twice a day vaginal micronized progesterone+10 mg twice a day dydrogesterone (no injectables favoured). Combination Therapy: Vaginal/progesterone gel (no vaginal tablet) + 10/20 mg per day

Duration of dydrogesterone treatment: For 14 weeks, extended duration up to 20 weeks, if the patient has a history of abortion or up to 32 weeks in cases of premature delivery.

Use in RPL: Dydrogesterone can be used from the day of ovulation for three months in patients with RPL who are planning pregnancy before doing the IUI. In such patients, start progesterone immediately after ovulation as per ESHRE guidelines.

Dosage: Twice a day.

Use of Dydrogesterone SR: Given to reduce the frequency of doses, especially for patients already on many medications. Dosage can be reduced to BD or OD with SR formulation, potentially improving patient compliance.

In vitro fertilization–FET: For LPS in fertility treatments, dydrogesterone (10 mg TDS) is often recommended alongside a multivitamin supplement (400 IU BD) to enhance overall reproductive health. The use of letrozole cycles is commonly preferred due to its effectiveness in stimulating ovulation. Typically, on the day of embryo transfer, serum progesterone levels are expected to be in the range of 20-30 ng/dl, indicating a well-prepared endometrial lining.

IVF treatment: Dydrogesterone 20 mg SR should be used for sustained hormone support. Combination of vaginal progesterone (400 mg, twice daily) and dydrogesterone (10 mg, twice daily) can be used for enhanced LPS. This approach improves endometrial receptivity and hormone balance for successful implantation.

For couples attempting natural conception, whether the woman has PCOS or infertility issues, the following regimen is recommended: From day 15 to day 30 of the menstrual cycle, take dydrogesterone 10 mg twice daily. Perform a urine pregnancy test on the last day of this regimen. Continue this protocol for three to six cycles to optimize the chances of conception.

THREATENED MISCARRIAGE AND RPL

Evidence

Dydrogesterone used for corpus luteal support has been proven to lower the risk of pregnancy loss during the first trimester in women experiencing threatened abortion who do not have a history of recurrent miscarriage.[23] In an analysis of 617 clinical records, 572 patients (92.71%) successfully continued their pregnancies with oral Dydrogesterone, while 45 patients (7.29%) experienced a miscarriage before 20 weeks of gestation. The median time to symptom relief was 3.32 days for low back pain, 3.9 days for abdominal pain, and 4.37 days for achieving haemostasis. The treatment was well-tolerated, with adverse events reported in only 3.72% of patients.[24] A retrospective cohort study showed that progesterone treatment is associated with an increased live birth rate in patients with RPL. After adjusting for maternal age, pregnancy loss ratio, other treatments, antiphospholipid syndrome, and body mass index, dydrogesterone treatment was independently linked to a higher rate of live births compared to the control group (p=0.028).[9]

Expert opinion

Dydrogesterone is a preferred treatment option for threatened miscarriage due to its effectiveness and favourable dosing regimen.

For threatened miscarriage:

Dosage: Initial loading dose of 40 mg followed by 10 mg BD of dydrogesterone is recommended.

Duration: For 14 weeks, extended duration up to 20 weeks, if the patient has a history of abortion or up to 32 weeks in cases of premature delivery and extended usage up to 18–20 weeks in twin pregnancies

Combination therapy: Vaginal/progesterone gel (no vaginal tablet) + 10/20 mg dydrogesterone per day.

For recurrent pregnancy loss:

Dose: The recommended dosage is 10 mg twice daily (BD).

Duration: Monitor the cycle and start dydrogesterone after ovulation, continuing until 16-20 weeks of pregnancy. For patients with a history of preterm labour, extend treatment until 34-36 weeks. In cases of twin pregnancies or a history of abortion, consider extending the duration to 20 weeks.

Dosage in clinical practice: Prescribed loading doses may vary from 20 to 40 mg, with maintenance doses at 10, 20, or 40 mg. Dydrogesterone administration results in substantial relief from symptoms, especially low backache. A 40-mg starting dose often leads to rapid cessation of bleeding (in 30-60 minutes), providing reassurance to patients. Four tablets can be replaced with less tablets of dydrogesterone 20 mg SR to reduce the patient anxiety and improve patient compliance.

POLYCYSTIC OVARY SYNDROME

Evidence

In women with PCOS, progesterone is beneficial during weight loss to regulate the menstrual cycle and protect the

endometrium, aiding in pregnancy preparation and boosting confidence during recovery. The experts recommend dydrogesterone at 10-20 mg/day, which does not inhibit ovulation, administered for 10-14 days during the second half of the menstrual cycle. For luteal support, particularly in natural and ovulation induction pregnancies, oral progesterone preparations are preferred, with dydrogesterone at 20-40 mg/day being the favoured choice.[25] A study comparing DYD and gonadotropin-releasing hormone (GnRH) antagonist protocols for ovarian stimulation in PCOS patients undergoing freeze-all cycles showed similar numbers of mature and fertilized oocytes between the DYD and cetrorelix (CET) groups. Clinical pregnancy rates for the first FET cycle were also comparable (56% for DYD vs. 55.6% for CET, p=0.283). No significant differences were found in biochemical pregnancy rates, implantation rates, miscarriage rates, or ongoing pregnancy rates (p>0.05). Dydrogesterone-primed ovarian stimulation is a viable alternative to the GnRH antagonist protocol for PCOS patients (Table 2).[26]

Table 2: Recommendations for dydrogesterone use in PCOS based on recent guidelines.

Guideline	Recommendation
ASRM (2023)[27]	Progestin only oral contraceptives may be considered for endometrial protection, based on general population guidelines, acknowledging that evidence in women with PCOS is limited. (LoE: very low, GoR: conditional recommendation for the option.

ASRM: American Society for Reproductive Medicine; GoR: Grade of Recommendation; LoE: Level of Evidence; PCOS: Polycystic Ovary Syndrome

Expert opinion

Dydrogesterone can be used for young women with amenorrhea who are planning for pregnancy and are concerned about the risk of pregnancy loss due to withdrawal medications. Dydrogesterone does not disturb ovulation, making it suitable for use starting from day 2 of the cycle.

Dosage: Initiate with 10 mg once daily (OD) from day 2 until ovulation, follow with 10 mg three times a day (TDS) after ovulation.

Dydrogesterone acts synergistically with endogenous progesterone, requiring a baseline level in the body to be effective. Optimal progesterone concentration for dydrogesterone action is around 1.5 mg per 100 ml of blood. On day 2 of menstruation, serum progesterone levels typically range from 0.2 to 0.4 mg per 100 ml of blood. A dosage of 10 mg of dydrogesterone taken twice daily (BD) will not inhibit ovulation. However, higher doses may have an inhibitory effect on ovulation.

Pregnancy planning: Schedule a scan around day 12 to check follicle readiness. Add dydrogesterone in the secretory phase to enhance pregnancy chances and make cycles more predictable.

Contraception: Dydrogesterone 20 mg is a viable option for adolescent women with PCOS who are hesitant to use oral contraceptive pills. It is also effective for hormone replacement therapy (HRT).

PROPHYLAXIS FOR PRETERM BIRTH

Evidence

Progesterone inhibits myometrial contraction by regulating progesterone receptors, interfering with corticotrophin-releasing hormones, and blocking proinflammatory cytokines. In vitro studies found that progestogens, particularly dydrogesterone, inhibit spontaneous myometrial contractility in a dose-dependent manner. A randomized, double-blinded, placebo-controlled trial evaluated the efficacy of oral dydrogesterone as adjunctive therapy for maintenance treatment in preterm labour managed with tocolysis and corticosteroids. While the latency period, gestational age at delivery, rates of preterm delivery before 34 and 37 weeks, pregnancy outcomes, and neonatal outcomes were similar between the dydrogesterone and placebo groups, the time to recurrence of uterine contractions in participants with recurrent preterm labour was significantly longer in the dydrogesterone group (30.6±12.3 vs. 13.7±5.0, p=0.01).[28]

Expert opinion

In cases at risk of preterm birth following IVF, patients often present with spotting around 8-9 weeks. The treatment protocol typically involves dydrogesterone, following the regimen for preterm abortion, which includes loading and continuous doses. A preferred dosage is 20 mg twice daily, supplemented with a weekly progesterone injection.

Limitations of hydroxyprogesterone therapy: In the first trimester, it might lead to anomalies, while in the second trimester, it may cause harm. Additionally, its use cannot be continued up to 32-34-36 weeks due to polystasis. Some patients also report itching as a side effect, in which case, injectables can be considered as an alternative.

PREVENTION OF PRETERM LABOUR

Evidence

Dydrogesterone treatment in women at risk of pre-term delivery has been shown to increase the production of progesterone-induced blocking factor (PIBF) and interleukin-10 (IL-10), while simultaneously reducing levels of interferon-gamma (IFNγ). These changes in immune markers suggest that dydrogesterone could be an

effective strategy for preventing or managing pre-term labour. By enhancing PIBF and IL-10, which are associated with anti-inflammatory and immune-regulatory effects, and reducing IFNγ, a pro-inflammatory cytokine, dydrogesterone helps create a more favourable environment for sustaining pregnancy and reducing the risk of preterm labour.[29]

Expert opinion

For prophylaxis of preterm labour, several strategies are employed to reduce the risk of preterm birth and ensure the well-being of both the mother and the baby.

Prophylaxis of preterm labour often involves the use of injection Proluton Depot once a week for 36 weeks. This approach is also applicable in cases of multiple pregnancy or when there is a risk of preterm labour. Dydrogesterone is frequently prescribed alongside, typically at a dose of 10 mg thrice a day. Natural micronized progesterone is known to have a calming effect. While the recommended dose for this is 40 mg vaginally, experts often prefer 200 mg SR orally daily for 20 weeks in typical cases. Continuation of progesterone therapy at this dose is considered until 36 weeks for patients with a history of preterm labour, previous preterm birth, suspicion of preterm labour, or in cases of twins. Intramuscular administration may be considered if the patient experiences nausea; otherwise, weekly injections of hydroxyprogesterone caproate are used.

HRT

Evidence

Dydrogesterone exhibits superior endometrial efficacy compared to progesterone, making it a favourable option in HRT. It has a neutral impact on vascular and metabolic systems and maintains the beneficial effects of oestradiol. Moreover, dydrogesterone effectively prevents endometrial hyperproliferation, thereby reducing the risk of endometrial hyperplasia. These attributes collectively enhance the safety and efficacy of dydrogesterone in HRT.[30]

Expert opinion

Dydrogesterone is an essential component in HRT preparations due to its strong endometrial efficacy and ability to maintain the benefits of oestradiol without causing endometrial hyperproliferation. Dydrogesterone is cost-effective, making it an accessible option for a wide range of patients. This affordability and its non-disruptive nature regarding ovulation make it particularly preferred for women planning pregnancy.

ADVANTAGES OF DYDROGESTERONE 20 MG SR

In clinical practice, dydrogesterone 20 mg SR offers several advantages that enhance patient compliance and treatment outcomes, as depicted in Figure 1.

A bioequivalence study was conducted with 23 healthy adult female subjects to compare the pharmacokinetic profiles of dydrogesterone formulations. The open-label, randomized, cross-over study evaluated a single 20 mg sustained-release dydrogesterone tablet against the reference formulation of 10 mg dydrogesterone tablets taken twice daily at 12-hour intervals. The objective was to assess the rate and extent of absorption under fasting conditions. The results indicated that the 20 mg sustained-release dydrogesterone tablet is bioequivalent to the twice-daily 10 mg formulation, demonstrating similar pharmacokinetic profiles and absorption characteristics.[31]

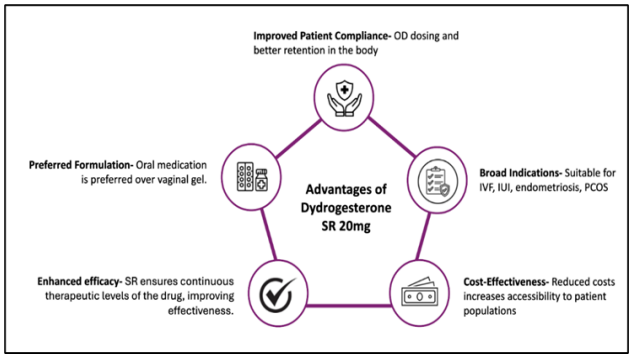

Figure 1: Clinical advantages of dydrogesterone 20 mg SR compared to other synthetic progestogen formulations.

FUTURE PERSPECTIVES

The suggestions for new dydrogesterone SR products focus on enhancing patient accessibility and convenience. Key recommendations include reducing the cost, introducing a combination pack for HRT during FET, developing an extended-release version of oestradiol valerate, and retaining the current tablet size. Additionally, experts suggest creating a gel form of dydrogesterone SR and combining it with other drugs for more effective HRT. These changes aim to make the treatment more affordable, user-friendly, and efficient for patients.

CONCLUSION

Endometriosis is a major cause of infertility, significantly impacting women's reproductive health and quality of life, thereby necessitating effective and comprehensive management strategies. Dydrogesterone has shown efficacy for endometriosis patients, especially those with RPL and progesterone resistance, and is recommended as an alternative to progesterone and a component of HRT. It supports the luteal phase in IVF, IUI, and FET, and reduces the risk of threatened abortion and preterm labour. Additionally, dydrogesterone helps regulate the menstrual cycle and protect the endometrium in PCOS. Dydrogesterone 20 mg sustained-release formulation provides numerous advantages in clinical practice, offering benefits in dosing frequency, safety, and efficacy, potentially improving patient compliance, cost-effectiveness and treatment outcomes. This expert opinion

emphasizes dydrogesterone well-established safety profile and minimal androgenic/estrogenic effects, making it an excellent option for the long-term management of endometriosis and related conditions.

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