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KEY PRACTICE POINTS 2024
INDIAN PERSPECTIVE

Management of women with threatened miscarriage: Role of medical therapy

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MANAGEMENT OF WOMEN WITH THREATENED MISCARRIAGE: ROLE OF MEDICAL THERAPY

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Background

As per the World Health Organization (WHO), threatened miscarriage (TM) is defined as pregnancy-related bloody vaginal discharge or frank bleeding during the first half of pregnancy (20 weeks) without cervical dilatation.[1] Reports have shown that around one-quarter of TMs usually proceed to a complete miscarriage over the subsequent weeks of pregnancy.[2,3] TM is associated with an increased risk of adverse pregnancy outcomes such as small-for-gestational-age babies (increased 3X risk), prematurity (increased 2X risk), and perinatal death.[3] Reports have shown that TM occurs in approximately 20% of all pregnancies. First-trimester vaginal bleeding is associated with an approximate 5.5%–42.7% risk for subsequent complete miscarriage.[4]

The exact etiology of a TM is unknown, and a vast majority of miscarriages are unavoidable due to chromosomal abnormalities in at least half of all case. However, maternal and paternal factors may play a significant role for those who have a normal chromosomal makeup (euploid abortions).[1] Various factors are responsible for increasing the risk of TM, such as increasing maternal age, overweight, anemia, and bad obstetric history.[4] As per a study, advanced maternal age was associated with an increased incidence of early miscarriage; from 10%–15% in women aged 20 to 34 years to 51% in women aged 40 to 44 years.[3]

Pathophysiological aspects involved in TM include a change and imbalance in the levels of proinflammatory cytokines (serum interleukin-receptors and tumor

necrosis factor [TNF]-α level, immunological dysfunction (presence of Anti β [2]-glycoprotein I antibodies, increased chemokines and epithelial cell-derived neutrophil-activating protein-78 [ENA-78] levels), oxidative stress (lipid peroxidation and antioxidant enzyme activity variation), and endocrine disorders (PCOS, obesity, placental thrombosis or insulin resistance). Several management approaches are suggested for TM, with bed rest being the most commonly used technique.[3] Few other approaches like pelvic rest, vitamins, uterine relaxants, and administration of beta subunit of human chorionic gonadotropin are not generally recommended.[5] Therefore, effective treatment options to increase the chance of a successful pregnancy are lacking. Progesterone is considered the choice of treatment for TM, as it has a demonstrated role in maintaining pregnancy. Progestogens, are agents that mimic the activity of progesterone, hence, are considered as a rational therapeutic option to treat TM.[5]

Scope

The aim of these key practice points is to develop a validated treatment approach for TM suitable for daily clinical practice.

Methodology

The task force comprised of six experts in the field of Obstetrics and Gynaecology. Task force reviewed the existing literature and developed the consensus statement based on published literature, their individual clinical experience and focused discussion within 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 task force were presented to 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

Use of progestogens during pregnancy

- Progestogens are steroid hormones that bind to and activate progesterone receptors, and are essential for conception and implantation, as well as throughout pregnancy.[6,7]
- The luteo-placental shift between 8 and 12 weeks of gestation is responsible for a plateau or decrease of circulating endogenous progesterone. A disturbance of the luteal-placental shift can result in limited corpus luteum function or delay/deficiency of placental progesterone production and secretion.[7]
- Not all progestogens are suitable for use during pregnancy due to their differences in chemical structure, which leads to variations in their receptor-binding selectivity, potency, and bioavailability can lead to various side effects. The only progestogens approved for use in pregnancy are progesterone, and dydrogesterone.[6] Although 17 alpha hydroxyprogesterone is used in managing TM, there are studies raising concerns regarding long-term safety in offsprings.[8]

Benefits of progestogens in women at risk of threatened miscarriage

- Progestogen treatment is beneficial in women experiencing bleeding and/or pain to decrease the

risk of TM as compared to placebo, no treatment, or any other treatment.[9]

- Oral progesterone is associated with a reduced risk of miscarriage and increased live birth rates vs. vaginal progesterone in women with the risk of TM.[10,11]

Clinical evidence

A Cochrane review has shown that progestogens are effective in the treatment of TM. Treatment with oral progestogen reduces the risk of miscarriage rate (Relative risk [RR] 0.57, 95% Confidence interval [CI] 0.38–0.85; 3 trials; 408 women; moderate-quality evidence) compared to no treatment. Treatment with vaginal progesterone has little or no effect in reducing the miscarriage rate (RR 0.75, 95% CI 0.47–1.21; 4 trials; 288 women; moderate-quality evidence) compared to placebo.[12]

A meta-analysis of randomized controlled trials (RCTs) was conducted that compared progestogen with placebo, no treatment, or any other treatment. It was found that progestogen was effective in reducing the incidence of miscarriage in women who faced TM. Oral dydrogesterone treatment was associated with a lower risk of miscarriage (RR = 0.49, 95% CI 0.33–0.75) than natural progesterone (RR = 0.69, 95% CI 0.40–1.19). Oral progestogen administration was demonstrated to have a lower risk of miscarriage (RR = 0.55, 95% CI 0.38–0.79) compared with vaginal administration (RR = 0.58, 95% CI 0.28–1.21).[10]

Another systematic review and meta-analysis has demonstrated that the use of progesterone increased the incidence of live birth (RR 1.07, 95% CI 1.00–1.15; p=0.04; I^2=18%), and reduced the risk of miscarriage (RR 0.73, 95% CI 0.59–0.92) in women with TM. This benefit of increased live births and reduced miscarriages was observed in groups treated with oral progestogen (dydrogesterone) and not with vaginal progesterone.[11]

Australia and New Zealand, RANZCOG guidelines have suggested that progestogen supplementation until the second trimester in women presenting with a clinical diagnosis of TM may reduce the rate of spontaneous miscarriage and may be considered.[13]

PRACTICE POINTS

For use of progestogens in women at risk of TM

- Oral progestogens can be considered over vaginal progestogens for decreasing the risk of threatened miscarriage and increasing live births. (Grade A/Level 1a)
- Oral progestogen supplementation can be prescribed until the second trimester in women presenting with a clinical diagnosis of threatened miscarriage. (Grade A/Level 1a)

Progestins for threatened miscarriage

Synthetic progestogens (or progestins), are laboratory-generated compounds with modified structures and do not correspond to a naturally occurring steroid.[14]

The administration of progestins is beneficial during early pregnancy and has been shown to increase implantation rates and successful pregnancies.[15]

Dydrogesterone in threatened miscarriage

- Dydrogesterone, a progestin, is a retro progesterone and a potent and selective oral progesterone receptor agonist. Its unique structure exerts high oral bioavailability.[6]
- The high selectivity for progesterone receptor allows the administration of oral dydrogesterone at doses 10–20 times lower than those of oral micronized progesterone.[6]
- Dydrogesterone does not exert androgenic or oestrogenic effects on the fetus and does not alter the normal secretory transformation of the endometrium. It also does not inhibit the formation of progesterone in the placenta. Therefore, is a suitable molecule for women with TM.[16]
- Dydrogesterone's main metabolite, 20α-dihydro dydrogesterone, exhibits similar progestogenic selectivity to the parent molecule and hence further minimizes unwanted adverse events (AEs).[6]

- Dydrogesterone reduces the rates of miscarriage in women with risk of TM.[16]
- Dydrogesterone improves delivery outcomes and is safe in the treatment of TM.[17]
- As per the European Progestin Club Guidelines 2015, for women presenting with a clinical diagnosis of TM, there is a reduction in the rate of spontaneous miscarriage with the use of dydrogesterone.[7]
- FIGO 2023 guideline suggests that oral progesterone supplementation during pregnancy may have some beneficial impact on first-trimester recurrent miscarriage.[18]

Clinical evidence

A systematic review was conducted to assess if oral dydrogesterone lowered the incidence of miscarriage in women with TMs. A 11% absolute reduction in the miscarriage rate was reported with dydrogesterone administration in women with TM. The AEs reported seemed to be minimal. Therefore, a significant reduction of 47% in the odds of TM was observed when dydrogesterone was compared to standard care.[19]

A systematic analysis was conducted to evaluate the efficacy of progesterone therapy for the prevention of miscarriages in 913 pregnant women experiencing threatened abortion. Around 322 were treated with oral dydrogesterone, 213 were treated with vaginal progesterone, and 378 control subjects. A significant difference between the incidence of miscarriage was observed in the oral dydrogesterone group and the control group (11.7% vs. 22.6%; odds ratio, 0.43; 95% CI, 0.26–0.71; p=0.001; I^2, 0%). The difference in the incidence of miscarriage was nonsignificant in the vaginal progesterone group than in the control group (15.4% vs. 20.3%; odds ratio, 0.72; 95% CI, 0.39–1.34; p=0.30; I^2, 0%). The authors concluded that oral dydrogesterone could effectively prevent miscarriage in pregnant women experiencing threatened abortion.[20]

Another pairwise and network meta-analysis including a total of 59 RCTs comprising 10,424 patients showed that oral dydrogesterone was effective in the treatment of TM. The surface under the cumulative ranking area (SUCRA) was calculated to determine the efficacy and safety of interventions. It was observed that oral dydrogesterone had the lowest risk of miscarriage (SUCRA 100.0%), followed by vaginal progesterone (SUCRA 67.9%). Oral micronized progesterone had the highest risk of miscarriage (SUCRA 15.7%).[21]

A real-world retrospective analysis of the case reports was conducted to evaluate the safety, effectiveness, compliance, and tolerability of oral dydrogesterone in the treatment of women with threatened abortion. Data was collected from 194 obstetricians and gynecologists in India, on the use of oral dydrogesterone in women presenting with threatened abortion in the first trimester of pregnancy. The analysis of 617 CRFs, showed that 572 (92.71%) patients successfully continued their pregnancy with oral dydrogesterone. 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. Drug compliance of >80% was reported in 88.35% of the patients treated with dydrogesterone.[22]

PRACTICE POINTS

For use of progestins for TM

- Progestin administration is beneficial during early pregnancy, and can be considered to increase implantation rates and successful pregnancies in women at risk of threatened miscarriage. (Grade A, Level 1a)
- Oral dydrogesterone is effective in reducing the incidence of miscarriages, hence, can be a preferred choice over vaginal progesterone or standard therapy in women at risk of threatened miscarriage. (Grade A/Level 1a)

Duration and dosage of dydrogesterone for TM

For TM, oral dydrogesterone 40 mg should be administered at once, and thereafter up to 40 mg/day (2 x 20 mg) orally, and should be continued as per clinician's advice.[23]

Clinical evidence

Various clinical guidelines recommend the use of dydrogesterone for TM (Table 1).

Table 1. Clinical guidelines recommending dydrogesterone for TM

Guideline	Recommendations
FIGO 2023[18]	Prescribing a daily dose of 20 mg oral dydrogesterone (twice-daily dose regime of 10 mg per dose) for recurrent spontaneous abortion would be optimal.
FOGSI[24]	Oral dydrogesterone (40 mg loading dose followed by 20–30 mg/day until 7 days after bleeding stops).
Taiwan Society of Perinatology 2022[25]	Oral dydrogesterone is the only recommended medicine: 40 mg immediately followed by 10 mg BID until symptoms are in complete remission; then continue dydrogesterone 10 mg BID for 1 to 2 weeks.
Saudi Arabian guideline[26]	Oral progestogens, namely dydrogesterone, are well tolerated and effectively reduce miscarriages in women at risk of threatened miscarriage.

FIGO: The International Federation of Gynecology and Obstetrics; FOGSI: The Federation of Obstetric and Gynecological Societies of India

A real-world retrospective analysis of the case reports demonstrated that the dose of dydrogesterone used in the treatment of women with TM 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.[22]

Dydrogesterone at a dose of 40 mg stat followed by 10 mg twice daily had beneficial effects on maintaining pregnancy in women with TM. The pregnancy success rate in the dydrogesterone group was statistically significantly higher than that in the control group (87.5% vs. 71.6%; $p<0.05$). Miscarriage occurred in 12.5% of women in the dydrogesterone group compared with 28.4% in the control group ($p<0.05$).[16]

Safety of dydrogesterone

Dydrogesterone has been used worldwide (>90 countries) since the 1960s for several conditions related to progesterone insufficiency. The cumulative exposure to dydrogesterone for all indications from 1960 to March 2017 is >113 million patients, including >20 million pregnancies.[27]

A scoping review and meta-analysis conducted on the risk of congenital abnormalities associated with the use of dydrogesterone during the first trimester demonstrated no significant increase in risk, with a pooled risk ratio of 0.96 (95% CI 0.57–1.62) for the six RCTs. None of the included studies indicated a significant risk. Therefore, the authors concluded that physicians and patients should have every confidence in using dydrogesterone when indicated in the treatment of threatened and/or recurrent miscarriage, and that the favorable safety profile should extend to its appropriate use in ART.[27]

A knowledge, attitude, and practice survey highlighted that 1168 Indian gynecologists valued dydrogesterone for its effectiveness and tolerability. Dydrogesterone 10 mg twice daily was found to be the most commonly preferred dosage by 823 (73%) gynecologists. Poor tolerability, compliance, and lower efficacy were reported as major limitations of micronized progesterone by 68% of doctors. Around 30% of doctors reported more than 40% clinical pregnancy rates after dydrogesterone usage. Almost 35% of doctors reported that the average live birth rate noticed after dydrogesterone usage was around 40%.[28]

PRACTICE POINTS

For dosage and duration of Dydrogesterone for TM

For women with risk of threatened miscarriage, oral dydrogesterone 40 mg should be administered immediately from the onset of vaginal bleeding, followed by 10 mg TID until bleeding stops, and then can be tapered to 10 mg BID up to 16 weeks of gestation. (Grade B/Level 2a)

PRACTICE POINTS

For safety of dydrogesterone in the management of TM

Oral dydrogesterone 10 mg twice daily has proven to be safe and well-tolerated than micronized progesterone in the treatment of threatened miscarriage. Majority of Indian Gynecologists consider dydrogesterone as a preferred choice, and that the physicians should have every confidence in using it in the management of threatened miscarriage. (Grade B/Level 2b)

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