International Journal of Reproduction, Contraception, Obstetrics and Gynecology
Nagarkatti R et al. Int J Reprod Contracept Obstet Gynecol. 2022 Aug;11(8):2096-2100
www.ijrcog.org
pISSN 2320-1770 | eISSN 2320-1789

DOI: https://dx.doi.org/10.18203/2320-1770.ijrcog20221833

Original Research Article

Real-world evaluation of safety and effectiveness of dydrogesterone in the management of threatened abortion

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Received: 24 June 2022
Accepted: 14 July 2022

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ABSTRACT

Background: Threatened abortion is a relatively common complication during pregnancy. Inadequate production of endogenous progesterone is implicated as a risk factor for miscarriages. Thus, supplementation of external progesterone can be used as a preventive strategy in these women. Dydrogesterone a stereoisomer of progesterone has a good safety and tolerability profile and is known to effectively prevent pregnancy loss in women with threatened miscarriage, however, real-world data safety and effectiveness analysis of dydrogesterone in Indian patients was lacking. Therefore, this real-world retrospective analysis of the case reports was done to evaluate the safety, effectiveness, compliance, and tolerability of oral dydrogesterone in the treatment of women with threatened abortion.
Methods: Data was collected from 194 obstetricians and gynaecologists in India, on the use of oral dydrogesterone in women presenting with threatened abortion in the first trimester of pregnancy.
Results: Completed case report forms of patients who met the eligibility criteria (n = 617) were considered for the analysis. The main presenting symptom was vaginal bleeding/spotting with an additional symptom of abdominal cramp/pelvic pain/low back pain in 364 (69.07%) patients. Miscarriage was reported in 45 (7.29%) patients and 23 (3.98%) patients needed surgical intervention before 20 weeks of gestation with dydrogesterone treatment. The median time for relief of symptoms from the start of dydrogesterone tablets was 3.32 days for low back pain, 3.9 days for abdominal pain, and 4.37 days for the establishment of hemostasis. Treatment with dydrogesterone was found to be well-tolerated and adverse events were reported in 3.72% of the patients.
Conclusions: This retrospective analysis suggests that dydrogesterone is safe and effective in reducing the incidence of pregnancy loss in women with threatened abortion.

Keywords: Dydrogesterone, Synthetic Progestogen, Early Pregnancy, Vaginal Bleeding, Vaginal Spotting, Threatened Miscarriage

INTRODUCTION

A threatened abortion is defined as vaginal bleeding before 20 weeks gestational age in the setting of positive urine and/or blood pregnancy test with a closed cervical OS, without passage of products of conception, and without evidence of fetal or embryonic demise.[1] It is a relatively common complication during pregnancy, occurring in about 20% of all pregnancies.[3,4] Vaginal bleeding during the first trimester is associated with a 5.5%-42.7% risk for subsequent complete miscarriage.[3] The risk of miscarriage before 20 weeks of gestation is 8.9% in women aged 20-30 years, which increases to almost 74.7% in women > 40 years of age. The risk of miscarriage in a future pregnancy is about 20% after 1 miscarriage, 28% after 2 consecutive miscarriages, and 43% after ≥ 3 consecutive miscarriages.[5]

Maternal comorbidities (thrombophilia, antiphospholipid antibody syndrome, hypertension), cigarette smoking, excessive use of caffeine, trauma, and malnutrition increase the risk of miscarriage.[5] Inadequate production of endogenous progesterone is also implicated as a cause that supports the use of progesterone supplementation as a preventive strategy.[6] Progesterone in early pregnancy is responsible for preparing the endometrium for implantation and maintenance of the gestational sac in the uterus.[7] Progesterone has an important role in the maintenance of pregnancy and has been prescribed by clinicians worldwide to reduce the risk of pregnancy failure, particularly first trimester.[2]

Dydrogesterone is a stereoisomer of progesterone, where the hydrogen atom at carbon 9 is in the β position and the methyl group at carbon 10 is in the α position, the reverse of the progesterone structure (hence denoted "retro" progesterone). There is also an additional double bond between carbon 6 and 7 whereby the flat steroid configuration is modified, creating a "bent" conformation with enhanced rigidity compared to progesterone which causes to have high selectivity for progesterone receptors with potent progestogenic activity but no or negligible agonistic activity at androgen, glucocorticoid, and mineralocorticoid receptors. Dydrogesterone has higher oral bioavailability compared to progesterone, lesser side effects due to its activity and high specificity for progesterone receptors, and efficacy at a relatively low dose.[8] Dydrogesterone is highly selective for the progesterone receptor, lacks estrogenic, androgenic, anabolic, and corticoid properties with no significant side effects, no masculinization of the female fetus, and congenital abnormalities.[7]

Evidence of benefit with dydrogesterone is particularly strong for the prevention of miscarriage in women experiencing threatened abortion.[6] The aim of this real-world retrospective analysis of the case reports was to evaluate the safety, effectiveness, compliance, and tolerability of oral dydrogesterone in the treatment of women with threatened abortion during their first trimester of pregnancy.

Aims and objectives

This retrospective study was performed to assess the real-world safety, effectiveness, compliance, and tolerability of oral dydrogesterone in the management of threatened abortion. The aims and the objectives were to evaluate: safety of dydrogesterone based on adverse events reported in the CRFs. Effectiveness in terms of miscarriage before 20 weeks of gestation. Effectiveness in terms of miscarriage and surgical intervention before 20 weeks of gestation, median time for relief of symptoms from the start of dydrogesterone treatment, tolerability and patient's compliance. Tolerability and patient compliance.

METHODS

This was a retrospective analysis of data collected from the case report forms (CRFs) from 194 obstetricians and gynaecologists across India between September 2021 and December 2021. Data related to women presenting with threatened abortion and managed with oral dydrogesterone were evaluated.

Data eligibility criteria

The selection of CRFs was assessed based on the below-mentioned criteria: women aged 18-40 years, gestational age between 6-12 weeks at presentation, symptoms of threatened abortion (vaginal bleeding/spotting with or without pelvic pain) at presentation, ultrasound proof of viable singleton intrauterine pregnancy (positive fetal heartbeat) at presentation, no history of recurrent miscarriage, and absence of fever at presentation. Eligible to take dydrogesterone treatment according to prescribing information and at the discretion of the treating physician.

Data collection and analysis

The CRFs were collected from September 2021 to December 2021. These forms were analyzed for various parameters including miscarriage and the requirement of surgical intervention before 20 weeks of gestation, time for relief of symptoms, compliance, and tolerability, and any adverse event. Data on demographics and vital signs were also obtained. Out of 2912 CRFs received, 1733 record forms met the data eligibility criteria. However, of these 1733 CRFs, in 1116 forms, the data were incomplete and hence were excluded from the final analysis. Therefore, the data of 617 CRFs of patients with threatened abortion were analyzed.

Statistical analysis

The parameters were summarized by suitable descriptive statistics such as mean and standard deviation or frequency and percentage. The outcomes of interest were associated with different demographic variables by the chi-square test of independence. The statistical software R version 4.1.0 (R Core Team, 2021, Vienna, Austria) was used to analyze the data.

RESULTS

Data from 617 CRFs of women diagnosed with threatened abortion presenting with vaginal bleeding/spotting were evaluated. From the available CRF data, 69.07% of patients presented with an additional symptom of abdominal cramp/pelvic pain/low back pain. The mean age of the patients (n=616) included was 27.61±4.28 years and the other baseline clinical characteristics are summarized in Table 1.

The dose of dydrogesterone used was varied across the patients. The standard loading dose used was 20-40 mg, followed by a maintenance of 10 mg/BID in the majority of the patients (Table 2).

Table 1: Patient characteristics and main complaints at presentation.

Variables (No. of participants)	Categories	N (%)
Age (n = 616) [Mean, 27.61±4.28 years]	<25 years	130 (21.1)
	25-30 years	367 (59.58)
	>30 years	119 (19.32)
Body Mass Index (BMI) (n=511)	Underweight	26 (5.09)
	Normal	325 (63.6)
	Overweight	128 (25.05)
	Obese	32 (6.26)
Gestation age at presentation (n=561)	<7 weeks	104 (18.54)
	7-8 weeks	324 (57.75)
	9-10 weeks	110 (19.61)
	>10 weeks	23 (4.1)
Gravidity (n=534)	<2	204 (38.2)
	≥2	330 (61.8)
Medical history		
Severity of vaginal bleeding (n=483)	Mild	295 (61.08)
	Moderate	161 (33.33)
	Severe	27 (5.59)
Abdominal cramp/pelvic pain/low back pain (n=527)	No	163 (30.93)
	Yes	364 (69.07)

BMI: Underweight, <18.5 kg/m^2; Normal range, 18.5-22.9 kg/m^2; Overweight, 23-24.9 kg/m^2; Obese, ≥25 kg/m^2.[14]

Table 2: Loading and maintenance dose of dydrogesterone.

Variable	Dose	N	Percentage
Loading dose (n=617)	20 mg	261	42.30
	30 mg	79	12.80
	40 mg	277	44.89
Maintenance dose (n=617)	10 mg/BID	393	63.70
	10 mg/TID	149	24.15
	20 mg/BID	50	8.10
	10 mg/OD	25	4.05

OD, once daily; BID, twice daily; TID, thrice daily.

Safety and tolerability

Of the 617 CRFs that were analyzed, adverse events were reported in 23 patients (3.72%) treated with dydrogesterone. The most common adverse events reported were bloating in 9 patients (1.4%), nausea in 4 patients (0.6 %), constipation in 4 patients (0.6 %), and giddiness in 2 patients (0.3%).

The tolerability of dydrogesterone was rated by the physicians as excellent and good on the global assessment of tolerability scale in 99% of the patients.

Effectiveness of dydrogesterone

Rate of miscarriage

The analysis of 617 CRFs, showed that 572 (92.71%) patients successfully continued their pregnancy with oral dydrogesterone, and 45 (7.29%) patients had a miscarriage before 20 weeks of gestation (Figure 1).

Surgical intervention

The 578 CRFs which had information regarding surgical intervention, showed that 23 (3.98%) patients required

intervention before 20 weeks of gestation. Out of these 23 patients, 18 patients had a miscarriage before 20 weeks of gestation (Figure 2).

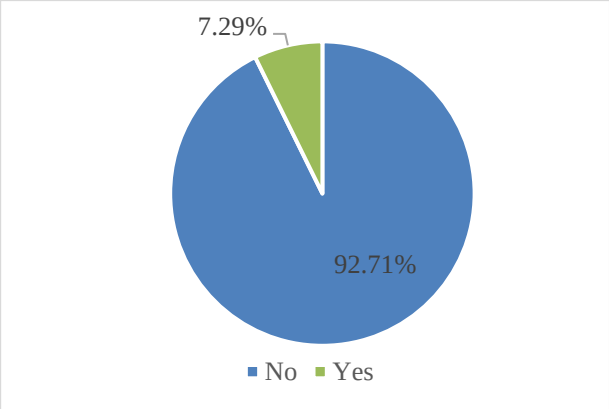

Figure 1: Miscarriage before 20 weeks of gestation.

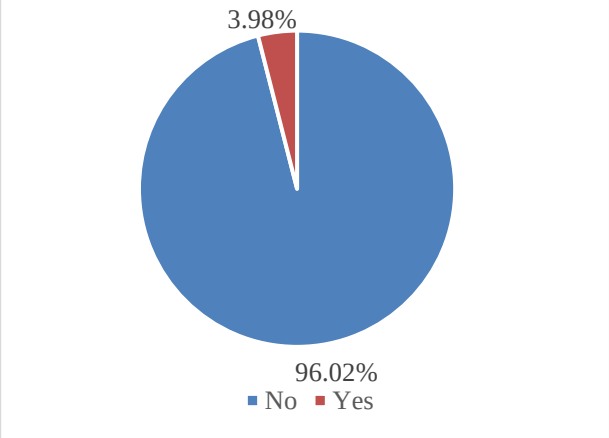

Figure 2: Surgical intervention before 20 weeks of gestation.

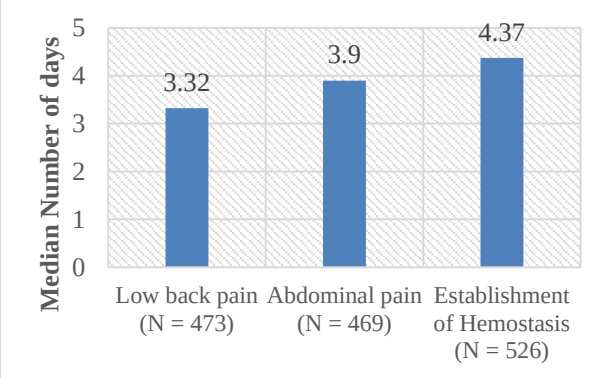

Figure 3: Median number of days for symptom improvement post-initiation of dydrogesterone.

Improvement in symptoms

The median time (from the start of dydrogesterone tablets) for relief of symptoms was 3.32 days for low back pain, 3.9 days for abdominal pain, and 4.37 days for the establishment of hemostasis (Figure 3).

Compliance to treatment with dydrogesterone

Drug compliance of >80% was seen in 455 (88.35%) of the patients treated with dydrogesterone.

DISCUSSION

Threatened abortion may complicate the pregnancy cases which may further progress to spontaneous incomplete or complete abortion. Thus, it makes it crucial to understand the aetiology or the underlying cause leading to the same. For most cases, the aetiology is unknown, however, some may be related to endocrine disorders. The clinical evidence suggests that the endocrine disorders may be responsible for miscarriages, specifically emphasizing the role of progesterone which is required in the maintenance of pregnancy. Though the role of progesterone in the early pregnancy is still debatable, however, therapeutic possibilities can be stated from the hormonal profile of the women with recurrent miscarriages when there is no obvious non-hormonal aetiology. Specifically, with the luteal phase defect commonly seen in the above-mentioned patient profile, a large number of studies have been undertaken to establish the role of progesterone in patients with threatened abortion.[2]

Dydrogesterone, an analog of the progestogen is very similar to endogenous progesterone in terms of its structure, function, and biological characteristics and has been widely used in the treatment of threatened miscarriage with promising outcomes.[9] Studies like Kumar et al. reported a significant decrease in the number of miscarriages after recurrent abortions and an increase in the mean gestational age at delivery with dydrogesterone (20 mg/day) from confirmation of pregnancy to 20 weeks of gestation.[10] Another trial conducted on women presenting with mild-to-moderate vaginal bleeding during the first trimester of pregnancy showed that the incidence of miscarriage with 10 mg oral dydrogesterone twice daily was found to be lower compared to no treatment, 17.5% vs. 25% respectively (p<0.05).[11] Even in a prospective, open, randomized study, when compared to conservative treatment, dydrogesterone was found to be more effective in preventing miscarriage in women with vaginal bleeding up to 16 weeks of pregnancy. The success rate of treatment with dydrogesterone was higher compared to conservative management, 87.5% vs. 71.6% respectively (p<0.05), and the rate of miscarriage was lesser with dydrogesterone compared to conservative management, 12.5% vs. 28.4% respectively (p<0.05).[12] Omar et al. also compared dydrogesterone to conservative treatment and it showed that the rate of continuing pregnancy beyond 20 weeks was significantly higher in the women treated with dydrogesterone vs. conservative treatment, 95.9% vs. 86.3% respectively (odds ratio [OR] of treatment success was 3.773, 95% confidence interval [CI], 1.009-14.108; p=0.037).[2] Additionally, a systematic review of 5

randomized trials (n=660 women) reported the rate of miscarriage after administration of dydrogesterone to be 13% vs 24% in the control group who received standard care (bed rest, vitamin supplementation, and placebo and/or bed rest) with an absolute reduction in the miscarriage rate of 11%. Administration of dydrogesterone was associated with a 47% reduction in the odds of miscarriage compared to standard of care which was indicative of real treatment effect.[13]

Though the above-mentioned results of the clinical evidence prove dydrogesterone to be safe and efficacious in women with threatened abortion, however, a real-world safety and effectiveness analysis of dydrogesterone in Indian patients was lacking. As a result, this retrospective analysis was conducted, which showed similar miscarriage trends when compared to previously completed control clinical studies.[2,10-13] The result of our study showed that dydrogesterone, administered to women with threatened abortion before 20 weeks of gestation but without a history of recurrent miscarriage, is beneficial in the maintenance of pregnancy and it was observed that 572 (92.71%) women successfully continued with their pregnancy with oral dydrogesterone. Thus, it demonstrates that in a real-world setting, this molecule is safe, effective, and well-tolerated in patients with threatened abortion.

Strengths and limitations

The strength of the present study is that it included participants from different centers spanning across various states of India. Therefore, the findings may present an overall view of the dydrogesterone treatment response in Indian women. However, the limitation of the study was that it involved retrospective data collection, hence the data variables were not available from the entire sample size.

CONCLUSION

To the best of our knowledge, this is the first real-world retrospective study on dydrogesterone in Indian women with threatened abortion. Our findings suggest that treatment with dydrogesterone appears to be safe, effective, and well-tolerated in real-world clinical practice.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: Not required

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Cite this article as: Nagarkatti R, Mehra D, Mandal S, Dhawan A, Joshi P, Nagarkatti N, et al. Real-world evaluation of safety and effectiveness of dydrogesterone in the management of threatened abortion. Int J Reprod Contracept Obstet Gynecol 2022;11:2096-100.