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KEY PRACTICE POINTS 2024
INDIAN PERSPECTIVE

# Improving live birth rates in recurrent pregnancy loss: Taking a step ahead in managing RPL

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# IMPROVING LIVE BIRTH RATES IN RECURRENT PREGNANCY LOSS: TAKING A STEP AHEAD IN MANAGING RPL

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## Background

The International Federation of Gynecology and Obstetrics (FIGO), the European Society of Human Reproduction and Embryology (ESHRE) guidelines, and the American Society of Reproductive Medicine (ASRM) defined recurrent pregnancy loss (RPL) as the loss of two or more clinical pregnancies.[1-3] The term encompasses pregnancy loss/losses occurring from the time of conception to the 20th week of gestation. It excludes cases of implantation failure, and ectopic and molar pregnancies, focusing solely on clinically recognized pregnancies.[1]

Approximately 5% of the women suffer from RPL. According to ESHRE guidelines, the assessment for women experiencing RPL including investigations on age, fertility/sub-fertility, pregnancy history, family history, previous investigations and/or treatments, acquired thrombophilia, uterine abnormalities, and thyroid factors.[1] The ASRM guideline also recommends screening for genetic factors, antiphospholipid syndrome, and lifestyle variables.[3] However, around 50% of cases of RPL remain unexplained if the product of conception is not subjected to karyotyping.[4] The management of RPL is multifactorial and should include lifestyle modification, and psychological support.[5] The treatment options include anticoagulation, immunological, surgical, and progesterone therapy. However, research suggests that treatment with progestin such as dydrogesterone is one of the interventions that is effective in improving the live birth rate in unexplained RPL.[6,7]

## Objective

This consensus meeting aims to formulate validated key practice points for developing RPL treatment approach.

## Methodology

The task force comprised of 9 experts in the field of Obstetrics and Gynaecology formed. The task force reviewed the existing literature and developed the consensus statement based on published literature, their individual clinical experience, and focused discussion within the task force. The task force members followed a well-defined grading system (Table 1) for the critical appraisal of evidence and grading strength of consensus statements. The consensus statements developed by the task force were presented to a larger group consisting of 39 experts in the field of Obstetrics and Gynecology. There was deliberation on each consensus point and later accepted, modified, or deleted. Thus, this document provides much-required insights and useful, practical, and accurate feasible guidance that aids a practicing clinician across the country.

**Table 1.** Level of evidence and grading strength of recommendations

| Grades of recommendation | Level of evidence | Type of Study |
|---|---|---|
| A | 1a | Systematic review of (homogenous) randomized controlled trials |
| A | 1b | Individual randomized controlled trials (with narrow confidence intervals) |
| B | 2a | Systematic review of (homogenous) cohort studies of "exposed" and "unexposed" subjects |
| B | 2b | Individual cohort study/low-quality randomized control studies |
| B | 3a | Systematic review of (homogenous) case-control studies |
| B | 3b | Individual case-control studies |
| C | 4 | Case series, low-quality cohort, or case-control studies |
| D | 5 | Expert opinions based on non-systematic reviews of results or mechanistic studies |

## Vaginal bleeding in early pregnancy

Vaginal bleeding is frequent in the first trimester of pregnancy. It is often considered as an indication of a potential pregnancy issue.[8] Bleeding has been related to spontaneous blood loss before 24 weeks of gestation and has been considered an independent risk factor for adverse obstetric outcomes.[9]

### Diagnostic evidence

A community-based pregnancy cohort study evaluated the strength of the association between first-trimester bleeding and miscarriage. The research included 1,204 women with first-trimester vaginal bleeding or spotting. The relative odds of miscarriage for women with bleeding was 1.1 (95% confidence interval [CI] 0.9–1.3). In women with heavy bleeding, the risk of miscarriage was nearly three times compared to women without bleeding during the first trimester (odds ratio [OR] 3.0, 95% CI 1.9–4.6).[8]

In another cohort study of 701 women, clinical pregnancy loss occurred in 7.1% of patients who experienced vaginal bleeding in 2 to <4 weeks of gestation. In women who experienced vaginal bleeding in their 4 to <6 and 6 to 8 weeks of gestation, the rate of clinical pregnancy loss was 18.6% and 32.4%, respectively. Therefore, bleeding was considered a risk factor for clinical pregnancy loss.[10]

A population-based study conducted by Sapra et al., evaluated the relationship between early pregnancy loss in women experiencing vaginal bleeding (n=341). The research revealed that the cumulative incidence of pregnancy loss was 52%. The incidence of pregnancy loss was increased among women with vaginal bleeding (hazard ratios (HR): 3.62, 95% CI: 2.29-5.74). Vaginal bleeding was associated with an increased risk of pregnancy loss.[11]

### PRACTICE POINT

**For clinical diagnosis of pregnancy loss associated with vaginal bleeding**

Vaginal bleeding before 24 weeks of gestation is considered as a risk factor for pregnancy loss (Grade B/Level 2a).

## Use of dydrogesterone in women with vaginal bleeding and RPL

Dydrogesterone is a stereoisomer of progesterone, designed to produce progesterone-like effects while overcoming the rapid metabolism and poor bioavailability issues associated with oral progesterone.[12,13,14] The modified structural configuration accounts for its high specificity to the progesterone receptor with potent progestogenic activity.[13] Compared to oral micronized progesterone, dydrogesterone is required in lower doses, which may minimize side effects such as drowsiness and liver toxicity.[14] Unlike progesterone, dydrogesterone has no detectable affinity for nuclear androgen, estrogen, glucocorticoid, or mineralocorticoid receptors thereby minimizing the activation of other steroid hormone receptors and unwanted side-effects.[13,14] When compared to vaginal progesterone, oral dydrogesterone is easier to use and has better compliance.[15]

Progesterone significantly contributes to the successful process of implantation and the development of pregnancy, inadequate progesterone levels, are presumed to be linked to vaginal bleeding and spontaneous pregnancy loss.[16,17] Approximately 50% of patients who experience vaginal bleeding in the first trimester will eventually undergo a miscarriage. Therefore, treatment that increases progesterone levels is frequently recommended for preventing miscarriage in women who experience any degree of vaginal bleeding in the early stages of pregnancy.[18]

Research has shown that dydrogesterone is safe, well tolerated, and has beneficial effects for managing vaginal bleeding, increasing the rate of live births, and lowering the incidence of RPL.

### Efficacy evidence: Management of vaginal bleeding in pregnant women

A comparative randomized clinical trial included 200 pregnant women with up to 12 weeks of gestation, a history of more than two early pregnancy losses, and vaginal bleeding. The patients received either 30 mg/day oral dydrogesterone (n=100) or 600 mg/day vaginal progesterone (n=100). The time ± SD required for complete cessation of bleeding was significantly lower in the dydrogesterone group compared to patients in the progesterone group (53.90 vs. 94.60±7.29 hours, p<0.0001). More number of patients in the dydrogesterone group successfully continued their pregnancies up to 24 weeks and full-term compared to the patients in the progesterone group (70 vs. 75). The research from the study suggested that dydrogesterone is preferred over progesterone in patients with vaginal bleeding and a history of early RPL.[18]

A piloted prospective observational study evaluated the clinical effectiveness of oral dydrogesterone 30 mg once daily (n=50) and vaginal progesterone 600 mg once daily (n=50) for the cessation of vaginal bleeding in 100 pregnant women. The results from the study revealed that the time required for complete stoppage of bleeding was significantly lower in the dydrogesterone group compared to the vaginal progesterone group (53.91 vs. 94.57 hours, p=0.001).[17]

## PRACTICE POINTS

### For progestin therapy in miscarriage management

- Dydrogesterone treatment is initiated at a loading dose of 40 mg and continued at 30 mg/day until symptoms subside (Grade A/ Level 1b).
- Micronized vaginal progesterone at 600 mg/day can be used when there is no bleeding (Grade A/ Level 1b).
- Dydrogesterone is preferable in patients who are experiencing vaginal bleeding (Grade A/ Level 1b)

### Efficacy evidence: Lowering the incidence of RPL with dydrogesterone

A randomized controlled trial conducted by El Zibdeh et al. reported that in a group of women who received

dydrogesterone treatment (n=82, 10 mg twice daily from the confirmation of pregnancy until 12th gestational week), the chances of spontaneous abortion were reduced compared to women in the control group (n=48), who received no additional treatment (13.4% vs. 29%, respectively; p≤0.05). The number of viable pregnancies was higher in the dydrogesterone group (87%) compared to the control group (71%).[19]

In a retrospective cohort study, women were divided into the dydrogesterone group (n=509) and the control group (did not receive dydrogesterone treatment, n=357). Dydrogesterone 10 mg was administered twice daily from the confirmation of pregnancy until 20 weeks gestation. Dydrogesterone showed a distinct and statistically significant positive correlation with live births (adjusted OR = 1.592; CI 95% 1.051–2.413; p=0.028).[6]

A systematic review and meta-analysis evaluated the efficacy of dydrogesterone for the management of recurrent miscarriage. Patients (n=2,454) were divided into dydrogesterone and the control group. The patients in the control group were treated with progesterone, human chorionic gonadotropin (hCG), placebo, or active immunization. The pregnancy success rate was significantly higher in the dydrogesterone group than in the control group (OR = 0.30; 95% CI: 0.22–0.40, p=0.000). The incidence of adverse reactions in the dydrogesterone group was significantly lower than in the control group (OR= 0.30; 95% CI: 0.22–0.40, p=0.000). The researchers concluded that dydrogesterone therapy was a safe and effective for the management of recurrent miscarriage.[20]

A systematic review conducted by Carp H investigated the effect of dydrogesterone in lowering the incidence of subsequent miscarriage in women with RPL. He collated data from three studies (n=509) and reported that the rate of miscarriage with dydrogesterone (10 mg twice daily from diagnosis of pregnancy until 20 weeks) was lower than with control (10.5% vs. 23.5%; OR 0.29; 95% CI 0.13–0.65; 13% absolute reduction in miscarriage). The control group received standard bed rest or placebo intervention. The results from the research further revealed a significant 29% reduction in the odds of miscarriage when dydrogesterone is compared to standard care indicating a real treatment effect and none of the patients discontinued dydrogesterone treatment prematurely.[21]

## PRACTICE POINTS

### For Dydrogesterone efficacy in treatment of RPL

- Oral dydrogesterone was found to be effective in reducing the incidence of miscarriages (Grade A/Level 1a).
- Oral dydrogesterone can be considered in women with RPL as it has shown beneficial effects in increasing the live birth rate and improving the pregnancy success rate (Grade A/Level 1a).

## Safety evidence of dydrogesterone

Most of the clinical studies have reported no significant side effects of dydrogesterone such as masculinization of the female fetus or congenital abnormalities. Dydrogesterone 10 mg twice daily for 2 weeks when compared with micronized progesterone 200 mg twice a day for 2 weeks was associated with significantly fewer cases of drowsiness (p=0.003), with no differences in nausea, vomiting, giddiness, bloating, diarrhea, or headache.[14]

Das et al., compared the adverse reactions between dydrogesterone 30 mg administered once daily (n=50) with vaginal progesterone 600 mg once daily (n=50). The research from the study revealed that there was no significant variation between the two groups. Vaginal irritation was observed solely within the group using vaginal progesterone.[17]

Queisser-Luft conducted a study to evaluate the adverse effect of dydrogesterone (daily dose ranged

from 10 mg to 30 mg) in 38 million with more than 10 million fetuses exposed in utero. The results from the research revealed that only 28 cases were considered as potential links for congenital birth. Hence, dydrogesterone is highly unlikely to be teratogenic.[22]

## PRACTICE POINT

### For administration of dydrogesterone

In patients with RPL, Dydrogesterone with a daily dose in the range of 10 mg to 30 mg appears to be a safe and well-tolerated with no significant side effects reported (Grade A/Level 1b).

## Duration and dosage of dydrogesterone for RPL

For RPL, dydrogesterone can be administered in doses ranging from 10 mg to 30 mg per day and can be extended for 24 weeks and if needed beyond on case to case basis.

### Clinical evidences

A survey-based study conducted among 1168 obstetricians and gynecologists in India revealed that dydrogesterone 10 mg twice daily was found to be the most commonly preferred dosage by 73% of the gynecologists. The survey further reported that 36% of gynecologists use dydrogesterone in RPL for up to 10 to 14 weeks.[23] Table 2 represents the guideline-recommended dose of dydrogesterone for the management of RPL.

**Table 2.** Guideline recommended dose of dydrogesterone for the management of RPL

| Guideline | Recommendations/statements |
|---|---|
| 2023 International Federation of Gynecology and Obstetrics (FIGO) position statement on the use of progesterone[2] | Dydrogesterone with a daily dose of 20 mg would appear to be optimal. |
| 2017 Guideline proposal for using dydrogesterone in the prevention or treatment of pregnancy disorders[24] | Dydrogesterone 20 mg twice daily per day should administered to pregnant women with a history of RPL and extended up to 24 weeks of gestation. |

## SUMMARY

| Key practice points | Grade of recommendation | Level of evidence |
|---|---|---|
| Vaginal bleeding before 24 weeks of gestation is considered as a risk factor for pregnancy loss. | B | 2a |
| Dydrogesterone treatment is initiated at a loading dose of 40 mg and continued at 30 mg/day until symptoms subside. | A | 1b |
| Micronized vaginal progesterone at 600 mg/day can be used when there is no bleeding. | A | 1b |
| Dydrogesterone is preferable in patients who are experiencing vaginal bleeding. | A | 1b |
| Oral dydrogesterone was found to be effective in reducing the incidence of miscarriages. | A | 1a |
| Oral dydrogesterone can be considered in women with RPL as it has shown beneficial effects in increasing the live birth rate and improving the pregnancy success rate. | A | 1a |
| In patients with RPL, dydrogesterone with a daily dose in the range of 10 mg to 30 mg appears to be a safe and well-tolerated with no significant side effects reported. | A | 1b |

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