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Original Research Article

Real-world evaluation of safety and effectiveness of dydrogesterone 20mg extended release in the management of recurrent early pregnancy loss

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Abstract

Background: Recurrent early pregnancy loss (REPL) is a distressing condition affecting 1% to 5% of couples globally. Progesterone plays a crucial role in maintaining pregnancy, and dydrogesterone, a synthetic progestogen, has emerged as a promising therapeutic option due to its selective action and favorable safety profile. With introduction of extended release (ER) formulations of dydrogesterone 20 mg, real-world data on its effectiveness and safety in REPL is not documented.

Materials and Methods: This was a retrospective, multicentric, observational study conducted from the data obtained of patients with history of REPL treated with dydrogesterone 20 mg ER at the discretion of treating physician. Patient data were collected using standardized Case Report Forms (CRFs), and outcomes included miscarriage incidence, pregnancy continuation, and adverse events. Data were analyzed to evaluate the safety, and effectiveness of dydrogesterone 20 mg ER.

Results: The study included data of 828 patients with history of REPL and treated with dydrogesterone 20 mg ER. The analysis reported an incidence of miscarriage in 64 patients (7.7%), with the majority of patients (92.3%) continuing pregnancy beyond 20 weeks of gestation. Among patients who experienced miscarriage (n=64), the mean gestational age at the time of visit was 6.88 ± 2.12 weeks and at the time of miscarriage was found to be 10.62 ± 3.17 weeks. A total of 77 (9.3%) patients developed adverse events during the treatment period and among them 80% of the adverse events were mild in nature.

Conclusion: Dydrogesterone 20 mg ER is safe and effective in managing REPL, demonstrating a low miscarriage rate and prolonged pregnancy continuation beyond 20 weeks. These findings provide real-world evidence supporting its role as a practical therapeutic option for REPL.

Keywords: Recurrent early pregnancy loss, Dydrogesterone extended release, Progesterone therapy, Pregnancy outcomes, Miscarriage prevention.

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1. Introduction

Recurrent early pregnancy loss (REPL), also known as recurrent pregnancy loss (RPL) is defined as two or more consecutive pregnancy losses before 20 weeks of gestation. It has multifactorial causes, including genetic abnormalities, uterine anomalies, hormonal disorders, and immunological or environmental factors.[1] REPL significantly impacts emotional and psychological well-being, often leading to anxiety and depression.[2] Around 2.6% of pregnancies worldwide are impacted, with most losses occurring during the first trimester. In India, the prevalence is notably higher, estimated at 7.4%, highlighting potential local factors and challenges in identifying definitive causes despite thorough evaluations.[3,4]

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The management of REPL involves a range of strategies tailored to address underlying causes. Globally, hormonal treatments like progesterone supplementation are widely used, especially for luteal phase defects.[5,6] In India, treatment options align with global practices but also consider local healthcare capacities, emphasizing progesterone therapy, surgical correction of uterine anomalies, and managing endocrine disorders to improve pregnancy outcomes.[7] Progesterone plays a crucial role in maintaining early pregnancy by preparing the endometrium for implantation and reducing uterine contractility, thereby supporting the continuation of pregnancy.[8] However, challenges like poor bioavailability, systemic side effects, and variability in patient responses have limited the efficacy of some progesterone formulations.

Dydrogesterone is a synthetic progestogen that has gained prominence in the management of REPL. It was developed as a synthetic alternative to natural progesterone, aiming to provide similar therapeutic benefits without the side effects associated with progestogens.[9] Dydrogesterone exerts its effects through selective binding to progesterone receptors (PR-A and PR-B) in the uterus, closely mimicking the action of natural progesterone. This selectivity minimizes interference with other hormonal pathways, thereby reducing the risk of side effects commonly associated with non-specific receptor activity. By promoting decidualization of the endometrium, dydrogesterone transforms the uterine lining into a receptive state for embryo implantation, ensuring optimal conditions for early pregnancy. Additionally, dydrogesterone supports pregnancy maintenance by stabilizing the uterine lining during the luteal phase, preventing premature shedding, and fostering a favorable environment for embryo development.[10] Unlike other progestogens, dydrogesterone is devoid of androgenic or estrogenic effects, making it a safer and more tolerable option for managing recurrent early pregnancy loss.[11]

Dydrogesterone, with its selective action on progesterone receptors, oral bioavailability, and minimal androgenic or estrogenic activity, offers a promising option for improving pregnancy outcomes in women with REPL.[12] However, real-world data on its safety and effectiveness in diverse populations are limited, particularly in countries like India, where the prevalence of REPL is relatively high. This study evaluates the safety and effectiveness of dydrogesterone 20 mg ER in managing REPL in a real-world, multicentric setting.

2. Materials and Methods

2.1. Study design

This is a retrospective, multicentric, observational study, conducted across multiple healthcare centres in India. The study included data collected from the patients with history of REPL and treated with dydrogesterone 20 mg ER for its prevention between the period of November 2023 to September 2024.

2.2. Study population

The study population comprised of female patients aged between 18 and 40 years with a history of two to three prior recurrent miscarriages occurring before 20 weeks of gestation. The data were collected from patients who were treated with ddrogesterone 20 mg ER, at the discretion of the treating physician. The data of patients with anatomical abnormalities or any known conditions that could contraindicate pregnancy or having contraindications to dydrogesterone were excluded from this analysis. The case record forms (CRFs) of all eligible patients were reviewed and analyzed to assess the safety and effectiveness of dydrogesterone 20 mg ER in managing recurrent early pregnancy loss.

2.3. Study objectives

The primary objective of this study was to evaluate the safety of dydrogesterone 20 mg ER in the management of REPL. The secondary objective was to determine the effectiveness of Dydrogesterone 20 mg ER. Treatment success was considered as continuation of pregnancy beyond 20 weeks.

2.4. Data collection and statistical analysis

Data for this retrospective study were collected from patient medical records across multiple participating centres. Patients with a history of REPL who were prescribed dydrogesterone 20 mg ER as per the discretion of the treating physician and met the inclusion criteria were included. Standardized CRFs were used to retrieve the anonymised baseline characteristics, including age, height, weight, gestational age, and obstetric history, along with details of dydrogesterone therapy, such as dosage and duration. Safety outcomes were assessed based on the incidence, type, severity, and resolution of adverse events recorded in clinical notes.

Continuous variables, such as age, weight, and gestational age, were expressed as mean ± standard deviation (SD), while categorical variables, such as adverse events and pregnancy outcomes, were presented as frequencies and percentages.

2.5. Procedure

The CRFs captured details such as baseline demographics and clinical information after the inclusion criteria were met. Patients aged between 18 and 40 years with a history of recurrent early pregnancy loss (REPL), having no anatomical abnormalities, and eligible to receive dydrogesterone 20 mg ER were considered for the study. The patients' previous obstetric history was noted, and details of dydrogesterone prescription, including dosage (once daily [OD], twice daily [BD], or three times daily [TID]), were recorded.

Safety assessments were based on documented records of any adverse events that had occurred during the treatment period. Adverse events were categorized according to their type, severity, and resolution status.

2.6. Ethical considerations

The study received Ethics Committee (EC) approval from Central Independent Ethics Committee, Pune, Maharashtra. Patient confidentiality was maintained by using only de-identified data to ensure compliance with ethical standards and privacy regulations.

3. Results

3.1. Baseline demographic parameters

The study included data of 828 patients from 166 healthcare centers across India. The mean age of the patients was 29.8 ± 4.52 years. The mean gestational age at the time of initiation of dydrogesterone 20 mg ER was 7.17 ± 1.7 weeks, and the mean number of previous pregnancy losses was 2.37 ± 0.97 (**Table 1**).

Table 1: Demographic analysis of patients

Variable	Mean ± SD (N=828)
Age (years)	29.8 ± 4.52
Height (cm)	156 ± 7.76
Weight (kg)	59.1 ± 10.5
Gestational Age (weeks)	7.17 ± 1.7
Previous recurrent miscarriages	2.37 ± 0.97

3.2. Dydrogesterone dosing and concomitant medications

The majority of patients (86.1%) were prescribed dydrogesterone 20 mg ER once daily (OD), while 12.8% received it twice daily (BD), and a small proportion (1.1%) were on a thrice daily (TID) regimen.

A significant proportion of patients received concomitant medications alongside dydrogesterone 20 mg ER to support pregnancy maintenance. The most commonly prescribed category was vitamin, mineral, and nutritional support (84.3%), followed by progesterone support therapies (22.1%). These included micronized progesterone (oral/sustained release), vaginal progesterone, hydroxyprogesterone injections, aqueous progesterone injections, progesterone tablets, gels, and natural micronized progesterone. Antithrombotic agents were used in 21.0% of patients, while other commonly prescribed medications included antiemetics and gastrointestinal agents (10.0%), hCG injections (4.5%), thyroid supplements (1.3%), and other supportive therapies (1.8%) (**Table 2**).

Table 2: Medications received concurrently with dydrogesterone 20 mg ER

Concomitant Medication Category	Frequency (n)	Percentage (%)
Vitamin, Mineral, and Nutritional Support	698	84.3%
Progesterone Support (Total)	183	22.1%
Micronized Progesterone (oral/SR)	70	8.45%
Vaginal Progesterone	24	2.90%
Hydroxyprogesterone Injection	29	3.50%
Aqueous Progesterone Injection	7	0.85%
Progesterone Tablets	24	2.90%
Progesterone Gel	2	0.24%
17-Hydroxyprogesterone	1	0.12%
Natural Micronized Progesterone (unspecified route)	4	0.48%
Antithrombotics	174	21.0%
Antiemetics and Gastrointestinal Agents	83	10.0%
hCG Injections	37	4.5%
Thyroid Supplements	11	1.3%
Other	15	1.8%

The occurrence of miscarriage with dydrogesterone 20 mg ER treatment was reported in 64 patients (7.7%), with the remaining 764 (92.3%) patients continuing pregnancy beyond 20 weeks (**Table 3**). Among the patients who experienced miscarriage, 84.4% (n=54) were on a once-daily (OD) dosing regimen and 15.6% (n=10) were on a twice-daily (BD) regimen. The mean gestational age at baseline and at the time of occurrence of miscarriage were 6.88 ± 2.12 weeks and 10.62 ± 3.17 weeks, respectively among the 64 patients who experienced miscarriage.

Table 3: Incidence of miscarriage before 20 weeks of gestation

Miscarriage before 20 weeks of gestation	Frequency (n)	Percentage (%)
Yes	64	7.7%
No	764	92.3%

3.3. Adverse events and safety profile

The adverse events were reported in 77 (9.3%) women of the total patients included in the study. The majority of adverse events were mild noted in 68 (80%) patients, while moderate and severe events were seen in 16 (18.9%) and 1(1.1%) patient, respectively. The most common adverse event noted was nausea, reported by nearly half of the affected patients, followed by headache, acidity, and vomiting (**Figure 1**). Importantly, nearly all adverse events (92.94%) resolved completely with 5.88% being partially resolved.

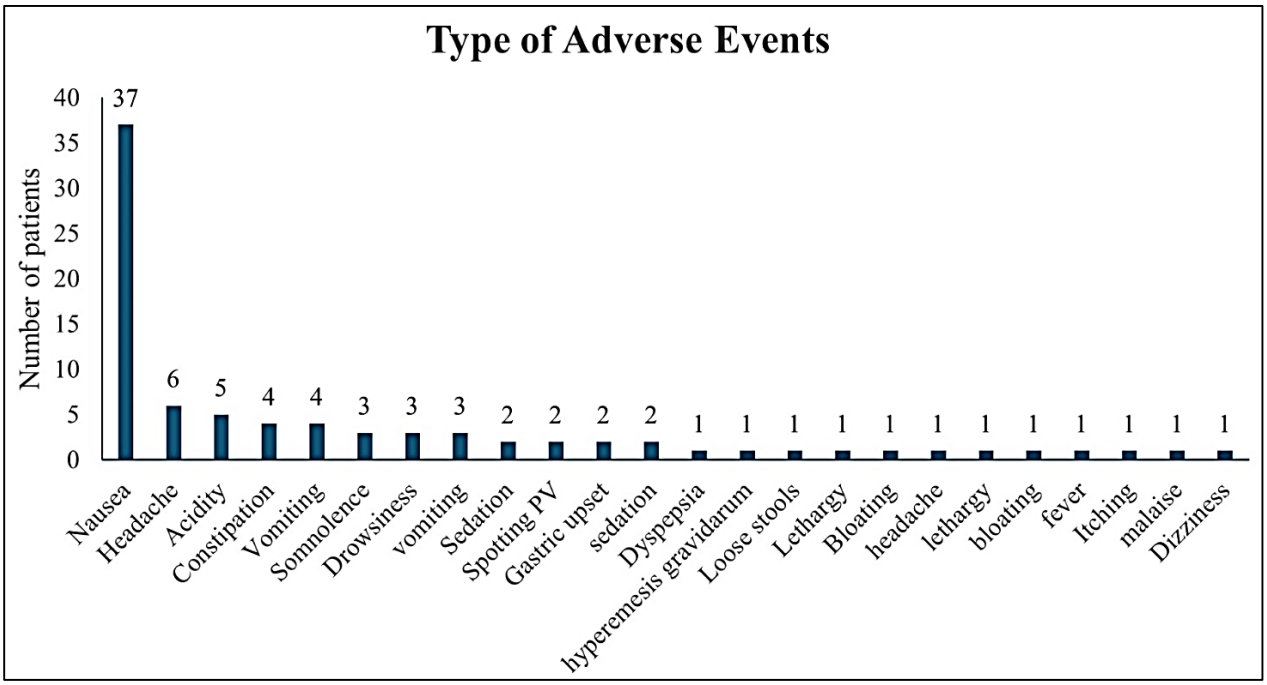

Figure 1: Distribution of reported adverse events

4. Discussion

Dydrogesterone 20mg ER has demonstrated a favorable safety profile over its extensive clinical use, with adverse events being predominantly mild and transient. This study demonstrated the effectiveness of dydrogesterone 20 mg ER in managing REPL, with a fewer incidence of miscarriage reported among the patient population.

The findings of this study align with the study of Mirza et al., were they reported that dydrogesterone treatment significantly increased the odds of continuing pregnancy beyond 20 weeks compared to standard care or placebo, with a reduction in miscarriage rates ranging from 12.5% to 28.4% in comparator groups.[13] In the randomized controlled study of El-Zibdeh et al., the abortion rate in the dydrogesterone group was 13.4%, markedly lower than the control group where it was 29%.[14] El-Zibdeh et al. also highlighted dydrogesterone's ability to sustain viable pregnancies, reporting an 87% viable pregnancy rate in their study. The findings of this study align with the results of Bashiri et al., which demonstrated an increased live birth rate among women with REPL treated with dydrogesterone.[15] In their retrospective cohort study, dydrogesterone treatment was independently associated with a higher live birth rate, as indicated by an adjusted odds ratio (OR) of 1.592 (95% CI: 1.051–2.413; p = 0.028). Bashiri et al. further noted that dydrogesterone's immunomodulatory effects and improved bioavailability might contribute to its positive impact on pregnancy outcomes.[16]

Dydrogesterone has demonstrated a favorable safety profile over its extensive clinical use, with adverse events (AEs) being predominantly mild and transient. Commonly reported AEs such as headache, dizziness, nausea, bloating, and abdominal pain are consistent with findings from previous studies, such as Ott et al. which attributed these effects to dydrogesterone's pharmacokinetics and receptor selectivity.[17] These AEs are likely due to dydrogesterone's role in modulating progesterone receptors, leading to physiological responses that mimic endogenous progesterone activity.[18] In our study, 9.3% of patients reported AEs, with nausea being the most frequent (48.05%). This is consistent with Ott et al.'s review, where nausea was highlighted as one of the most common AEs during dydrogesterone treatment. Other AEs, such as headache (7.79%) and sedation (2.6%), were also observed.

These results provide valuable real-world evidence supporting dydrogesterone 20 mg ER as a practical and effective therapeutic option for improving pregnancy outcomes in women with a history of recurrent miscarriages. The extended-release formulation could have an enhanced compliance due to the advantage of reduced frequency of drug administration. The study demonstrated a low incidence of miscarriage and prolonged the pregnancy duration beyond 20 weeks. However, the retrospective nature of the study and reliance on existing clinical records may introduce biases, and the absence of a control group limits direct comparisons with other treatments. Additionally, the study does not address long-term maternal and neonatal outcomes, emphasizing the need for future prospective research to validate these findings and further explore the broader implications of dydrogesterone use. Investigational findings related to the cause of miscarriage (e.g., sonographic or pathological findings) were not consistently available in patient records and could not be analyzed, limiting the ability to draw conclusions on miscarriage etiology in this cohort.

5. Conclusion

Dydrogesterone 20 mg ER demonstrates effectiveness and safety in managing REPL, with a low incidence of miscarriage. This real-world study supports its role as a practical therapeutic option, offering significant benefits for women with recurrent miscarriages. While promising, further prospective research is necessary to validate these findings and explore long-term outcomes for maternal and neonatal health.

6. Source of Funding

None.

7. Conflict of Interest

Dr. Ashok Jaiswal and Dr. Bhavya Shetty are employees of Zydus Healthcare Limited.

8. Authors' Contribution

All authors contributed substantially to the study conception and design, supervised data collection, and supported the manuscript drafting and revision. All authors reviewed and approved the final manuscript and agree to be accountable for the work.

9. Data Availability Statement

None.

10. Ethical Committee Approval

The study received Ethics Committee (EC) approval from Central Independent Ethics Committee, Pune, Maharashtra. Patient confidentiality was maintained by using only de-identified data to ensure compliance with ethical standards and privacy regulations. (CIEC/2025/03)

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NA.

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