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Role of Oral Natural Micronized Progesterone Sustained Release in Threatened Miscarriage and Preterm Labor

A Supplement to American Journal of Perinatology

Guest Editors

Alpesh Gandhi, MBBS, DGO, FRCOG, FICOG
Reena Wani, MD, FRCOG, FICOG, DNBE, FCPS, DGO, DFP

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Role of Oral Natural Micronized Progesterone Sustained Release in Threatened Miscarriage and Preterm Labor

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Preface

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It is not only what we do, but also what we do not do, for which we are accountable

—Moliere

Pregnancy is a journey in which the obstetrician is responsible for two patients, and aim of obstetrics is to have a healthy mother and baby at the end of this 9-month journey. Progesterone is an essential hormone, associated with pregnancy, which has been widely used in clinical interventions to improve and prevent threatened miscarriage, recurrent miscarriage, and preterm labor. In the current situation of COVID-19 (novel coronavirus disease 2019) pandemic and need for evidence-based medicine, it was thought that we must scientifically look at why, how, and when it is used, with a focus on types of progesterone and routes of administration.

The purpose of this review is to evaluate the clinical efficacy and safety of natural progesterone for the treatment of threatened miscarriage and preterm labor, which are two conditions that often pose management dilemmas being common and challenging situations, which can lead to adverse outcomes. In this project, therefore, many aspects have been critically and comprehensively reviewed: from pharmacokinetics, pharmacodynamics, clinical trials on oral and vaginal administration of natural micronized progesterone to clinician perceptions and neonatal outcomes. Finally, the synopsis of all the information is provided at the end for easy assimilation.

The subsections presented are contributed by national experts and encompass the latest guidelines, as well as research conclusions. We sincerely thank the editors, authors, and coauthors for their contributions to the chapters. We thank the executive committee of the Federation of Obstetric and Gynaecological Societies of India (FOGSI) for endorsing our white paper. The editors and contributors have worked hard to bring forth the latest evidence-based recommendations on pertinent topics in a concise manner. This will benefit the practicing clinicians, gynecologists and obstetricians, residents, as well as teaching faculty, and provide good scientific basis on threatened miscarriage and preterm labor in Indian population.

Conflict of Interest
None declared.

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Background

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Progesterone deficiency has been implicated as one of the causes of euploid miscarriages, preterm births (PTBs), and infertility.[1] Miscarriage has been variably defined, with recent consensus emerging at termination of pregnancy before 23 weeks, while the PTB is usually defined as delivery at less than 37 weeks of gestation.[2] The overall miscarriage rate is estimated to be 15 to 20%, with almost 80% of the miscarriages occurring in the first trimester.[3] Although a multifactorial causation of miscarriage has been suggested, the individual causes attributed to threatened miscarriage are mainly genetic, contributing to approximately half of the cases, and the remaining half being attributed to anatomical, metabolic, infectious, hormonal, and immunological causes.[3] ►**Table 1** summarizes the important risk factors associated with miscarriage.

Table 1 Important risk factors associated with miscarriage

First trimester vaginal bleeding
Increased maternal and paternal age
History of miscarriage
Obesity
Low serum progesterone levels
Lifestyle factors (coffee, physical activity, tobacco, alcohol intake, and stress)
Diet (low micronutrient intakes)
Thyroid issues

PTBs complicate approximately 13.6% of live births in India according to recent estimates.[2] Notably, India accounts for 23.4% of the global burden of PTBs but only 18.5% of the global live births are recorded in India. This indicates that the burden of PTB is much higher than the proportion of live births which can be attributed to inadequate access to high-quality obstetric care. Additionally, the prevalence of primary infertility in India has been estimated[4] between 3.9 and 16.8% which indicates a high burden of infertility and the need for high-quality assisted reproductive technology (ART) services.

Progesterone plays a central role in maintenance of pregnancy. A protein known as the progesterone-induced blocking factor probably acts as an immunological suppressant by inducing production of a T-helper type-2 dominant cytokine and blocking T-helper type-1 activity that mediates the immunological effects of progesterone. It has an essential role in supporting the luteal phase. It has been widely accepted because of its effect on the endometrium and its immunomodulatory and anti-inflammatory actions in the maintenance of pregnancy. Accordingly, women with threatened miscarriage have been treated with the supplementation of progesterone with varying degrees of success.

Since the 1940s, progesterone supplementation has been suggested in patients with habitual spontaneous abortion associated with luteal phase deficiency and in women with recurrent miscarriage.[5] In addition, the measurement and evaluation of serum progesterone levels have been considered as a biomarker in evaluation of pathological pregnancies.[3] Supplementation with natural micronized progesterone has a high bioavailability for cellular and subcellular organelles, and the data support a positive benefit–risk profile by improving live birth rates in those women. The risk factors for threatened miscarriage are polycystic ovary syndrome, smoking, obesity, and a previous history of miscarriage.

In progesterone deficiency states, its supplementation offers hormonal and nonhormonal (anti-inflammatory, immunomodulatory, and uterine relaxant) benefits, prolong pregnancy, and enables fetal viability and maturity.[6]

For progesterone supplementation, several progesterone formulations have been developed over the last six decades. However, strictly speaking, only compounds chemically identical to the progesterone of ovarian origin have been referred to as the natural progesterone.[7] The natural progesterone has the same structure as that of endogenously secreted progesterone; however, dydrogesterone, a commonly used synthetic oral formulation, has a retrostructure: 6-dehydro-retro-progesterone.[3]

Historically, there had been a reluctance to use natural progesterone via the oral route since that undergoes rapid first-pass metabolism leading to a low bioavailability. This eventually caused a mushrooming of synthetic progesterones.

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However, the synthetic compounds do not precisely replicate the biologic activities of the parent hormone. For example, the synthetic progestins may affect lipoprotein metabolism and cardiovascular health adversely through their actions at the androgenic receptors.[7]

The poor bioavailability of older formulations of natural progesterone also increased the focus on other routes of progesterone administration, such as the vaginal, rectal, and parenteral routes. However, the Indian cultural sensitivities and patient expectations favor oral use of medicines over the parenteral and vaginal routes. Therefore, it is imperative to meet the patient expectations by encouraging development of safe and effective oral formulations of progesterone.

Nevertheless, the cultural reasons cannot be considered sufficient to prevail over the medical needs of the patients. Thus, the scientific community rose to this challenge of developing effective and safe oral formulations of progesterone that require once daily dosing and are thus patient centric, which is the natural micronized progesterone sustained release (NMP SR) formulation. The NMP SR tablet formulation is available in India since 2011.[3] The NMP SR formulations utilize newer technologies and show slow sustained release pattern over 24 hours, avoiding sudden drug release and minimizing the loss of drug in the first-pass metabolism.[6]

In the era of evidence-based medicine, a critical appraisal of the evidences on different formulations of progesterone is necessary. More importantly, it is essential to utilize this hormone in its natural form with precise knowledge of the optimal timing, mode, and dose. Furthermore, it is important to validate the newer formulations for their efficacy and clinical effects in different progesterone deficiency states such as unexplained infertility, threatened miscarriage, and preterm labor.

At the same time, it is of paramount importance to evaluate the fetal and maternal safety of the different formulations of oral progesterone, especially the synthetic ones, which are more likely to be associated with adverse effects on the fetal development.

It is in this context that this supplement attempts to critically examine the recent evidences on natural and synthetic oral progesterone formulations and their supplementation.

In addition, this supplement also aims to identify the existing knowledge gaps that should be prioritized in future clinical studies on oral progesterone formulations. Lastly, one of the goals of this supplement is to update the reader on recent evidences, researches, and guidelines on progesterone supplementation in luteal deficiency states from across the globe, while at the same time, focusing on the Indian clinical setting.

Conflict of Interest
None declared.

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Threatened Miscarriage and Preterm Labor: A Clinical Challenge

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Threatened miscarriage is defined as bleeding in early pregnancy up to 20 weeks of gestation with a closed cervix and presence of fetal heart activity in ultrasound examination.[1,2]

It is prevalent among one in five pregnancies.[3,4] The prevalence of threatened miscarriage is not known in India[5] but the rate of spontaneous miscarriage is identified by a study done in Karnataka. In this study, the rate of miscarriage per 1,000 ongoing pregnancies between 6 and 12 weeks is 101.9 to 115.3 and between 12 and 20 weeks is 60.3 per 1,000.[6]

The common reasons for a threatened miscarriage are extremes of maternal age and chromosomal abnormalities. The less common causes are Mendelian and polygenic multifactorial etiologies, luteal phase defects, thyroid abnormalities, uncontrolled diabetes mellitus, and uterine anatomical and pathological abnormalities like intrauterine adhesions, leiomyomas, Müllerian fusion defects, cervical insufficiency, infections, and acquired and inherited thrombophilias. Very rare causes are exogenous agents like radiation, alcohol, caffeine, contraceptive agents, chemicals, trauma, psychological stress, common medications, and smoking.

In India, one of the common reasons identified for miscarriages are older mothers and higher educated women.[6]

Clinical Features

Period of amenorrhea, positive urine pregnancy test, and vaginal bleeding are the presenting symptoms of threatened miscarriage.[7] Patient can have pain. The precipitating factors need to be identified.[8]

Clinical Challenges

There are challenges in the clinical features and evaluation of the condition. Vaginal bleeding does not lead to a spontaneous abortion always. It does not guarantee a live birth also. Evaluation of the condition is also not straight forward. The evaluation and management need to be individualized for each patient.

Spontaneous abortion can happen if there is vaginal bleeding. If fetal heart activity has been established, the chances are reduced to 2 to 3% in low-risk pregnancies. In women with high-risk pregnancies, like older mothers and patients who have undergone infertility treatment, presence of fetal heart does not guarantee a good outcome. If there is a subchorionic hemorrhage, the miscarriage rate is around 15%.[7]

Evaluation

An ultrasound should be done. A transvaginal ultrasound is preferable but if unacceptable, transabdominal scan can be done after explaining the limitations.[2]

The viability of the pregnancy is confirmed. If viability is not confirmed, an attempt is made to prevent a false positive diagnosis.[9] This is facilitated with the use of ultrasound and biomarkers.

Transvaginal Ultrasound

Recommendation from the Society of Radiologists in Ultrasound Panel[9]

- Check for fetal heart rate.
- If no fetal heart is visible, search for fetal pole.
- If fetal pole is seen, measure crown rump length (CRL).
- If CRL is less than 7 mm and no fetal heart is present, an ultrasound should be done after 7 days.
- If CRL is more than 7 mm and no fetal heart is present second opinion for viability should be made.
- If no fetal heart or fetal pole is present, measure gestational sac diameter (GSD).
- If GSD is less than 25 mm, a scan should be done after 1 week.
- If GSD is more than 25 mm, (no fetal pole), second opinion is advisable.

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Transabdomen Ultrasound

- If no fetal heart is visible, measure CRL.
- Repeat scan after 2 weeks.
- If no fetal pole is present, measure GSD.
- Repeat scan after 2 weeks with precautions.
- Do not use last menstrual period (LMP) for diagnosis of miscarriage.
- Before diagnosing complete abortion at first scan, be aware of "pregnancy of unknown location."
- May need β human chorionic gonadotropin (HCG) estimation for follow-up.

Pregnancy of Uncertain Viability (Society of Radiologists in Ultrasound Panel)

Pregnancy of unknown viability is an entity which needs to be remembered while investigating a threatened miscarriage.[9] The diagnostic features are as follows:

- CRL of 7 mm and no heartbeat.
- Sac diameter is more than 25 mm and no fetal pole.
- No yolk sac at first scan and after 2 weeks, no fetal pole, and no heartbeat.
- Yolk sac seen and after 11 days, no fetus and no heartbeat. The features which should raise a suspicion are:
  - Enlarged yolk sac more than 7 mm.
  - Less than 5 mm difference between GSD and CRL.
- Repeat ultrasound after 7 to 10 days. Chromosomal abnormality is suspected if the following features are present:
  - Thick nuchal translucency.
  - Absent nasal bone.
  - Abnormally fast or slow heart rate.
  - Structural malformations.

Biomarkers

Several biomarkers have been studied that can be used to predict the outcome in threatened miscarriage. They are serum progesterone, estradiol, HCG, pregnancy-associated plasma protein (PAPP-A) and cancer antigen (CA)-125. Serum CA125 is considered better for prediction. Serum progesterone and HCG are less accurate after viability of the fetus is established.[10]

Ultrasound needs to be combined with biomarkers for an accurate prediction of threatened miscarriage.[10]

The presence of fetal heart activity and lack of adverse prognostic factors convey a favorable prognosis.

Management

- If the fetal heart is visible and even if there is an ongoing bleeding, it is better to wait for 14 days unless there is heavy flow or increasing pain.[2]
- If the bleeding has subsided, a repeat ultrasound is needed after 14 days to confirm an ongoing pregnancy.[2]

Preterm Labor

Introduction

There is a need to predict preterm labor in women because it contributes to almost 1 million deaths worldwide creating a great economic burden. Children born preterm have life-long problems.

Benefits of prediction include the following:

- Help to guide antenatal management decisions.
- Reassurance.
- Identify at risk.
- Planned interventions like tocolysis, steroids, in utero transfer, and magnesium sulfate for neuro protection.
- Accurate prediction will avoid unnecessary and harmful treatments (►**Fig. 1**). Predictors of preterm labor are as follows:
  - Biochemical markers in blood, urine, cervical secretions and amniotic fluid.
  - Ultrasound-based tests.
- The biological basis for preterm labor is the following:
  - Uterine stretch.
  - Congenital or acquired cervical insufficiency.
  - Decidual hemorrhage.
  - Infection and inflammation.
  - Cervical ripening.
  - Fetal membrane disruption.

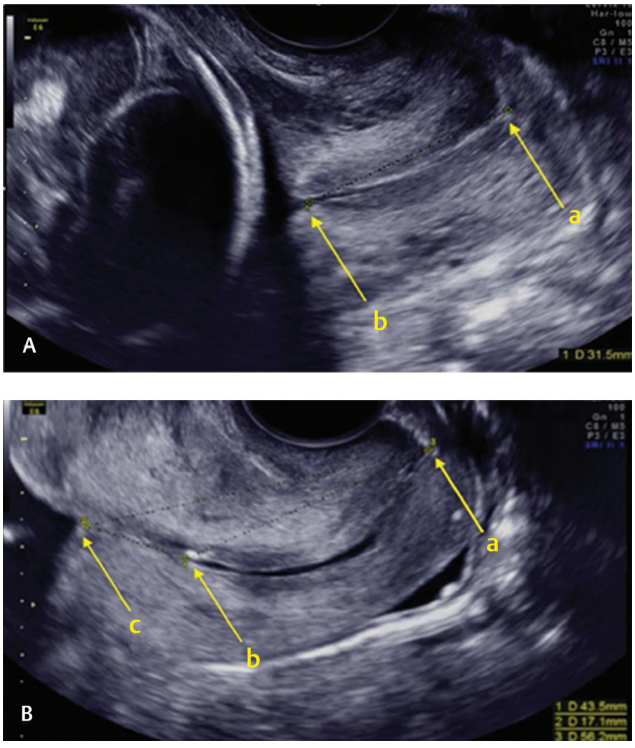

Fig. 1 Measurement of cervical length when isthmus is absent (**A**) or present (**B**). Isthmus is the lowest part of the uterine corpus that develops into the lower uterine segment as pregnancy progresses. The letter "a" denotes the external os. "b" denotes the internal os. "c" (which we call the "virtual inner os") is the innermost end of the juxtaposed anterior and posterior isthmus. Measurements were taken as a straight line from a to b (endocervical length), from b to c (isthmus length) and from a to c (second-trimester transvaginal ultrasound measurement of cervical length for prediction of preterm birth: a blinded prospective multicenter diagnostic accuracy study). Prediction of preterm birth is mandatory if there is history of previous preterm birth, previous late miscarriage, and excisional surgery on the cervix has been done.

Table 1 Risk factors for preterm birth

Maternal factors	Fetal factors
Ethnicity	Multi fetal pregnancy
Age of the mother	Hydramnios
Certain lifestyle and environmental factors	Fetal anomalies
Late or no health care during pregnancy	
Smoking	
Drinking alcohol	
Using illegal drugs	
Domestic violence, including physical, sexual, or emotional abuse	
Maternal infections	
Bleeding	
Uterine fundal abnormalities	
Cervical insufficiency	
Maternal autoimmune diseases	
Gestational hypertension	

Principles of management: if the patient is asymptomatic, there should be modalities to identify silent labor. If the patient is symptomatic, there should be a method to identify whether preterm delivery is imminent (►**Table 1**).

Prediction

Cervical ultrasound and fetal fibronectin measurement are the best performing tests for prediction at this point of time.

Cervical Length Changes

- Detected by ultrasound before inspection or digital examination.[11,12]
- Remains constant between 14 and 28 weeks.
- 50th centile is 35 mm and 5th centile is 20 mm.
- Short cervix: 25 mm or less.
- No cut-off is confirmatory.
- Only 18% of women with cervical length less than 25 mm at 24 weeks delivered at a gestational age less than 35 weeks. Almost 50% of women with cervical length less than 13 mm at 24 weeks delivered at a gestational age less than 35 weeks.
- Gold standard is transvaginal ultrasound measurement.
- Image should fill 75% of the screen.
- Bladder should be empty.
- Anterior and posterior lips of cervix should be of equal width.
- Funnel length should not be included.
- Internal os to external os should be measured. Universal screening is as follows:
  - Not recommended by many groups.
  - In two clinical trials with universal screening, pregnant women with 30-mm length cervices were treated with vaginal progesterone and showed benefit.[13]
- The International Federation of Obstetricians and Gynecologists (FIGO) guidelines:[14] sonographic cervical length screening in all pregnant women is advised by FIGO for the prevention of preterm birth (PTB).
- The following are the recommendations:[14]
  - Done at $19^{0/7}$ to $23^{6/7}$ weeks using transvaginal ultrasound.
  - Women with a cervical length <25 mm should be treated with daily vaginal progesterone.
  - Universal cervical length screening and vaginal progesterone are a cost-effective model for the prevention of PTB.

Targeted Screening

Targeted screening is advised when there is a history of PTB and multiple pregnancy.[15]

If there is a history of PTB, the screening modalities are still unclear. It is better to screen for a short cervix at an appropriate time. Prophylactic treatment in the form of cervical encerclage or vaginal progesterone can be started.

In multiple pregnancy, where there is a higher chance for preterm labor, there are no established recommendations for prediction and prevention. If on screening ultrasound, the cervix length is less than 25 mm, progesterones or cervical pessary may help. The pathogenesis of preterm labor onset in multiple pregnancy is proposed to be increased uterine distension or an endocrine environment where there are more estrogen, progesterone, and sex steroids compared with singleton pregnancies.

In patients with prior preterm singleton birth and current twin pregnancy with normal cervix length, there is no consensus regarding screening and treatment as prior PTB is an independent and additive risk factor.[15] If there is a prior PTB, there is a 69% risk of repeat preterm labor pains in multiples and 50% risk in singleton. Treatment of this condition is unclear. FIGO endorses routine cervix length screening without an exclusion for multiple pregnancy.[16]

Fetal Fibronectin

- The next test which can be utilized to predict the occurrence of PTB is the measurement of fetal fibronectin (fFN) from a swab from the posterior fornix of the vagina through a speculum. There is a qualitative testing which is considered positive if fFN is more than 50 ng/mL. It is a solid-phase immunochromatographic assay. There is a newer quantitative assay which is more prognostic at extremes of levels. This test kit can be stored at room temperature.
- The fFN is an extracellular matrix glycoprotein which promotes adhesion at the placental and decidual chorionic interfaces. It is not normally seen in cervical secretions between 25 and 35 weeks. It can be identified when the interface is disrupted in early labor. The concentration of fFN and risk of preterm labor are linearly related.

If there is a high risk for PTB, a single cervix length measurement is done at 16 to 24 weeks. If it is less than 25 mm, interventions are needed.[17]

In symptomatic women, cervix length measurement is not beneficial. A quantitative fFN may help in such conditions. If there is a negative fFN, it rules out PTB in the next 7 days. FFN will also help in classifying whether a patient is at low risk or high risk for PTB. In high-risk cases, sequential testing may be done. Cervical length is measured and if it is between 15 and 30 mm, fFN quantification testing will help in classification of risk levels. If fFN is between 10 and 49, patient is not at high risk. If the levels are more than 500, she is at high risk for PTB.[10,18-20]

Conclusion

Threatened miscarriage and preterm labor may be considered as a continuum of obstetric complications. The risk factors need to be identified at the earliest and management should be done for each patient on an individual basis. If proper treatment is instituted at the proper time, it will result in a good outcome for both the mother and fetus.

Conflict of Interest
None declared.

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Pharmacokinetic and Pharmacodynamic Features of Progesterone: A Special Focus on the Efficacy of Different Oral Natural Micronized Sustained Release Progesterone Formulations

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How a drug is delivered can have a significant effect on its efficacy, safety, and patient compliance. Evolution of existing drug molecules using novel delivery systems can significantly affect their pharmacokinetic and pharmacodynamic properties, thus improving their clinical utility. For example, the absolute bioavailibity of metformin is about 50 to 60%. Its incomplete absorption is improved by using drug delivery system. It does not undergo hepatic metabolism like oral natural micronized progesterone sustained release (NMP SR) and the main route of elimination is renal tubular secretion.

The pharmacokinetic and pharmacodynamic parameters of oral progesterone formulations have been extensively reported in literature. In this chapter, we discuss the practical aspects of pharmacokinetics and pharmacodynamics of oral progesterone formulations used in pregnancy in the clinical setting for different indications. The oral progesterone formulations that are clinically supplemented can be either natural or synthetic. While the natural progesterone has the same structure as that of endogenous progesterone secreted by the corpus luteum, synthetic formulations have modified structures. For instance, dydrogesterone, a commonly used synthetic oral formulation, has a retrostructure: 6-dehydro-retro-progesterone.[1]

Pharmacokinetic Parameters of Oral Natural Micronized Sustained Release Progesterone Formulations Used in Pregnancy

Historically, there had been reluctance to use natural progesterone via oral route since that undergoes rapid first-pass metabolism to form its hydroxylated metabolites and their sulfate and glucuronide derivatives. Although this caused mushrooming of synthetic progesterones and increased focus on other routes of administration, such as vaginal, rectal, and parenteral, however, this problem has also been addressed by using technique of micronization to improve the bioavailability and developing sustained-release formulation based on matrix technology.[2]

The smooth release pattern seems to avoid sudden drug release and therefore loss of drug via hepatic metabolism. Furthermore, as the dosage form transits in the small intestine, gradual dissolution and erosion of polymeric matrix result in the release of micron-sized drug particles that undergo micellar solubilization by bile salts that facilitates its absorption through the lymphatic circulation.[1] Hence, the lymphatic absorption limits hepatic first-pass metabolism, and thus intact drug reaches the systemic circulation (►**Fig. 1**). In addition, it was also shown that there was minimal effect of natural progesterone supplementation on liver enzymes and lipoproteins in postmenopausal women.[3]

The pharmacokinetic parameters of oral NMP SR were initially defined in healthy postmenopausal women who received either placebo, 100-, 200-, or 300-mg tablets per day for 2 weeks.[4] The median time to reach maximum serum progesterone concentration was approximately 3 hours for all doses. There was no statistically significant difference among the three doses for area under the curve, half-life, or Cmax. Thus, the absorption and elimination of sustained-release oral micronized progesterone seem to be dose-independent. Notably, the average elimination half-life in this study was approximately 18 hours, supporting once daily dosing. The clinical results of an open-label observational study to determine the success rate of the first IUI cycle with oral NMP SR found that the serum progesterone levels in patients were 46.2 ng/mL with NMP SR 400 mg, 36.1 ng/mL with NMP SR 300 mg, and 20.6 with NMP SR 200 mg.

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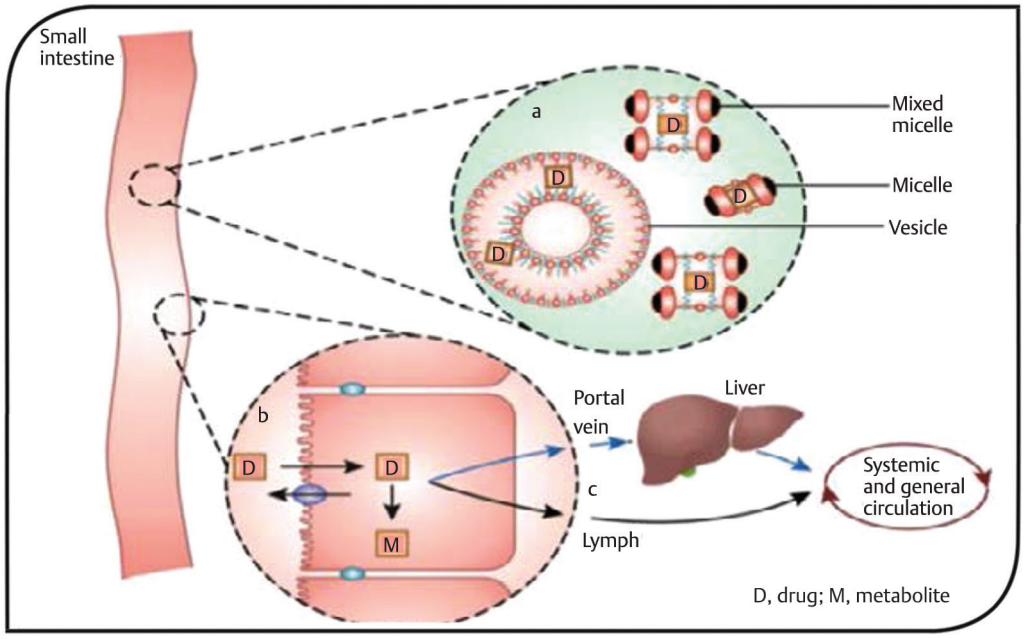

Fig. 1 Sustained release formulation bypasses the systemic circulation.[2]

However, in the case of nonsustained-release formulations of oral micronized progesterone, it was reported that the plasma levels peaked at approximately 2 hours, and declined to pretreatment levels at approximately 8 hours because of the rapid first-pass metabolism in the liver, supporting more frequent dosing.[5,6] Moreover, with the immediate-release formulations, the metabolites that were produced in high concentrations had been linked with the higher occurrence of adverse effects.[6]

Expected Increase in Progesterone Levels with Therapeutic Doses of Oral Progesterone

In a recent study from China, Wang and colleagues[7] reported progesterone levels of women with threatened abortion receiving different formulations of progesterone (200-mg daily oral progesterone or 20-mg intramuscular [IM] injection) before and after treatment. In both the groups, the progesterone levels after the treatment were significantly higher than corresponding pretreatment levels. However, the levels of progesterone in both groups after treatment were raised similarly that is, both oral and injectable natural progesterone showed a similar efficacy (►**Fig. 2**).

In addition, various studies have shown that the mean plasma levels achieved with therapeutic doses of oral progesterone in women receiving assisted reproductive technology (ART) are at least as high as luteal phase levels. In a study reported by Gopinath and Desai,[8] over 90% of women receiving ART treated with NMP SR, as well as dydrogesterone, achieved luteal-phase plasma levels of progesterone (►**Fig. 3**). Similar results were also reported by another

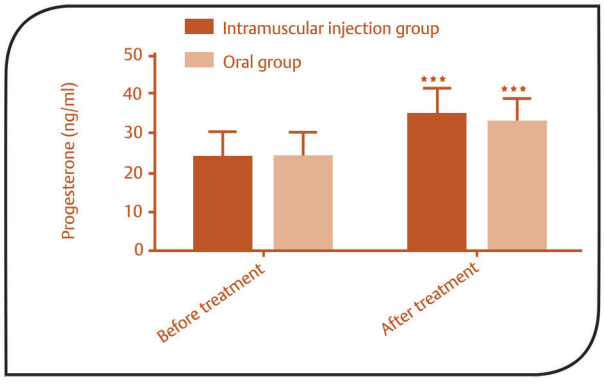

Fig. 2 Significant increase in progesterone levels on supplementation.[7]

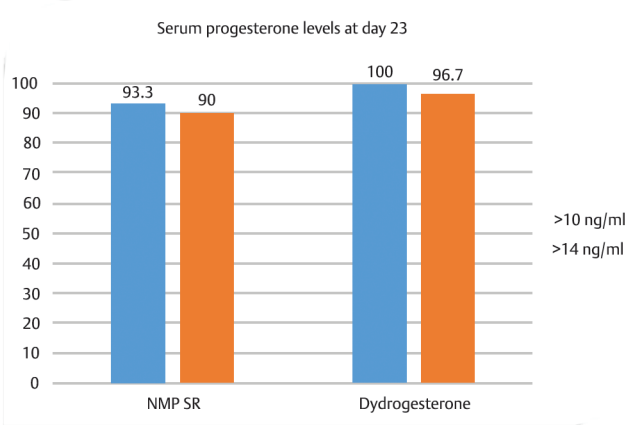

Fig. 3 Progesterone levels in women receiving ART after oral supplementation.[7] ART, assisted reproductive technology; NMP SR, natural micronized progesterone sustained release.

study on NMP SR and dydrogesterone by Malhotra and Krishnaprasad who found that the percentage change of values was over 90% with a mean progesterone levels of 28.5 ng/mL.[9]

Molecular Sites of Action of Progesterone

The actions of progesterone are mainly mediated via the progesterone receptor (PR), which is a ligand-activated transcription factor closely related to the steroid (androgen, glucocorticoid, and mineralocorticoid receptors) and nuclear receptors. The PR exists in two isoforms, PR-A and PR-B, which are variably expressed in the female reproductive organs, central nervous system, and immune cells. Through the genomic receptor binding, progesterone activates approximately 300 distinct coregulators that act on ribosomal RNA and result in the production of corresponding proteins that affect female reproduction.[10]

Besides the nuclear mechanism, progesterone also exerts nonnuclear effects on multiple tissues that are mediated by activation of secondary messengers (►**Table 1**). A reproductive nonnuclear receptor has also been localized in the cell membrane and is called PGRMC1.[10]

Table 1 Nonnuclear actions of progesterone[12]

Physiological action	Cell/tissue/ organism	Signaling pathway
Acrosome reaction/ capacitation	Human spermatozoa	Calcium influx, chloride efflux, cAMP increase
Immunoregulatory function	Human T-lymphocytes	G-protein activation, Potassium channel inhibition
Platelet aggregation	Human platelets	Calcium influx, chloride efflux, cAMP increase
Muscle contraction	Human intestinal smooth muscle cells	Calcium currents reduction
Transepithelial resistance	Human fetal membranes	Unknown
Actin cytoskelton-remodeling	Human umbilical vein endothelial cells	G-protein activation, PI3 kinase and RhoA/ ROCK-2 cascade activation
Neuroprotection	Mouse cerebral cortex, rat hippocampal neurons	PI3 kinase activation, ERK 1/2 activation, calcium flux inhibition
Steroidogenesis	Rodent leydig cells	Sodium influx
Oocyte maturation	Amphibian and fish oocytes	G-protein activation and cAMP decrease, ERK 1/2 activation, PI3 kinase activation

Clinical Effects of Progesterone Supplementation

The main clinical effects of progesterone supplementation are hormonal. It helps in implantation of fertilized egg in several ways by stimulating the growth of uterus, maintaining uterine quiescence, inhibiting myometrial contractility, and promoting secretory endometrial changes.[11]

Additionally, several nonhormonal effects of progesterone have been proposed. First, an immunomodulatory or anti-inflammatory action, which blocks chemokine secretion and upregulates Th2 immune response, has been suggested that inhibits tissue rejection and protects the conceptus. Second, it has been suggested that a relaxant effect is also exerted on the uterus by progesterone via blocking the effect of oxytocin and related substances and by lowering the amount of phosphorylated myosin.[12]

Moreover, it has been proposed that progesterone acts on the hypothalamic–pituitary–adrenocortical axis by modulating luteinizing hormone (LH) secretion, thereby establishing a feedback mechanism on ovarian steroidogenesis and inhibiting sexual desire in women. In addition, allopregnanolone, a metabolite of progesterone is supposed to exert neuroprotective and restorative effects on brain, and thus considered a neurosteroid.[10] It has also been suggested that the allopregnanolone might be a neuroprotective factor in the fetus.[2]

Rationale of Progesterone Supplementation in Pregnancy-Related Clinical Conditions

A. Threatened miscarriage: high-dosage progesterone is known to exert a tocolytic action in early pregnancy (►**Fig. 4**), and oral dosages of a minimum 200 mg/day for 2 weeks have been successfully used in clinical trials.[7] This dosage has also been used in the maintenance of uterine quiescence in patients with cervical cerclage.[12]

B. Recurrent miscarriage and ART: luteal phase defects and immune derangements are the most common causes of recurrent miscarriage in patients receiving ART. Progesterone facilitates favorable immunotolerance by stimulating the production of progesterone-induced blocking factor against natural killer cells which play

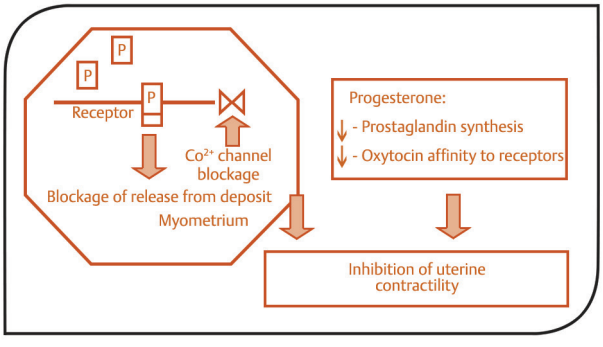

Fig. 4 Tocolytic effect of progesterone.[12]

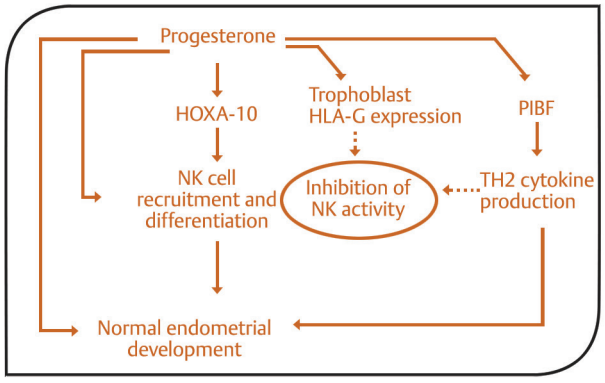

Fig. 5 Immunomodulation by progesterone to facilitate implantation.[11] NK cell, natural killer cell; PIBF, progesterone-induced blocking factor.

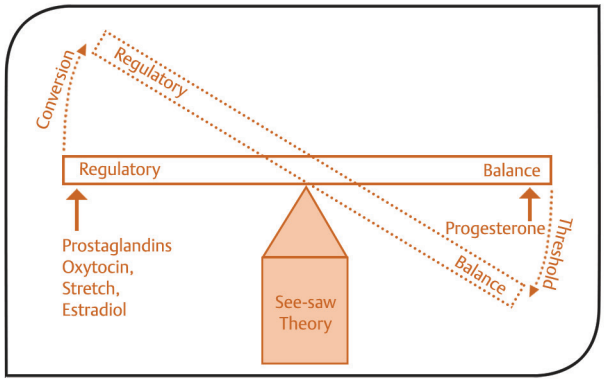

Fig. 6 Progesterone balance and parturition.[12]

an important role in implantation and the interaction between the conceptus and the host (►**Fig. 5**).[11-13] Oral natural progesterone, at a dose of 200-mg daily, has been used to improve luteal function while prolonging pregnancy significantly in patients with second-trimester loss and in those receiving ART.[8,14]

C. Preterm labor: progesterone withdrawal has been long associated with the onset of labor (►**Fig. 6**). The administration of high-dose oral progesterone has been advocated for tocolysis, especially in women with previous spontaneous preterm delivery.[12]

Conclusion

Acting on multiple molecular sites and via hormonal and nonhormonal actions, NMP SR supplementation provides clinically meaningful luteal support throughout pregnancy. Oral, vaginal, and parenteral routes have been used to deliver therapeutic doses. Recent advances in oral formulations, such as NMP SR, have achieved once daily dosing and shown high clinical activity.

Conflict of Interest
None declared.

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A Prospective Comparative Study of Oral NMP SR Tablets and Vaginal NMP Capsules in Women with Threatened Abortion and Patients at Risk of Preterm Labor

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Abstract

Introduction Miscarriage and preterm labor still remain the main cause of perinatal mortality in India, posing a serious clinical challenge. Progesterone has been used widely for these indications but there do not exist an adequate number of Indian studies to compare the routes of administration of this hormone. There have been many studies done with different types of progesterone, but very few Indian studies have compared oral and vaginal routes of NMP SR preparations. This study was conducted to evaluate the efficacy of oral NMP SR progesterone therapy for (1) the prevention of miscarriages in pregnant women experiencing threatened abortion and (2) the prevention of preterm labor.

Objective This prospective study was conducted to evaluate the efficacy of oral natural micronized progesterone sustained release (NMP SR) therapy in pregnant women experiencing threatened abortion, with the ultimate aim to prevent preterm labor.

Methods This is a prospective, randomized, multicentric clinical study in Indian pregnant women with threatened abortion to determine the safety, efficacy, and tolerability of oral NMP SR tablets administered as 400 mg once daily or 200 mg twice daily in comparison with vaginal NMP 200 mg capsule twice daily. The safety and efficacy of oral NMP SR was evaluated with the help of results and outcomes for pregnant women in terms of completing the full term of gestation, representing no major side effects, and also preventing miscarriage and preterm labor. The statistical analysis is performed by analysis of variance (ANOVA) test, where a significance level of 0.05 indicates a 5% risk of concluding that a difference exists when no actual difference was found among the three groups (SS = 20, $p = 0.947$).

Results A total of 150 patients were allocated for this clinical study. Of all the patients, 96% crossed 20 weeks in groups A and C, while 94% crossed 20 weeks in group B. The rate of first-trimester abortion in each group was 4% while in group B, one case of the second trimester was also noted. Most patients who enrolled in the study were primigravida (46% in group A, 62% in group B, and 50% in group C). The most common complaint was abdominal pain (66% in group A and 62% in group C) followed by vaginal bleeding (30% in groups A and B and 36% in group C). All the patients who presented with symptoms of threatened abortion continued to take progesterone supplementation. 43 patients in group A, 41 patients in both groups B and C continued pregnancy until term successfully. With regard to route of administration, oral and vaginal routes seem equally efficacious in the management of threatened abortion and prevention of preterm labor. Oral route offers similar efficacy and better compliance due to acceptable route, very few side effects, dosage convenience, and

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no discharge and chances of vaginal infection. Further, oral route showed better compliance, due to ease of administration and lesser side effects.

Conclusion Progesterone therapy in the form of oral NMP SR is as effective as vaginal route in preventing miscarriage in pregnant women at risk of threatened abortion and further helps to prevent preterm labor with better compliance. With respect to route of administration, it was seen that oral and vaginal routes are equally efficacious for management of threatened abortion and prevention of preterm labor.

High-risk pregnancy still remains a clinical challenge for many clinicians across the globe, including India. Among many representations of high-risk pregnancy conditions, gestational diabetes mellitus (GDM), preeclampsia, bad obstetrics history (BOH), and preterm birth (PTB) have been associated with high rates of fetal morbidity or mortality.[1]

Progesterone is an essential hormone that has been widely used in clinical interventions to improve and prevent threatened miscarriage, recurrent miscarriage, and preterm labor. A protein known as the progesterone-induced blocking factor probably acts as an immunological suppressant by inducing production of a T-helper type-2 dominant cytokine and blocking T-helper type-1 activity that mediates the immunological effects of progesterone. It has an essential role in supporting the luteal phase. It has been widely accepted because of its effect on the endometrium and its immunomodulatory and anti-inflammatory actions in the maintenance of pregnancy. Supplementation with natural micronized progesterone has a high bioavailability for cellular and subcellular organelles, and the data support a positive benefit–risk profile by improving live birth rates in those women. The risk factors for threatened miscarriage are polycystic ovary syndrome, smoking, obesity, and a previous history of miscarriage. The clinical supplementation with progesterone is required for the maintenance of pregnancy for early embryonic development, implantation, and fetal development, suggesting therapeutic compliance and a safety profile for long-term administration. Several routes of administration (i.e., oral, vaginal, intramuscular [IM], and transdermal) and various formulations of progesterone are available and clinically used in the treatment of threatened miscarriage. The oral progesterone may be preferable in view of patient compliance. Oral supplementation with sustained release (SR) progesterone may show improved patient compliance. In conclusion, there has been lack of available data for large-scale multicenter randomized controlled and comparative studies to evaluate the superiority of different types and routes of progesterones in threatened miscarriage and preterm labor.[1]

Many studies have been performed with various types of progesterone, but more Indian evidences and studies are required to compare NMP SR preparation with oral and vaginal routes of administration. This clinical trial was performed to evaluate the efficacy of oral NM SR progesterone preparation for (1) the prevention of threatened miscarriage and (2) the prevention of preterm labor.

Role of Progesterone

Progesterone (►**Fig. 1**) is an essential hormone that plays an important role in woman's normal reproductive cycle. The name progesterone is derived from "progestational steroid hormone," since it helps to prepare and maintain the uterine bed for conception. Progesterone is secreted by ovaries, placenta, and adrenal glands and is essential during luteal phase to sustain pregnancy.[2]

In early pregnancy, progesterone is produced by the corpus luteum whose duration has been estimated 12 ± 2 days. This organ is fundamental for pregnancy maintenance until the placenta (syncytiotrophoblast) takes over its function at seventh to ninth weeks of gestation, just after the expression of major histocompatiblity complex, antigens are suppressed in extraembryonic fetal tissue.[3]

Progesterone is an essential hormone in the process of reproduction. It is rightly called the "pregnancy hormone," as it is crucial in the maintenance of pregnancy.[4] Indeed, it induces secretory changes in the lining of the uterus and is essential for a successful implantation of the embryo. Moreover, progesterone modulates the immune response of the mother to prevent rejection of the embryo and enhances uterine quiescence and suppresses uterine contractions. Therefore, it is theoretically plausible that progesterone supplementation may reduce the risk of miscarriage in women with a history of recurrent miscarriages. Several studies have used progesterone and related steroids (progestogens; ►**Fig. 1**) in the attempt to prevent spontaneous miscarriage and to increase the embryo implantation rates in assisted reproduction programs. The term "progestogens" covers a group of molecules, including both the natural female sex hormones progesterone and 17-hydroxyprogesterone (17P), as well as several synthetic forms, all displaying the ability to bind progesterone receptors.

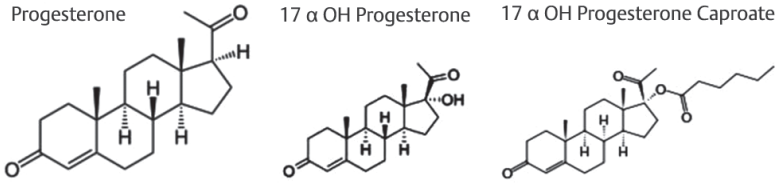

Fig. 1 Natural progesterone and synthetic progestogens with their chemical structure.[16]

Materials and Methods

Study Design

This is a prospective, randomized, multicentric clinical trial among Indian pregnant women with threatened abortion to determine the safety, efficacy, and acceptability of Oral NMP SR tablets (SUSTEN SR of Sun Pharma) administered as 400 mg once daily or 200 mg twice daily in comparison with NMP capsules (MIPROGEN of Bharat Serums & Vaccines) 200 mg per vaginum twice daily. Detailed history for risk factors in past pregnancies and current gestation was documented. Patients were randomized into three groups using table of random numbers after taking written informed consent to participate in the study. Medication continued till at least 20 weeks of gestation and risk assessment for preterm labor is done, and option of continuing medication till 34 weeks was also given to the patients. All of our patients consented to continue till 34 weeks.

Randomization: This is an open-label, three-arm, and randomized study conducted at two centers, one at the Department of Obstetrics and Gynecology, H.B.T. Medical College, Dr. R.N. Cooper Hospital, Mumbai, and other at Kiran Care and Cure Center, Andheri East, Mumbai.

Study Groups

Group A: 50 pregnant women with threatened abortion who received Oral NMP SR tablets 400-mg orally once a day.
Group B: 50 pregnant women with threatened abortion who received Oral NMP SR tablets 200-mg orally twice a day.
Group C: 50 pregnant women with threatened abortion who received NMP 200 mg capsule per vaginum twice a day.

Inclusion Criteria

Inclusion criteria of the study are as follows:

- Willing to participate in the study.
- Gestation of less than 20 weeks.
- Symptoms and signs of threatened abortion, like pain in abdomen, bleeding per vaginum, and ultrasonography suggestive of subchorionic hematoma.
- Documented viable intrauterine pregnancy on ultrasound.

Exclusion Criteria

Exclusion criteria of the study are as follows:

- Inevitable or incomplete abortion.
- Not willing for the study.
- Multifetal gestation.
- Patients with more than 20 completed weeks of gestation.

The study was started after taking approval from ethics committee of the H.B.T. Medical College and Dr. R.N. Cooper Municipal General Hospital. Patients were followed-up in person and telephonically till the pregnancy reached termination or abortion. Due to onset of corona crisis, some of the patients were tracked by video call and telephone. The patients were managed by antenatal protocol as followed in the hospital and received iron, folic acid, and calcium tablets as per national guidelines. Specific treatment for additional condition (e.g., hypertension in pregnancy) was noted and documented. In all three groups, medication was decided and continued till 20 weeks of gestation.

The efficacy assessment was performed at 20 weeks and follow-ups were done at 28 weeks, 34 weeks, at term, and after delivery.

If the patient did not complete therapy in either arm, due to allergy to drug, or lost to follow-up, the patient was removed from the study.

Study Duration

The total duration of study was approximately 1 year, till required number of patients was completed. Follow-up till delivery/pregnancy termination was done for all groups.

End Points

Primary End Points

- To determine the safety and tolerability of oral progesterone, oral NMP SR tablets 400-mg single dose and 200-mg twice daily dose in comparison to micronized progesterone capsule 200-mg twice daily per vaginum for the management of threatened abortion.
- To evaluate the efficacy in prevention of complete abortion by 20 weeks.

Secondary End Points

- To evaluate the number of cases reaching near term (34 weeks or more).
- To determine the perinatal and early neonatal outcomes in the form of neonate mortality and mode of delivery in all the three groups.

Safety, tolerability, and efficacy were assessed in the form of questionnaire at every 2 weeks on routine follow-up. Further side effects (such as dizziness, acceptability, nausea/vomiting, and vaginal discharge), compliance, completion of medications, development of any other symptoms, and occurrence of complete abortion were also assessed.

Statistical Analysis

The analyses were performed according to the *p*-value test. Analysis of variance (ANOVA) test was used to determine the relative rates for the primary outcome and other binary outcomes with adjustment for the minimization of variables. The data were analyzed and mean data were subjected to statistical analysis using ANOVA test for significance between all three groups. The significance was noted if $p < 0.05$.

20 weeks of gestation: the statistical analysis was performed by ANOVA test. A significance level of 0.05 was considered for 20 weeks of gestation and indicating a 5% risk.
34 weeks of gestation: the statistical analysis was performed by ANOVA test. A significance level of 2.8% risk was considered during 34 weeks of gestation.
37 weeks of gestation: the statistical analysis was performed by ANOVA test. A significance level of 2.66% risk was considered during 37 weeks of gestation.

Results

Demographics

The demographics is considered in parity and gravida in study population (►**Table 1**). The flowchart and profile of this prospective, randomized, multicentric clinical study is represented in ►**Fig. 2**.

Parity

Table 1 The results of parity in three groups (groups A, B, and C)

Gravida	Group A (*n* = 50)	Group B (*n* =50)	Group C (*n* =50)
G1	28	31	25
G2	14	15	18
≥G3	8	4	7

Complaints

Most common complaint seen in study population was abdominal pain (66% in group A, 50% in group B, and 62% in group C) followed by bleeding per vaginum (30% in group A, 30% in group B, and 36% in group C). Few patients (4% in group A, 18% in group B, and 2% in group C) also presented with both abdominal pain and bleeding per vaginum (►**Table 2**).

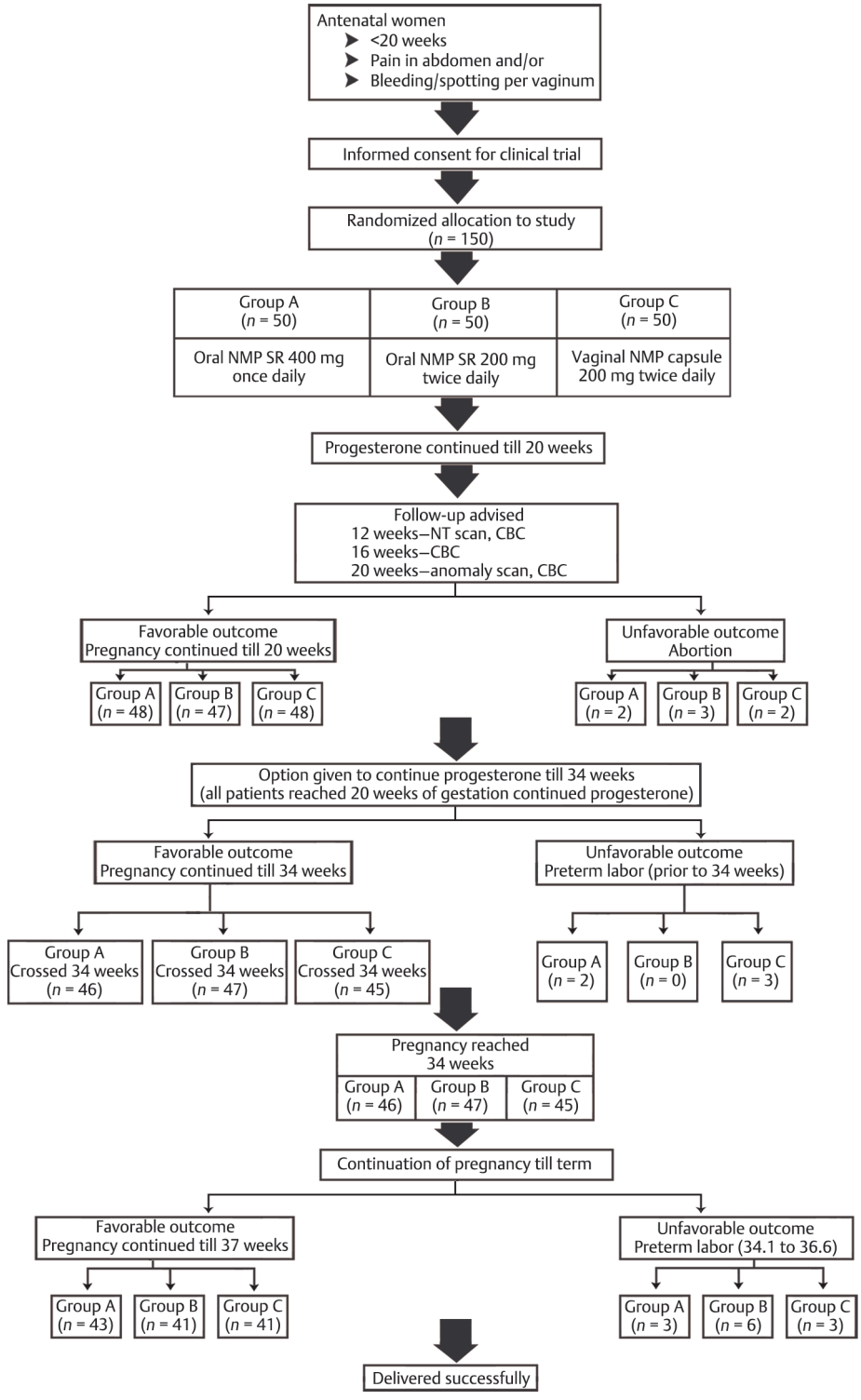

Fig. 2 Flow chart and profile of the clinical trial. CBC, complete blood count; NMP SR, natural micronized progesterone sustained release; NT scan, nuchal translucency scan.

Table 2 Complaints among antenatal women with threatened abortion

Complaints	Group A	Group B	Group C
Abdominal pain	33	25	31
Bleeding per vagina	15	15	18
Both	2	9	1

Outcomes

Of all the patients allocated, 96% (48) crossed 20 weeks in groups A and C, whereas 94% (47) crossed 20 weeks in group B. The first trimester abortion in each group was 4%. There is only one case of second trimester abortion noted in Group B.

Crossed 20 weeks: the results showed there was no actual difference found among three groups (SS = 4.83). Oral routes have shown significant effects in the prevention of threatened miscarriage (►**Table 3**).

Crossed 34 weeks: the results showed that a difference exists when no actual difference was found among the three groups (SS = 2.883). Both the routes have shown significant effects in the prevention of threatened miscarriage and preterm labor (►**Table 4**).

Crossed 37 weeks: the results showed that difference exists when no actual difference was found among the three groups (SS = 2.66, *df* =11). Both the routes have shown significant effects in the prevention of threatened miscarriage and preterm labor (►**Table 5**).

Of the total patients who delivered in all the respective groups, one perinatal death was reported each in groups A and B due to preterm very low birth weight. Out of the two perinatal deaths reported in group C, one was due to birth asphyxia and other was due to meconium aspiration of the baby (►**Tables 6** and **7**).

Table 3 Outcome of pregnancy crossed 20 weeks of gestation

Outcome		Group A	Group B	Group C
Abortion	First trimester	2	2	2
	Second trimester	0	1	0
Crossed 20 wk		48	47	48
Total		50	50	50

Table 4 Outcome of pregnancy crossed 34 weeks

Outcome		Group A	Group B	Group C
Abortion	First trimester	2	2	2
	Second trimester	0	1	0
Crossed 20 wk		48	47	48
Crossed 34 wk (out of 50)		48	47	48

Table 5 Outcome of pregnancy crossed 37 weeks by completing full-term

Outcome	Group A	Group B	Group C
Abortion	2	3	2
Crossed 20 wk	48	47	48
Crossed 34 wk (out of 50)	48	47	48
Crossed 37 wk (out of 50)	48	47	48

Table 6 Tabular representation of outcome in terms of mode of delivery

Outcome	Group A	Group B	Group C
FTVD (≥37 wk)	24	26	27
PTVD (<37 wk)	2	4	4
FT LSCS (≥37 wk)	16	14	12
PT LSCS (<37 wk)	3	2	3
Outlet forceps	3	1	2
Aborted	2	3	2
Total	50	50	50

Abbreviations: FTVD, full term vaginal delivery; FT LSCS, full term lower segment caesarean section; PTVD, preterm vaginal delivery; PT LSCS, preterm lower segment caesarean section.

Table 7 Neonatal outcome

Outcome of newborn	Group A	Group B	Group C
Perinatal death	1	1	2
Live newborn	47	46	46
Total delivered	48	47	48

Oral route offers better compliance due to (1) acceptable route, (2) very less side effects, (3) dosage convenience, and (4) no vaginal discharge and chances of vaginal infection.

Oral route has shown more acceptability (100%) in groups A and B (50 patients in each group) as compared with group C. Furthermore, only 45 patients got convinced to use the oral route of medication in group C. Dizziness, a common side-effect, was noted in 12 patients in group A, 8 patients in group B, and 4 patients in group C. Nausea/vomiting was observed in 24 patients in group A, 14 patients in group B, and 12 patients in group C. Further, vaginal discharge was seen in 2 patients in both groups A and B and 42 patients in group C. The maximum convenience was found in groups A (50 patients) and B (48 patients), as compared with group C (42 patients).

Discussion

The clinical supplementation with progesterone is required for the maintenance of pregnancy for early embryonic development, implantation, and fetal development, suggesting requirement of therapeutic compliance and a safety profile for long-term administration. Several routes of administration (i.e., oral, vaginal, IM, and transdermal) and various formulations of progesterone are available and clinically used in the treatment of threatened miscarriage. The oral progesterone may be preferable in view of patient compliance. Oral supplementation with SR progesterone may show improved patient compliance. Oral route offers better compliance due to the acceptable route, very less side effects, dosage convenience, and no vaginal discharge and chances of vaginal infection, suggesting therapeutic compliance and a safety profile for long-term administration.[1]

Progesterone can be administered through a variety of routes including oral SR tablets, vaginal capsules, IM injection, vaginal suppository, and vaginal gel. The oral route is

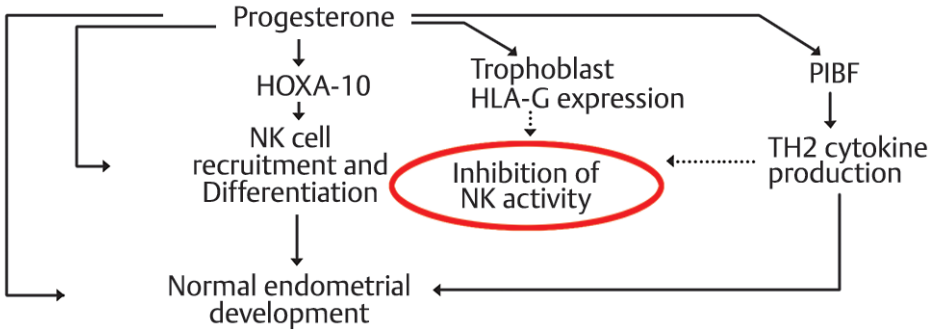

Fig. 3 Mechanism of progesterone. NK cell, natural killer cell; PIBF, progesterone-induced blocking factor.

the most convenient mode of administration in the management of threatened miscarriage. Although pharmacokinetics and pharmacodynamics features of progestogens have been studied, their use in human pregnancy remains controversial, that is, the way of administration. Indeed, progestogens could be administered by three routes: orally, vaginally, or intramuscularly. Oral administration guarantees optimal compliance by patients but shows many disadvantages; this route also results in side effects such as nausea, headache and sleepiness. The vaginal route results in higher concentrations in the uterus but does not reach high and constant blood levels. IM drug administration occasionally induces nonseptic abscesses, although it is the only route which results in optimal blood levels.[5]

Oral progesterone has a poor bioavailability and is rapidly metabolized by first-pass effects in the liver. Therefore, for a long time, oral progesterone could not be used in clinical applications due to rapid metabolic inactivation by the liver. Synthetic versions are available, which produce adequate plasma and tissue levels. Oral NMP SR is a natural and bioidentical progesterone. NMP offers complimentary immunomodulatory and anti-inflammatory actions in various therapeutic conditions including luteal phase support by offering a safety profile for long-term administration. This formulation represents a therapeutic approach by offering "therapeutic compliance" with oral formulation and hence avoiding the side effects related to long-term patient compliance in various reproductive disorders. NMP SR tablet formulation was introduced in India in 2011 and is available in oral formulation. NMP SR formulation releases progesterone gradually, minimizing first-pass metabolism. Currently, NMP SR formulation is available in tablet form that consists of progesterone in a methylcellulose base. This formulation provides a slow-release matrix for a moderate release of progesterone by hydrating in the gastrointestinal tract.[6]

The therapeutic use of progestogens not only supports endometrial development, natural progesterone also potentially sustain the survival of the embryo by shifting the immune system towards the production of non-inflammatory T-helper (Th)2 cytokines, and by increasing nitric oxide (NO) production thus improving blood flow and oxygen supply (►**Fig. 3**). It also inhibits NK cell activity, Th2 dominant cytokine response, upregulates TF, and PAI-1 activity.[7]

In 2018, a Cochrane review reported the pooled outcomes in pregnant women with threatened miscarriage up to 23 weeks of gestation. The authors found that treatment of threatened miscarriage with progestogens compared with placebo reduced the risk of miscarriage. In the subgroup analysis according to the route of administration, treatment with oral progestogens reduced the miscarriage rate; however, vaginal progesterone had little or no effect in reducing the miscarriage rate.[8]

In 2019, Wang et al[9] reported the results of a clinical trial that compared IM progesterone with oral progesterone in the setting of early threatened abortion. They found that both the routes were effective for patients with early threatened abortion, without significant adverse effects on perinatal outcomes and fetal heart rate and recommended that both injectable and oral formulations of progesterone could be chosen for the treatment of early threatened abortion.

Recently, a systematic review by Li et al[10] concluded that the use of progesterone increased the incidence of live birth but this benefit was only observed with the use of oral progestogens but not with vaginal progesterone.

Preterm Labor Studies

There are various references and clinical studies to support the use of progesterone in preterm labor. PTB complicates one in eight deliveries and remains a major cause of perinatal morbidity and mortality. Strategies to prevent PTB have, to date, been largely unsuccessful. On February 3, 2011, the FDA approved the use of progesterone supplementation to prevent recurrent PTB. Although questions about the optimal formulation, dose, and route of administration remain, this approval coupled with supportive statements by the American College of Obstetrician and Gynecologist (ACOG) and the absence of proven alternatives means that the use of progesterone supplementation to reduce the risk of recurrent PTB in women with a history of a prior preterm delivery can no longer be regarded as investigational. Appropriate candidates should be counseled about the potential benefits of progesterone supplementation from 16 to 20 weeks through 36 weeks of gestation to prevent PTB in any subsequent pregnancy. There is evidence that women with cervical shortening (≤1.5 cm) on transvaginal ultrasound may also benefit, although this indication has not yet been approved by the FDA. Women with multiple pregnancies do not appear

to benefit. Even in ideal candidates, progesterone supplementation has been shown to prevent recurrent PTB in only one-third of patients.[11]

Prabhat and Korukonda[12] conducted a retrospective study among 185 patients who presented with high-risk pregnancy at 40 centers. Oral NMP SR group was administered in a mean dosage of 271 mg for 18 ± 5 weeks. The results showed long-term administration of oral NMP SR group suggesting therapeutic compliance and a safety profile for high-risk pregnancy.

The National Institute of Clinical Excellence in the United Kingdom, International Federation of Obstetricians and Gynecologists (FIGO), and the Society of Maternal Fetal Medicine (SMFM) in the United States recommend the use of progestogens for women at high risk of PTB. The latter advises that women between 20 and 36 gestational weeks can receive 17 hydroxyprogesterone caproate (17p) (250-mg IM/week) starting at 16 to 20 weeks until 36 weeks or delivery for women with a singleton gestation and a history of prior spontaneous PTB.[13]

There was probably a slight benefit for women receiving progestogen seen in the outcome of live birth rate (risk ratio [RR] = 1.07, 95% confidence interval [CI]: 1.00–1.13, six trials, 1,411 women, and moderate-quality evidence).[14,15]

With respect to route of administration, oral and vaginal routes seem equally efficacious for management of threatened abortion and prevention of preterm labor. The results are comparable to Cochrane Review by Wahabi et al.[8]

Limitations of the Study

The number of patients were assigned and decided for the study after statistical inputs. We feel that more large-scale, multicenter, randomized, and controlled studies are required. Due to onset of corona pandemic and national lockdown, in-person follow-up was not possible for all the pregnant women; however, this clinical data was documented and managed by virtual communication and online consultation.

Conclusion

In conclusion, based on our clinical trial, we suggest that progesterone therapy, including oral NMP SR, may effectively prevent miscarriages in pregnant women with threatened abortion and reduce risk of PTB. Oral and vaginal routes seem equally effective. Large-scale, multicenter, randomized, and controlled studies are needed to better evaluate the efficacy of progesterone therapy in pregnant women with threatened abortion. All the patients who presented with symptoms of TA were continued to take progesterone supplementation, 43 patients in group A, 41 patients in group B, and 41 patients in group C were continued till full term successfully.

Ethical Approval and Consent

This prospective, randomized, multicentric clinical trial was performed by obtaining written approval of clinical study protocol, written patient-informed consent updates, and other written information provided to patients by Ethics Committee. Written approval of the study was obtained from Ethics committee before study commencement.

Authors' Contributions

Reena Wani and Neerja Mistry participated in designing the research. All authors searched the studies, extracted the data of interest, and performed the data analysis. The authors drafted the manuscript, and all other authors commented on it. All authors read and approved the final manuscript.

Conflict of Interest

None declared.

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Various Clinical Trials on Oral Administration of Natural Micronized Progesterone Sustained Release: A Systematic Review

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Oral natural micronized progesterone sustained release (NMP SR) formulation has been developed and marketed internationally by Madison Pharmacy Associates, Madison, Wisconsin, since 1986.[1] The NMP SR formulations utilize matrix-releasing technology and show slow sustained release pattern over 24 hours. Therefore, it avoids sudden drug release and minimizes the loss of drug in the first-pass metabolism. This formulation was introduced in India in the last decade and since then it has been increasingly adopted in the clinical practice because of the promising advantages of improved compliance and convenience for the patients.[1]

Since NMP SR with its immunomodulatory, antiprostaglandins and uterine relaxant properties play an important role in secretory transformation of estrogen primed endometrial lining to ensure adequate oocyte implantation, it is increasingly being used in luteal deficiency states. Accordingly, there has been an increasing volume of scientific information on the subject of NMP SR. However, a systematic review of the clinical literature is lacking.

Therefore, we decided to systematically review the literature published on NMP SR in the last decade via conducting an electronic search in PubMed and Google Scholar using the following keywords: NMP SR progesterone and natural micronized progesterone sustained release. A total of six unique papers[1-6] were identified of which one was excluded[6] as that focused on the marketing aspects instead of clinical aspects. Below, we present the results of the review and highlight the existing knowledge gaps related to NMP SR.

Results of the Systematic Review

While analyzing the recent clinical evidences, we found five unique articles related to NMP SR (►**Table 1**). Of the five articles,[1-5] four were original research articles and only one was a narrative review.[1] All the articles were published from 2014 to 2018, and were authored by Indian researchers.

In addition, most of the original articles were related to the assisted reproductive technology (ART; ►**Table 2**) with one study included mixed etiologies, two studies examined patients with unexplained infertility alone; while only one study, the most recently published in 2019,[5] investigated the value of NMP SR in high-risk pregnancy states, comprising a diverse set of conditions. However, as a common feature, most of the studies included small number of patients with one condition and one dosage regimen.

As can also be seen from ►**Table 2**, the 300-mg once daily dosage has been the most frequently used dose in these studies. While only two studies had a control group of oral dydrogesterone.

The outcomes used in the studies have also been diverse (►**Table 3**). While the initial studies mostly focused on the safety aspect, the more recent ones have focused on both efficacy and safety. In general, the adverse events reported with NMP SR have been clinically insignificant with none of the events causing discontinuation of treatment or hospitalization.

Regarding efficacy of oral NMP SR tablet, the outcomes were comparable to the control groups. In the study on NMP use in high-risk pregnancy, the primary outcome of pregnancy continuation till 34 weeks was 100% (►**Table 3**).

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Table 1 Research articles on NMP SR reported in the last decade

Author	Year	Title	Study type
Purandare et al[2]	2014	Prescription Event Monitoring Study to Assess the Safety Profile of Oral Natural Micronized Progesterone Sustained Release in India	Original research article
Gopinath and Desai[3]	2014	Open-Label Observational Study to Determine the Success Rate of First Cycle Intra Uterine Insemination (IUI) Involving Luteal Phase Support with Oral Natural or Synthetic Progesterone	Original research article
Malhotra and Krishnaprasad[4]	2016	Open-label, Prospective, Investigator Initiated Study to Assess the Clinical Role of Oral Natural or Synthetic Progesterone During Stimulated IUI Cycles for Unexplained Infertility	Original research article
Malik and Krishnaprasad[1]	2016	Open-label, Prospective, Investigator Initiated Study to Assess the Clinical Role of Oral Natural or Synthetic Progesterone During Stimulated IUI Cycles for Unexplained Infertility	Narrative review
Piyush and Krishnaprasad[5]	2018	A Drug Utilization Surveillance Study to Assess the Clinical Utility and Safety of Oral Natural Micronized Progesterone SR in High Risk Pregnancies: NAP-DELAY Study	Original research article

Table 2 Indications and patient groups investigated in original studies

Author	Indications	Study group	Control group
Purandare et al[2]	Assisted reproductive technology (bad obstetric history, unexplained fertility, and secondary amenorrhea)	153 women receiving NMP SR 300 or 400 mg, once daily	None
Gopinath and Desai[3]	Assisted reproductive technology (unexplained infertility)	30 women receiving NMP SR 400 mg once daily	30 women receiving dydrogesterone 10-mg twice daily
Malhotra and Krishnaprasad[4]	Assisted reproductive technology (unexplained infertility)	22 women receiving NMP SR 200 mg, once daily; 23 women receiving NMP SR 300 mg once daily	33 women receiving dydrogesterone 10-mg twice daily
Piyush and Krishnaprasad[5]	High risk pregnancy (first or second trimester loss cases, cervical factor, still birth, spotting, and placenta previa)	28 bad obstetrics history cases with RPL; 22 cases with spontaneous pregnancy loss; 19 cases of spotting while receiving infertility treatment; 12 cases with previous preterm birth Patients administered NMP SR 200/300/400 mg once daily as needed	None

Table 3 Key outcomes and results in original studies

Author	Outcome measures	Study results
Purandare et al[2]	Safety profile (incidence of side effects; severity of side effects; treatment discontinuation)	Drowsiness (0.6%), hyperemesis (1.3%) and giddiness (0.6%); mild and transient
Gopinath and Desai[3]	Serum progesterone levels at 23 days and pregnancy rates after first cycle; safety profile	90% women receiving NMP SR had progesterone over 14 ng/mL at 23 days Pregnancy rate was 6.6% in the NMP SR group. No side effects were reported
Malhotra and Krishnaprasad[4]	Serum progesterone levels at 21 ± 2 days and pregnancy rates after first cycle; safety profile	82.2% women receiving NMP SR had mid-luteal progesterone over 14 ng/mL Pregnancy rate was 11% in the NMP SR group Three cases of drowsiness and 1 case of nausea were seen with OMP SR
Piyush and Krishnaprasad[5]	Pregnancy continuation till 34 weeks and safety profile	In all cases (100%), pregnancy continued until 34th week Treatment emergent adverse events included gastritis (2.2%), vomiting (2.2%), drowsiness (4.3%), dizziness (3.2%); none requiring hospitalization

Discussion

There is an increasing trend of scientific reports on NMP SR use in the last decade in India, and more clinical indications are being covered. This shows increasing confidence of the practitioners in using this formulation. This can be attributed to the improved patient compliance with sustained release formulation ensuring once daily oral dosing. The demonstrated safety profile of the NMP SR formulation could also be a supporting factor for its growing research interest.

Most studies have focused on the achievement of serum progesterone levels with NMP SR as per the Medicine and Healthcare Products Regulatory Agency (MHRA) guidelines, which had been a limitation of micronized progesterone vaginal capsules. Therefore, this limitation seems to have been overcome by the use of NMP SR formulation.

However, there are certain common methodological issues involving most published studies. Most studies have included a diverse set of patients in smaller numbers and allowed multiple dosages. In addition, control groups and randomization have not been used in several studies. Future studies should include more narrow and refined inclusion criteria and larger sample sizes to increase the robustness of their results. Moreover, studies on high-risk pregnancy states, such as previous preterm birth (PTB) and threatened abortion, need to be separately evaluated and a greater number of studies are needed in this regard when compared with ART, for which there is a larger available dataset.

Conclusion

In conclusion, this systematic review evaluated recent literatures on clinical utility of NMP SR and identified a clustering of research articles in the last 5 years. Although the safety and efficacy of NMP SR in ART has been satisfactorily demonstrated in several studies, and the single study on its usage in pregnancy demonstrated excellent results, more studies with robust methods are desirable to realize the full clinical benefits of NMP SR.

Conflict of Interest
None declared.

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Clinician Perceptions of the Available Progesterone in Clinical Practice: Threatened Miscarriage and Preterm Labor

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Progesterone therapy is a commonly used treatment for threatened miscarriage, threatened preterm labor, and prevention of both miscarriages and preterm labor. This is based on the fact that progesterone is essential for the notation and continuation of pregnancy.[1]

There is an increasing evidence of the utility of such an approach in both these conditions though some robust data are still awaited to support this approach. The doubts about the efficacy of progesterone treatment are probably due to many other confounding factors responsible for both miscarriages and preterm deliveries even though many of the pathogenic mechanisms seem to be routed through progesterone deficiency of inefficiency. Despite every clinician's recommendations, progesterone therapy for such obstetric situations in the perceived belief of progesterone deficiency could be possibly ameliorated. This article will address these clinician perceptions based actually on a meagre evidence with no head-to-head comparison among the formulations but with an intention to achieve successful pregnancy outcomes in the form of live births. The dilemma further is made complex due to the various formulations of progesterone that are available for use in clinical practice.

Introduction

Use of antiprogesterone drugs for medicated termination of pregnancy has proved that progesterone withdrawal can cause pregnancy discontinuation. This strengthened the hypothesis that progesterone has a central role in the maintenance of early pregnancy and progesterone deficiency or insufficiency can be the cause of some miscarriages. A study from China with 726 participants presented that threatened miscarriage revealed a greater risk of abortion when the serum progesterone level was less than 90.62 nmol/L.[2] Furthermore, pathways leading to occurrence of preterm delivery seem to be having a common factor which is influenced by progesterone inadequacy. Such hypotheses have resulted in numerous clinical trials of progesterone supplementation in women at high risk of miscarriage and preterm delivery. Especially women with bleeding in the first half of pregnancy, history of recurrent pregnancy losses, and short cervix are identified to be at risk and several trials have shown some benefit of progesterone therapy in these situations. In 1953, the first randomized trial of progesterone was conducted in women with recurrent miscarriage and subsequently 11 such trials were conducted till date that are referred.[3] In 1987, the first trial of use of progesterone in women with threatened miscarriage was published followed by seven similar trials.[4]

These trials failed to give any solid foundation to create evidence-based recommendations with regard to the efficacy of progesterone therapy or type of formulations and preferred route owing to weak methodology and small cohort size. Thus the two most influencing organizational guidelines, such as the American College of Obstetricians and Gynecologists (ACOG) and the National Institute for Health and Care Excellence (NICE), could not mention the use of progesterone therapy with conviction with ACOG concluding the use of progestins in threatened miscarriage as controversial,[5] while the NICE expecting a larger multicentric, randomized cohort to rely on such a therapy.[6] Additionally, progesterone formulations used were heterogenous and therefore choosing a particular progesterone formulation and a requisite dose is completely based on the perceptions of the clinicians offering these treatment.

Recently two trials, PROMISE (progesterone in recurrent miscarriage) and PRISM (progesterone in spontaneous miscarriage), have been conducted to generate well-powered

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data to establish robust evidence on the role of progesterone therapy to prevent miscarriage and increase the live birth rate. Despite the discordant opinion published in NEJM,[7] depicting the failed promise by the progesterone in the PROMISE trial, the same group republished its advantage in the ACOG journal. Progesterone, as the name suggests, is the hormone especially made for the promotion or protection of pregnancy and its deficiency and inefficiency are believed to cause implantation failure, threatened miscarriages, and preterm deliveries. Actions of progesterone are understood today and are primarily through luteal phase support. Insufficiency of progesterone is proposed to be associated with improper formation of the implantation mechanics, as well as the immunologically tolerant and noninflammatory milieu. Progesterone helps implantation[8] and has an immunomodulatory function. Immunomodulation is brought about by hosting and modifying the expression of the natural killer (NK) cells[9] and by advantageously altering the immunological mechanism at the fetomaternal interphase. Anti-inflammatory actions of progesterone are found to be influencing the cytokines toward suppressing the inflammatory responses. Promotion of local vasodilatation thus enhancing better angiogenic responses is attributed to progesterone.[10] Maintaining myometrial quiescence and helping in prevention of preterm delivery and also as a maintenance tocolysis used after active tocolysis and in concurrence of cervical encerclage have been proposed when progesterone is supplemented.

The types of progesterone available for use in clinical practice today are many. Formulations such as oral sustained release tablets, capsules, gels, injectables, and vaginal tablets are available for use in a clinical context and widely used today with variable preferences by practitioners. Although different formulations of synthetic progesterone are available, they are less popular and less commonly used now than earlier. Many formulations also are perceived to be better than other and patient preference and compliance are considered while prescribing these medications.

Historically, progesterone was used for treatment of threatened miscarriages and especially when patients presented with history of recurrent miscarriages or a previous unexplained miscarriage. Over a period of time, progesterone started being used as a luteal phase support medicine primarily, as clomiphene citrate was used for ovulation induction and the understanding of endometrial influence was understood in induced cycles. Progesterone mechanism of action was accepted but not appreciated through investigations of progesterone levels. Conditions, such as out of phase endometrium, midcycle progesterone deficiency, low levels of progesterone periimplantation in early pregnancy loss, were attributed to a condition called as luteal phase defect and at risk of miscarriages.[11] Serum progesterone cut-off value of <35 nmol/L was validated as clinically useful predictor of miscarriage prior to 16 weeks of pregnancy was implicated in a large prospective study.[12] The prescription of progesterone in such situations became acceptable as rate of abortion was reduced in women treated with progesterone, irrespective of their gestational age.[13] Such prophylactic use of progesterone is undertaken in women perceived to be at a potential risk of developing miscarriages (►**Table 1**).

There have always been concerns of such progesterone supplementations during the critical period of organogenesis giving rise to congenital defects in the baby. Especially, the androgenic progesterone were much perceived to be responsible for the same, especially occurrence of virilization, hypospadias, etc. This thought also is fuelled by the past experiences of the diethylstilbesterol (DES) spectrum disorders.

Eventually, the benefit and the safety of the natural progesterone therapy in threatened abortion, including assisted reproductive techniques, have been discussed in the next chapter by Malhotra et al. In some conditions, such as recurrent pregnancy losses or previous spontaneous miscarriages, progesterone starting from luteal phase has been proposed to be beneficial.[14] In the past decade or so, there is resurgence of use of progesterone also to prevent midtrimester losses and preterm births (PTBs). This got reinstated nearly after a lull of over 14 years by the observation that weekly injections of 17-α-hydroxyprogesterone caproate (17OHPC) caused considerable reduction in the rate of recurrent preterm delivery in women at risk and reduced the possibility of neonatal complications.[15] The incidence of spontaneous PTB is higher in singleton pregnancies conceived by the assisted reproductive technology (ART; in vitro fertilization [IVF]/intracytoplasmic sperm injection [ICSI]) as compared with spontaneously conceived singleton pregnancies. In twin ART (IVF/ICSI) pregnancy, there is a 10-fold increased age and parity-adjusted risk of delivery before 37 weeks and 7.4-fold increased risk before 32 weeks as compared with singleton pregnancy.[16] This was further reiterated by a cohort study and metanalysis[17] which stated that the risk of spontaneous preterm delivery in singleton pregnancies resulting from IVF/ICSI is significantly greater than that in spontaneously conceived singletons with a caution from the authors of interpreting the data with caution in view of the weak powered study. French clinical practice guidelines were the first to recommended that women with a threatened late miscarriage and sonographically identified short cervix (<25 mm on trans-vaginal scan) with no uterine activity can be given daily treatment with progesterone up to 34 weeks of gestation.[18]

Clinicians' perceptions about progesterone use: the choice made by a clinician is based on (1) the experience in the individual clinical practice, (2) recommendations by the organizations, (3) evidences available, and (4) acceptabilities and compliance of the patient. The choice also will get influenced by the appearance of any adverse effects immediate or long-term adverse outcomes. Every formulation is perceived as different and the preferences would vary from practice to clinician. Each type of progesterone formulation is described

Table 1 Clinically perceived risks of spontaneous miscarriages

Older women: age >35 years, obesity
Short cycles hypothyroidism polycystic ovary syndrome
Previous spontaneous miscarriage recurrent pregnancy losses autoimmune disorders, e.g., antiphospholipds antibodies/systemic lupus erythematosus-induced ovulation

here with its subtle characteristics and recommendations as perceived by the clinician.[19]

Progesterone type: choice of progesterone formulation is individual based on the clinicians' perception and every such type of formulation is described here briefly to understand this better.

- Allylestrenol is a synthetic progestogen that has been used for a long period and is used in threatened miscarriages, threatened preterm labor, fetal growth restriction (FGR), and gestational hypertension. Allylestrenol is a 19-nortestosterone derivative, attributed with advantageous mechanism of action consisting of a triple effect—trophoblastic, placentotropic, and β2-adrenergic.[19] Because of its subtly altered chemical structure believed to not cause any virilization, its additional attribute seems to be improved placental perfusion and therefore perceived to be safe. It is perceived to be causing androgenization and ineffective as it does not have any overt actions to prove its efficacy. It is also used as maintenance tocolysis after acute tocolytic measures succeed in threatened preterm labor.
- Dydrogesterone, a synthetic stereoisomer of progesterone, is available in an oral form with high oral bioavailability and has potent progestogenic activity, but with no androgenic, glucocorticoid, or oestrogenic activity. It is found to be effective in luteal phase support in ART cycles and for prevention of recurrent miscarriages. Its immunomodulatory properties are considered to be the reason that why it is chosen in prevention of threatened miscarriages. The fact that it is synthetic and with some evidences of its use after 8 weeks of gestation associated with congenital urogenital and cardiac anomalies in the fetus raise concerns. Its use in threatened preterm labor is not established. It has not been studied for prevention of preterm deliveries.
- 17OHPC is a synthetic progestogen recommended for use in prevention of midtrimester miscarriages and preterm deliveries possibly by achieving myometrial relaxation. The randomized controlled trial (RCT) using this progesterone was the one which initiated a renewed interest in progesterone treatment for prevention of PTBs.[15] The advantages identified are assured compliance of the treatment as it is in injectable form and effective uterine relaxation. Clinically perceived disadvantages are that the injections are painful, may cause cervical dystocia eventually and gestational diabetes, water retention, and intrahepatic cholestasis in mothers. Also there was a nonsignificant increase in stillbirths and miscarriages in women receiving 17OHPC and ineffective action in twin gestation with short cervix.[20]
- Micronized progesterone: natural micronized progesterone is perceived to be effective in short cervix compared with a placebo when used as a vaginal 200-mg micronized suppository[21] The PREGNANT trial is a multicentric double-blind RCT demonstrated the efficacy of vaginal gel in women identified with short cervix.[22] The safety of use of vaginal progesterone was established by a study which followed-up in utero exposed fetuses for a period of 2 years of life.[23] Natural micronized progesterone has established its safety and efficacy in prevention of miscarriages, as well as PTBs, in properly selected groups and is found to have anti-inflammatory, immunomodulatory, angiogenetic, and myometrial quiescing actions. It also does not increase the risks of cholestasis and gestational diabetes in the mother.

Route of administration: the route is defined for the dydrogesterone and allysterenol to be oral and for the 17OHPC as intramuscular (IM). Both these routes have the possibility of the liver first -pass effect and increasing the associated extraneous side effects. The injectable route is also associated with pain and sometimes injection site abscesses. Natural micronized progesterone can be delivered via a gel, injections both water and oil based, vaginal suppositories, and oral sustained release tablets, as well as capsules. All these routes have been studied to understand their pharmacokinetics and pharmacodynamics and the way of administration is as perceived by the clinician or the patient. Oral administration guarantees optimal compliance by patients but shows disadvantages such as nausea, headache, and sleepiness due to the release of pregnane metabolites. The vaginal route results in higher concentrations in the uterus as caused due to the first-pass effect channels through the vaginouterine lymphatic pathway and does not reach high and constant blood levels. Also, it is found as cumbersome by patients and cause a flare of bacterial vaginosis. The IM administered drug causes discomfort and rarely can induce nonseptic abscesses, although it is the only route which results in optimal blood levels. Oral sustained release formulations are known to achieve the recommended therapeutic levels, increased compliance, and advantage of once daily dose. These use a special technology due to which the drug is transported unmetabolized to the enteric passage where its micellar solubilization technology causes slow release of the active molecule at a gradual pace and is absorbed by the enteric lymphatic pathway to reach the recommended therapeutic levels. Additionally, it bypasses the liver metabolism and uptake thus reducing extraneous side effects. Thus, a useful pharmacotherapy is delivered with advantage of compliance, convenience, and efficacy.

Clinicians' perceptions and attitudes in practice: in a self-administered survey among obstetricians–gynecologists regarding use of progesterone and prevention of PTB, 74% reported recommending or offering progesterone for prevention of PTB. Almost all reported use for the indication of previous spontaneous PTB. Many other indications also were considered such as dilated/effaced cervix (37%), short cervix on ultrasound (34%), and cerclage (26%). These results suggest that most obstetricians recommend or offer progesterone to prevent PTB for women with a previous spontaneous PTB and many also offer it to women with other high-risk obstetric conditions.[24]

Conclusion

Progesterone therapy has been used for a long period of time and there is much evidence now to support the rationality of its use. Despite the absence of robust evidences, clinicians seem to be using progesterone therapy based on the understanding of the actions of the natural progesterone in vivo.

Many confounding factors are seen to result in occurrence of miscarriages and preterm deliveries and at some point in the pathogenesis, progesterone inefficiency seems to be a possibility. To not miss the opportunity of supporting the pregnancy progesterone supplements that are used as preventive or therapeutic mechanisms.

Conflict of Interest
None declared.

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Progesterone for Threatened Miscarriage Including Assisted Reproductive Technology: Special Clinical Indications

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The modern history of progesterone began with its discovery and isolation by Professor Willard Allen, who published the first paper on extracting progesterone from corpus luteum on September 23, 1929.[1]

Progesterone, so called "pregnancy hormone," helps in preparing the secretory endometrium for implantation and maintenance of early pregnancy in many ways by:

- Modulating the maternal immune response.
- Suppression of inflammatory response.
- Reduction of uterine contractility.
- Improvement of uteroplacental circulation.
- Luteal-phase support.

It is well understood that majority of the early losses in pregnancy are because of genetic causes, and cytokine-mediated immune reactions are responsible for 40 to 60% of idiopathic recurrent spontaneous miscarriages. Today, we do understand that maternal immune tolerance of the fetus plays a key role in promoting fetal survival in utero. Progesterone helps the human T-cells production of Th2 cytokines and blocks the production of Th1 cytokines, thus balancing both in pregnancy maintenance.

What is Micronized Progesterone?

Progesterone is available as both natural progesterone and synthetic progestin. The natural progesterone is obtained from soybeans and Mexican yam roots.[2] Micronization of the natural progesterone confers the following characteristics:[3]

1. It is a natural progesterone (decreasing the particle size increases absorption and bioavalability).
2. Dose-dependent increase of serum progesterone can be achieved.
3. Maximum absorption after food than on an empty stomach.
4. Short acting and needs multiple doses.
5. Lipid friendly.

Progesterone in Threatened Miscarriage

Approximately one in five pregnant women will experience threatened miscarriage which is defined as bleeding through the vagina, with a closed cervix, that occurs before the gestational age at which a fetus would be viable ex utero.[4] Unfortunately, about half of them will eventually suffer an actual miscarriage.

Mechanism of Action

Corpus luteum progesterone production is critical for pregnancy maintenance until the placenta takes over this function at 7 to 9 weeks of gestation. In fact, removal of the corpus luteum[5] or administration of a progesterone receptor antagonist[6] readily induces abortion before 7 weeks (49 days) of gestation. Progesterone induces secretory changes in the lining of the uterus, which are important for implantation of the fertilized ovum.[7]

The benefit of supplemental progestin treatment among women with threatened abortion has been unclear, in part because of small study sizes, differing types of progestins, varying routes of administration, and differing outcomes assessed. A large RCT called the PRISM (progesterone in spontaneous miscarriage) trial evaluated the role of progesterone in women with bleeding in early pregnancy included 4,153 women and found that progesterone therapy administration during the first trimester did not result in a significantly higher incidence of live births than placebo. Vaginal micronized progesterone of 400 mg, administered twice daily, was associated with increasing live birth rates according to the number of previous miscarriages. In a subgroup analysis among women with a history of one or more miscarriage(s) and bleeding in current pregnancy, the live birth rate was 75% (689/914) with progesterone versus 70% (619/886) with placebo (rate difference 5%; risk ratio = 1.09, 95% confidence interval: 1.03–1.15; p = 0.003). The benefit was greater for the subgroup of women with three or more previous miscarriages and current pregnancy bleeding.[8]

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However, a recent meta-analysis conducted by Li et al on the effect of progestogen for women with threatened miscarriage including 10 trials and 5,056 participants concluded that progestogens may have benefits on live birth rate and miscarriage rate for women with threatened miscarriage. These benefits appear to be confined to the use of oral progestogen, and no statistically significant improvements were seen with vaginal progesterone.[9]

Oral Progesterone versus Vaginal Progesterone

RCT: miscarriage rate	Oral progesterone (%)	Vaginal progesterone (%)
Czajkowski et al[10]	8.3	13.8
Vincze et al[11]	8.1	7.9
Siew et al[12]	15.3	10.2

Possible explanations for differences observed between oral progestogen and vaginal progesterone are vaginal progesterone causes local irritation, discharge, and bleeding.[13]

Oral administration is the easiest route and is generally the most acceptable route.[14] The drug effect of vaginal progesterone is reduced in women after intercourse.[15] Micronization and sustained release formulations make better compliance.

A systematic review and meta-analysis done by Lee et al in 2017 on "The Influence of Oral Dydrogesterone and Vaginal Progesterone on Threatened Abortion" concluded that progesterone therapy, especially oral dydrogesterone, may effectively prevent miscarriages in pregnant women with threatened abortion.[16]

Wahabi et al[17] performed an interventional Cochrane review on the use of progesterone for treating threatened miscarriage including seven trials (696 participants) made the following conclusion:

Progesterone	Placebo/no treatment	Probably reduces the risk of miscarriage	Moderate quality of evidence
Oral progestogen	No treatment	Probably reduces miscarriage rate	Moderate quality of evidence
Vaginal progesterone	Placebo	Probably has little or no effect in reducing miscarriage	Moderate quality of evidence

The subgroup interaction test indicated no difference according to the route of administration between the oral and vaginal subgroups of progesterone.[17] It seems that micronized sustained release formulations are better accepted.

Progesterone in Recurrent Miscarriages

The PRISM and progesterone in recurrent miscarriage PROMISE trials found a small but positive treatment effect that seems to be dependent on the number of miscarriages. The benefit was greater for the subgroup of women with three or more previous miscarriages and current pregnancy bleeding. Therefore, women with a history of miscarriage who present with bleeding in early pregnancy may benefit from the use of vaginal micronized progesterone 400-mg twice daily. Finally, the PROMISE and PRISM trials did not find any evidence of an increase in congenital abnormalities or short-term harm.[8,18]

Progesterone in ART: Special Clinical Indications

Role of progesterone in assisted reproductive technology (ART) is well understood. The main function of progesterone is to induce "secretory" changes in endometrium that is further complimented by its immunomodulatory and anti-inflammatory actions. It positively modulates progesterone-induced blocking factor (PIBF), natural killer (NK) cells, and *HOXA10* genes for better implantation.[19]

Stimulated in vitro fertilization (IVF) cycles are known to be associated with luteal phase defect and different doses, types, and duration of luteal phase support (LPS) have been recommended. There is still no agreement regarding the optimal dose supplementation. Intramuscular (IM) progesterone, though widely used, is inconvenient for patients and the vaginal progesterone gels/pessaries have been found to be more acceptable.

Progesterone Pretreatment before Ovarian Stimulation

Pretreatment with a progestogen or estrogen alone to suppress intrinsic hormone production has been widely studied in IVF/intracytoplasmic sperm injection (ICSI) cycles to prevent side events such as cyst formation and probably improving the pregnancy outcomes.

A Cochrane review of four RCTs including 421 women on progestogen pretreatment for ovarian stimulation protocols for women undergoing assisted reproductive techniques concluded that progestogen pretreatment may reduce the risk of ovarian cysts in agonist cycles. However, there is no demonstrable beneficial effect of progesterone in agonist or antagonist protocol on live birth rate/ongoing clinical pregnancy rate. There is low-quality evidence of an increased clinical pregnancy rate with progestogen pretreatment in gonadotrophin-releasing hormone (GnRH) agonist protocols.[20]

Progesterone in Luteal Phase Support

It has been well known since the 1980s and is today universally accepted that the luteal phase subsequent to IVF cycles in the absence of exogenous hormonal support is characterized by early luteolysis, followed by premature decline of estrogen and progesterone levels. These abnormalities have a negative impact on endometrial receptivity and embryo implantation, with a significant reduction in success rates of IVF treatments.[21,22]

Safety and Efficacy of Luteal Phase Support Protocols: Dose, Timing, and Route?

Stimulated Intrauterine Insemination Cycles

In a meta-analysis of five randomized controlled trials[23] comparing LPS in a clomiphene citrate cycle versus gonadotrophin cycle and clinical pregnancy rate (CPR) as their primary outcome showed significantly increased CPR.

ART cycles have an insufficient luteal phase, which might be due to the supraphysiologic estrogen levels in the follicular phase, as a result of ovarian stimulation, thus requiring sufficient LPS to improve implantation and pregnancy rates.[24]

Adequate luteal support may be achieved by the following:

- Use of progesterone.
- Substituting deficient luteinizing hormone (LH) with GnRH agonists.
- Human chorionic gonadotrophin (HCG).[24]

ESHRE 2019 recommendations based on Cochrane meta-analysis 2015 strongly supports the use of progesterone for luteal phase support after IVF/ICSI. The meta-analysis involving five RCTs and 642 women reported a higher live birth/ongoing pregnancy rate with progesterone compared with placebo/no treatment.[24]

Dose: micronized vaginal progesterone of 200-mg thrice daily in-oil capsules or 100-mg two or three daily for micronized vaginal progesterone in starch suppositories. IM progesterone is used in dosage of 50/100 mg/d, oral dydrogesterone used in dosage of 20 to 30 mg/d.

Timing: progesterone for LPS should be started in the window on the day of oocyte retrieval and should be administered at least until the day of the pregnancy test.

Route: Cochrane 2015 found no difference in pregnancy outcomes when different routes of administration were compared: vaginal/rectal to oral route and also vaginal/rectal to IM route.[24] Another RCT including 400 women also investigated the IM compared with vaginal route and reported no difference in clinical pregnancy rate (26.5 vs. 26.5%).[25]

Dydrogesterone versus Progesterone for LPS

Dydrogesterone being a retroprogesterone has a good oral bioavailability in 30-mg doses is the most frequently used for LPS. A recent RCT including 1,034 women compared dydrogesterone with vaginal progesterone gel and reported no significant difference in live birth rate (34.4 vs. 32.5%).[26] Another meta-analysis (eight RCT) comparing the use of oral dydrogesterone and vaginal progesterone for LPS also had similar findings. Based on these findings, ESHRE 2019 offers a probable and conditional recommendation for dydrogesterone in luteal phase support.

Role of Oral Natural Micronized Progesterone Sustained Release

Oral natural micronized progesterone sustained release (NMP SR) shows slow sustained release pattern over 24 hours while demonstrating long elimination half-life of 18 hours with high protein binding of 90 to 99% leading to once a dosage convenience.[27] The monolith dissolution controlled delivery system of oral NMP SR offers improved patient compliance and convenience due to once a day dosing and clinically feasible option as it achieves midluteal "therapeutic" levels of Sr. progesterone ≥14ng/mL as suggested by the MHRA (Medicine and Healthcare products Regulatory Agency) guidelines.[3]

When oral route is preferred for progestin LPS, dydrogesterone, an oral synthetic progestin is reported to be almost as efficacious as vaginal or IM route in supporting the luteal phase.[24]

Luteinizing Hormone Suppression Regimens

The use of oral progestins to prevent LH surge is a novel protocol in which GnRH analogues are not used. Progestin administration along the whole stimulation maintains the pituitary suppressed and has shown to prevent LH surge effectively. Nevertheless, the use of this protocol implies the freezing of all the embryos and transfer in a subsequent endometrial preparation cycle, as the endometrium would not be receptive in a fresh cycle due to the effect of the progestins. Oral progestins are efficient in terms of LH suppression, with comparable oocyte yield and pregnancy outcomes as the GnRH short agonist protocol. This approach is easy, cheap, and patient friendly.[28]

However, the available evidence is limited. In addition, this approach is only feasible for OS cycles in which a fresh embryo transfer is not scheduled, such as fertility preservation, oocyte donors, or freeze-all cycles.[29]

Safety Concerns

The most commonly reported adverse events were abdominal pain, nausea and/or vomiting, perineal irritation, and vaginal itching.

Both diabetogenic and antidiabetogenic effects have been attributed to progesterone, the net effect on risk of gestational diabetes in exposed pregnancies is unclear. A possible increase in risk of hypospadias in male offspring exposed to exogenous progestins before 11 weeks of gestation has been described. However, these findings were not confirmed by any large trials and systematic reviews (including Cochrane analysis).

Miscarriage is associated with considerable physical and psychological morbidity. Women who had threatened miscarriage were found to have increased rate of antepartum hemorrhage, prelabor rupture of the membranes, preterm delivery, and intrauterine growth restriction when compared with women who did not have threatened miscarriage.[29] The emotional response to miscarriage can be profound and hence any intervention that could possibly prevent these consequences must be implemented based on the best evidences.

Threatened miscarriage is a fairly common complication of pregnancy and mostly due to progesterone (endocrine) deficiency. Progesterone can be administered vaginally and orally, as well as progestogen (help in immunological factor T-cell mediated immunity). Micronized natural progesterone taken orally in divided doses is more acceptable and has equal benefits.

Conflict of Interest
None declared.

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Progesterone in Management of Preterm Labor: Current Evidences

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Progesterone derives its name from pregestational steroid hormone which has the primary function of preparing and maintaining the uterus for conception. Preterm labor represents a clinical enigma with several management strategies for prophylaxis, as well as therapeutic modality.

Natural progesterone offers complimentary anti-inflammatory, immunomodulatory, and uterine quiescence actions that go a long way in continuing pregnancy till term and therefore avoiding complications of preterm delivery or infant mortality. Preterm birth (PTB) is defined as delivery at less than 37 weeks of gestation and it complicates approximately 26% of pregnancies in India.[1] PTB can be suppressed or prevented with the complimentary use of progesterone supplementation in various forms of formulations.

Progesterone is a hormone naturally produced by the corpus luteum and the placenta that offers hormonal and non-hormonal actions involving uterine quiescence. Clinician and researchers[1-3] have utilized that this hormone in its natural form to prevent PTB or habitual abortion. Challenges still remain on the optimal timing, mode, and dose of various types of progesterone molecules including natural micronized progesterone (NMP) particularly with sustained release formulations.[4]

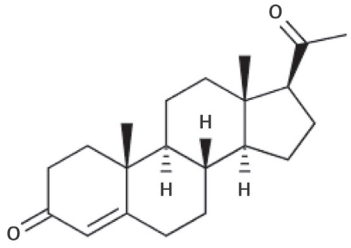
The history of progesterone is as old as the walnut tree and as new as the ongoing research which has shown in animal experiments that progesterone and the progestin Nestorone have positive effects on neuroregeneration, repair of brain damage, and myelin repair.[5]

Progesterone is available as natural progesterone, obtained from soyabeans, and Mexican yam roots.[3] It shows the same chemical structure as that of physiological progesterone found in the human body.[6] However, the micronization process of the natural progesterone reduces the average diameter of the particle size and increases the half-life of progesterone with the metabolites including allopregnanolone by enhancing dissolution of progesterone. When the hormone is taken along with food, the absorption of micronized progesterone is enhanced twofold, demonstrating an indirect stimulatory effect on progesterone receptor. Micronization decreases particle size and enhances the dissolution of progesterone. It offers greater bioavailability of up to 33% with the current formulations involving hydroxy polymethyl cellulose polymer or matrix technology imparting improved half-life kinetics from 4 to 18 hours following oral ingestion.[7,8]

History of Progesterone

1672: Corpus luteum was first described clearly by Regner de Graaf.
1928: G.W. Corner demonstrated the necessity of the corpus luteum for survival of the pre-implantation embryo.
1929: Allen isolated the hormone progesterone and first maintained pregnancy with corpus luteum extracts after early ablation of the ovaries.[4]

Structural formula was worked out by Adolf Butenandt (shown below).



Progesterone is critical for pregnancy maintenance and a withdrawal is believed to cause initiation of labor. Decline in progesterone action has been proposed as key control mechanism for cervical ripening. Progesterone inhibits oxytocin activation, directly inhibits prostaglandins (PG) production, promotes myometrial quiescence, and inhibits gap junction formation. Progesterone inhibits cervical ripening by downregulating the production of cytokines and it also has effect on the chorioamniotic membranes. Myometrial quiescence is maintained by relaxation of the myometrium.[4]

Progesterone inhibits connexin 43: gap junction protein. Estrogen increases connexin 43, blocking the action of oxytocin and there is inhibition of formation of gap junction (►**Fig. 1**). Furthermore, there are various international guidelines that support the use of progesterone for prevention of PTB.[4]

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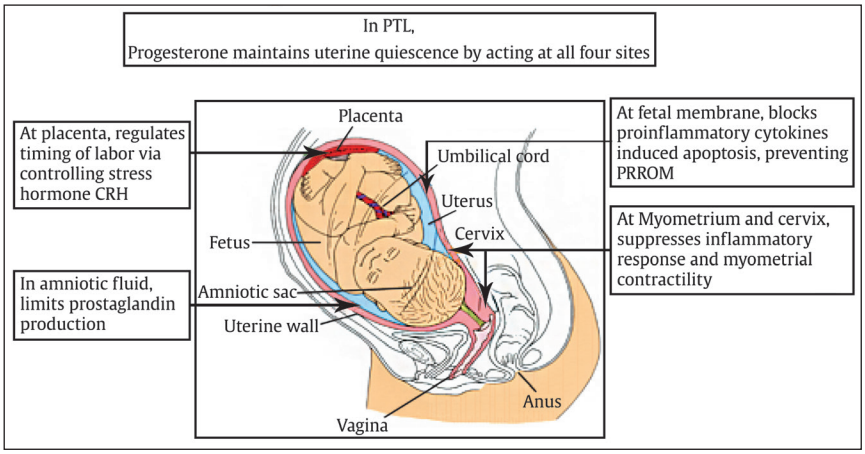

Fig. 1 Mechanisms of action: progesterone in prevention of PTL. CRH, corticotrophin-releasing hormone; PRROM, preterm premature rupture of the membranes; PTL, preterm labor.

Table 1 International guidelines and references supporting the use of progesterone for prevention of PTB[23,24]

Reference	Patients at risk	Daily dose and duration
Western Australia 2017	Short cervix between 16 and 24 wk gestation	200 mg until 36 wk
	Cervix length is <10 mm, management can include cervical cerclage, vaginal progesterone, or both	
	History of spontaneous preterm birth (with or without preterm pre-labor rupture of membranes) between 20 and 34 wk gestation	200 mg each night from 16 to 36 wk gestation
European Association of Perinatal Medicine 2017	Short cervix (25 mm) at mid gestation, either with singleton or twin pregnancy and regardless of their obstetrical history	–
French Clinical Practice Guidelines 2016	Threatened late miscarriage characterized by an isolated undilated short cervix (< 25 mm) and no uterine contractions	90–200 mg upto 34 wk
NICE Guideline 2015	With or without history of spontaneous preterm birth or mid-trimester loss between 16–34 wk and short cervix at 16–24 wk	–
FIGO 2015	Short cervix (<25 mm at 19–24 wk)	90–200 mg from diagnosis of short cervix up to ~37 wk
StratOG 2015	As an alternative to cervical cerclage in woman with prior PTB or short cervix CL <25 mm at 20 to 37 wk	Up to 37 weeks
ACOG 2012	Woman with or without prior PTB and short cervix CL ≤ 20 mm at ≤ 24 wk	From 16–24 wk of gestation
SOGC 2008	Prior PTB or Short cervix CL <15 mm at 22–26 wk	100 or 200 mg

Abbreviations: CL, cervical length; PTB, preterm birth.

Prophylactic Cervical Cerclage

The strongest predictors of preterm labor are as follows:

1. Women: with a history of spontaneous PTB or midtrimester loss between 16 and 34 weeks of pregnancy.
2. A transvaginal ultrasound scan has been performed between 16 and 24 weeks of pregnancy that reveals a cervical length of less than 25 mm.

The treatment of choice will be (1) prophylactic natural progesterone or (2) prophylactic cervical cerclage. There are various types of progesterone preparations and formulations that are described in ►**Table 2**.

It is essential to discuss the benefits and risks of prophylactic progesterone and cervical cerclage with the patient and take her preferences into account.

Prophylactic natural progesterone can be advised to women with no history of spontaneous PTB or midtrimester loss in whom a transvaginal ultrasound scan has been performed between 16 and 24 weeks of pregnancy that reveals a cervical length of less than 25 mm.[9]

Table 2 Types of progesterone preparations[25]

Types of available progesterone	Dosage
Oral micronized progesterone sustained release tablet	300 mg sustained-release tablet/day
Vaginal micronized progesterone capsule	100-200 mg twice or thrice a day
Vaginal progesterone gel 8%	90 mg every night
Intramuscular (IM) progesterone injection	100–200 mg at alternate day
IM 17-hydroxyprogesterone	250 mg/wk

Progesterone administration is as effective as cervical cerclage in prevention of premature labor in women with singleton pregnancy with short cervix.[10]

Progesterone as an Alternative to Cervical Cerclage: An Indian Experience

A prospective randomized study of 50 cases of short cervix was performed. Out of 50 cases, 25 cases each were divided in two groups as follows:

- Group A: given vaginal NMP capsule, either 200 mg BID or 300 mg SR OD.
- Group B: underwent cerclage procedure.

Natural micronized progesterone is as effective as cervical cerclage in prevention of premature labor in women with singleton pregnancy with short cervix.[11]

Routes of Administration

Injectable

Administration of progesterone through an IM injection using oil-based preparation acts as a depot at the site of injection, releasing progesterone gradually over a long period of time. Therefore, longer duration of action with 100/200-mg IM injection preparation results in benefits of alternate day injection and elevates serum progesterone levels. Patients with threatened miscarriage and a history of miscarriage can benefit from longer duration injection as it minimizes injection frequency. When progesterone is administered through the IM route, the plasma levels of progesterone are considered to be most reliable and consistent. Within 2 to 8 hours, a 100-mg injection is rapidly absorbed, producing plasma concentrations of 40 to 50 ng/mL, and up to 72 hours, there is an elevation of plasma progesterone levels. (These data on the administration of IM injection of natural progesterone in oil are in marked contrast to the long-acting physiological effects of the injectable synthetic progestins).[12]

17-hydroxyprogestrone caproate (17P) as recommended by Society of Maternal Fetal Medicine (SMFM)[13] clinical guidelines that is administered 250-mg intramuscularly (IM) on weekly basis. It is often compounded by site reactions involving irritation, injection site infection, and discomfort leading to compliance issues.[14]

Progesterone is not the same as 17-α-hydroxyprogesterone caproate (17OHPC). Progesterone and 17OHPC have different physiologic properties and pharmacologic profiles. Moreover, there are different indications for their use in obstetrics. Ruddock et al[15] reported that progesterone suppresses myometrial contractility in strips that were obtained at the time of caesarean delivery; however, 17OHPC did not have this effect and, at high concentrations, it stimulated myometrial contractility. The use of 17OHPC in patients with a history of PTB is largely based on the findings of the trial by Meis et al.[16]

17OHPC administration was associated with a significant reduction in the rate of PTB at <37 (36.3% in 17OHPC group vs. 54.9% in placebo group; relative risk [RR] = 0.66; 95% confidence interval [CI]: 0.54–0.81), <35 (20.6 vs. 30.7%; RR = 0.67; 95% CI: 0.48–0.93), and <32 (11.4 vs. 19.6%; RR = 1.58; 95% CI: 0.37–0.91) weeks of gestation (other studies have been performed before and summarized by an aggregate meta-analysis by Marc Kierse).[17]

Vaginal Progesterone

Vaginal micronized capsule dose 200 to 300 mg/day or vaginal progesterone gel 8% at a dose of 90 mg every night can be administered in these patients. Micronized progesterone containing progesterone gel has increased surface area, reduced particle size, and a higher rate of absorption. These features contribute to an exponential increase in bioavailability with reduced metabolic and vascular side effects of vaginal moisturizing properties.[18]

Vaginal Capsule

The advantages of the first uterine pass effect are provided by the vaginal route. Progesterone suppositories for the treatment and control of infertility and threatened miscarriage have been used for years. Within a few hours, the formulation of 100-mg progesterone vaginal suppositories induces an elevation in serum progesterone levels between 9.5 and 19.0 ng/mL, while plasma progesterone levels decrease steadily throughout the next 8 hours. Overall, it is also difficult to inject progesterone vaginal suppositories into the vagina since they typically liquefy at body temperature, resulting in vaginal discharge. The findings indicate elevated plasma levels of substantial progesterone elevation on the first day of treatment with these suppositories but decreased levels with continued administration.[19]

Vaginal Gel

Vaginal gel is available with polycarbophil base, which slowly releases progesterone throughout the day, allowing a day dosing. A nonliquefying vaginal cream containing micronized progesterone was developed to overcome the problems with these suppositories that offer a risk of vaginal irritation, pruritus, vaginal discharge, and monilial infections, whereas this product results in reliable plasma levels of progesterone.[12]

Recently, an SR vaginal gel with 90 mg of progesterone in 1.1 g of gel with a polycarbophil base has been developed that slowly releases progesterone throughout the day, allowing a single-day application. There are several reports of vaginal suppositories gels that indicate preventing endometrial stimulation caused by estrogen in relatively low quantities. There are numerous studies of vaginal suppositories gels that suggest the prevention of estrogen-induced endometrial stimulation in relatively low plasma levels of progesterone, indicating a direct uterine effect of vaginal administration at doses that result in lower plasma levels as compared with other systemic routes of administration.[20]

Progesterone plasma levels suggest a direct uterine impact of vaginal administration at doses that decrease plasma levels relative to other systemic routes of administration.

A 2016 meta-analysis including data from five large trials and from OPPTIMUM study reaffirms that vaginal progesterone reduces the risk of PTB and neonatal morbidity and mortality in women with a singleton gestation and midtrimester Cervical length (CL) < 25 mm without any deleterious effects on neurodevelopmental outcome. Clinicians should perform universal transvaginal CL screening at 18 to 24 weeks of gestation in women with a singleton gestation and to offer vaginal progesterone to those with a CL less than or equal to 25 mm.[9] In our country, there is some reluctance to the use of vaginal progestogen.[21]

Oral Sustained Release Micronized Progesterone Tablets

SR tablet of 300 mg/day is usually administered orally. Several clinical studies[1-3] have evaluated the protective role of immediate release (IR) formulations of NMP capsule at differing daily dosages of 100, 200, or 400 mg given orally to prevent recurrent PTB. The most commonly preferred dosage in most cases remained as 300-mg single dose or oral NMP SR tablets formulations.

Also, the Monolith dissolution controlled delivery system of oral NMP SR may offer improved patient compliance and convenience. In the study conducted at 40 centers by Prabhat and Korukonda, they found that clinical supplementation with oral NMP SR can be suggested for primary or secondary prophylaxis approach in high-risk pregnancy and also offer a safety profile for long-term administration.[22]

Conclusion

Guidelines across globe support progesterone treatment for prevention of preterm labor and associated morbidity and mortality. Micronized progesterone vaginal capsule/gel and oral NMP SR tablets are better options over 17OHPC in terms of safety profile. Looking at the multifaced etiology of preterm labor and the huge financial burden involved in taking perinatal morbidity, due to PTB, we can conclude that using NMP SR as a cotreatment to prevent preterm labor specially in women with a definitive history of PTB in the past and those with accidental short cervical length on routine screen would be a safer bet as it is cheap, easily available and doesn't pose any serious threat to either mother or the fetus. At the same time, a blanket approach of taking progesterone as a panacea cannot be recommended and we need to find other more effective medication to improve the prolongation of labor.

Conflict of Interest

None declared.

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Usage and Safety Profile of NMP SR in Threatened Miscarriage and Preterm Labor

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Progesterone is an essential hormone and plays a critical role in the maintenance of pregnancy. The sustained-release tablet formulation of natural oral micronized progesterone (NMP SR) contains natural progesterone that is slowly released in the gastrointestinal tract thereby avoiding sudden drug release and loss of drug to the first-pass metabolism.[1] Additionally, this may also potentially reduce the dose-related side effects.

The clinical usage and safety profile of NMP SR in pregnancy has been recently assessed in several studies. The largest of those was the NAP-DELAY study,[2] which was a multicenter drug utilization surveillance study conducted in 2016 on 185 high-risk pregnancies receiving NMP SR. In this retrospective case-cohort analyses, the oral NMP SR formulation was prescribed for several indications, including patients with bad obstetric history with first or second trimester loss, cervical factor, still birth, threatened miscarriage with or without spotting, placenta previa, primary and secondary prophylaxis of preterm birth (PTB), elderly primi, polyhydramnios, uterine fibroid, twin gestation, and septate uterus. Mostly, the oral NMP SR formulation was initiated between 16 and 26 weeks of pregnancy and was continued until 34 weeks. The most common preferred dosage in the study was 300-mg single dose, with the mean dose of NMP SR used in the study ranging from 271.4 to 311.1 mg, depending on the indication.

According to the results of the NAP-DELAY study, in all the 185 cases, the pregnancies continued till 34th week with no significant adverse events, except for two cases of spotting, who were receiving 200-mg once daily for subchorionic hemorrhage, or 400-mg once daily for uterine fibroid with subchorionic hemorrhage. The other adverse events comprised gastritis, vomiting, drowsiness, and dizziness, with none of them requiring hospitalization or referral (►**Fig. 1**). The study also noted that the rates of these centrally mediated adverse events were comparatively lower than those previously noted with the immediate-release formulations of oral natural micronized progesterone. Therefore, the study concluded that the natural progesterone remained a physiological and safer option for long-term progesterone supplementation in high-risk pregnancies.

In a multicenter prescription event monitoring study by Purandare and colleagues[3] reported the safety profile of oral NMP SR in the outpatient settings on 153 patients for luteal phase support in unexplained infertility, bad obstetric history, and secondary amenorrhoea, supplemented with NMP SR for 2 months following induction. Again, the 300-mg once daily was the most commonly prescribed formulation. The formulation was well tolerated, and the side effects comprised drowsiness (0.6%), hyperemesis (1.3%), and giddiness (0.6%), which were all mild and transient.

In an open-label prospective observational study by Gopinath and Desai[4] on 60 patients receiving intrauterine implantation, the 400-mg dose of oral NMP SR, once daily was well tolerated and none of the patients reported any central side effects.

In an open-label, prospective, multicenter, investigator initiated observational surveillance study by Malhotra and Krishnaprasad[5] on 120 patients receiving intrauterine insemination (IUI), a total of 22 and 23 patients received 200- and 300-mg NMP SR, respectively. Oral NMP SR was found to be safe and well tolerated in both cohorts, with occurrence of three cases of drowsiness and one case of nausea with NMP SR.

Regarding the fetal safety, it is noteworthy that natural progesterone is considered as a category-A medicine by the prescribing medicines in pregnancy database of the Australian Government[6] and a category-B drug by the U.S. Food and Drug Administration (FDA).[7] In addition, a large study from the Pope Paul VI Institute also characterized the natural progesterone supplementation as nonteratogenic.[8]

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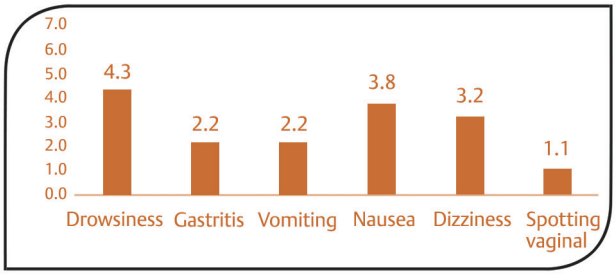

Fig. 1 Adverse events in the NAP-DELAY study.[1]

Conclusion

Based on the above evidences, it can be suggested that treatment with the recommended therapeutic dosages of NMP SR is likely to cause only mild and transient side effects, such as drowsiness, dizziness, and nausea, that too only in a small fraction of the patients receiving the treatment. NMP offers complimentary immunomodulatory and anti-inflammatory actions in various therapeutic conditions including luteal phase support by offering a safety profile for long-term administration. This formulation represents a therapeutic approach by offering "therapeutic compliance" with oral formulation and hence avoiding the side effects related to long-term patient compliance in various reproductive disorders.

Conflict of Interest
None declared.

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Neonatal Outcomes Associated with Maternal Usage of Different Progesterone Formulations

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In this article, we review the evidences from clinical studies that revealed relationship between oral supplementation of natural micronized progesterone (NMP) and dydrogesterone with neonatal outcomes and fetal safety. Several clinical trials on preterm labor have evaluated the neonatal outcomes and fetal safety including birth weight, Apgar's score, neonatal intensive care unit's (NICU) stay, neonatal mortality, and fetal anomalies in women receiving oral progesterone supplementation.

Maternal Usage of Oral Natural Progesterone and Neonatal Outcomes

In 2009, Rai and colleagues[1] were the first to report on neonatal outcomes in women receiving oral NMP supplementation through a randomized, double-blind, placebo-controlled trial on 150 women with previous preterm birth (PTB). They revealed more favorable neonatal outcomes in the NMP group. For instance, in women receiving 100 mg of oral NMP, twice a day, from recruitment (18–24 weeks) until 36 weeks, the neonatal age at delivery (34 vs. 32 weeks, $p < 0.001$), birth weight (2,400 vs. 1,890 g, $p < 0.001$), length of NICU stay (>24 hours, $p < 0.001$), and Apgar's scores ($p < 0.001$) were significantly better compared with women receiving placebo, suggesting the benefits of NMP in high-risk cases.

In 2014, Choudhary and colleagues[2] reported the results on neonatal outcomes in 90 patients with arrested preterm labor at 24 to 34 weeks in the ongoing pregnancy who were treated with 200-mg oral NMP, once daily or placebo (45 each). They revealed that the proportion of low birth weight neonates (37 vs. 64%; $p = 0.017$), and the mean birth weight (2.44 ± 0.58 vs. 2.14 ± 0.47 kg; $p = 0.009$) were both significantly higher in the NMP group, suggesting the efficacy of NMP in maintenance tocolysis.

In 2017, Ashoush and colleagues[3] reported the results of a randomized, placebo-controlled trial on 212 women with prior spontaneous PTB who were treated with 100-mg NMP, 6-hourly, or placebo (106 each) in current singleton pregnancy. They reported that compared with NMP group, the placebo group had significantly higher rates of neonatal complications, including low birth weight and respiratory distress syndrome. The placebo group also required a longer duration of admission to NICU and had relatively higher neonatal mortality (►**Table 1**).

In 2019, Boelig and colleagues[4] published the first systematic review and meta-analysis on the prevention of recurrent PTBs via oral NMP. They also reported on key neonatal outcomes and revealed that there was moderate-quality evidence that supplementation with oral NMP increased the birth weight and reduced the risk of perinatal death. In addition, there was low-quality evidence that the intervention reduced NICU admissions (►**Table 2**).

Regarding the fetal safety, the supplementation with the natural progesterone has failed to demonstrate any teratogenic effects, regardless of the timing of progesterone support, that is, in either early pregnancy or late pregnancy. In one of the largest studies on the fetal safety of natural progesterone in pregnancy, Hilgers and colleagues[5] from the Pope Paul VI Institute for the Study of Human Reproduction, NE, examined the data of 1,310 pregnancies from the high-risk reproductive medicine/infertility population supported with natural progesterone over a period of 35 years, and compared their fetal outcomes with 453 pregnancies that did not receive progesterone supplementation. Though the supplementation with natural progesterone was evaluated throughout the pregnancy; however, nearly all of the patients were exposed to natural progesterone during the first 4 months of pregnancy. Additionally, the standard progesterone curves for normal pregnancy were established using radioimmunoassay procedures and chemiluminescence technology, and the goal of the supplementation was to achieve the serum progesterone levels in zone 3 or zone 4 of the curve. The study revealed that pregnancies supplemented with oral progesterone ($n = 142$) received a total of 37,245.8 mg of progesterone. The authors found that there was no statistically significant difference between the two groups for any of the fetal anomalies (►**Table 3**). The study concluded that there was no

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Table 1 Better neonatal outcomes in the natural micronized progesterone group[3]

Outcome	Progesterone group	Placebo group	*p*-Value
Birthweight (g)	2,312 ± 77	1,878 ± 74	0.03
Low birth weight (<2.5 kg)	29 (33.7)	48 (52.8)	0.003
Admission to NICU	22 (22.9)	42 (46.1)	< 0.001
Duration of NICU stay (d)	15.4 ± 5.5	19.5 ± 5.8	0.008
Neonatal mortality	7 (7.3)	23 (25.2)	< 0.001
Respiratory distress syndrome	21 (21.8)	39 (42.8)	0.004

Abbreviation: NICU, neonatal intensive care unit.

Table 2 Grading of evidence for key neonatal outcomes[4]

Outcomes	Participants (studies)	Relative effect (95% CI)	Certainty of evidence
Preterm birth (<37 wk)	386 (3 RCTs)	0.68	Low
Preterm birth (<34 wk)	386 (3 RCTs)	0.55	Moderate
NICU admission	368 (3 RCTs)	0.39	Low
Perinatal death	368 (3 RCTs)	0.32	Moderate

Table 3 No significant difference in fetal anomalies in the progesterone group.[5] Furthermore, the NaProTechnology database, in its discussion on progesterone support

Anomaly observed	On progesterone (*n* = 1,310)		Not on progesterone (*n* = 453)		*p*-Value
	n	%	*n*	%	
Down syndrome	5	0.4	0	0	0.19
Cardiac Anomaly	4	0.3	1	0.2	0.77
Trisomy 13	3	0.2	1	0.2	0.97
Cleft lip/palate	3	0.2	1	0.2	0.97
Other chromosome anomalies	2	0.2	1	0.2	0.76
Polydactyly	2	0.2	0	0.0	0.41
Renal anomalies	1	0.1	1	0.2	0.43
Omphalocele	1	0.1	1	0.2	0.43
Imperforate anus/clubfoot/ectopic anus	2	0.2	0	0.0	0.41
Aqueductal stenosis	1	0.1	0	0.0	0.56
Labial fusion	1	0.1	0	0.0	0.57
Hypospadias	1	0.1	0	0.0	0.53
Wilms tumour	1	0.1	0	0.0	0.56
Rhabdomyoma of heart	1	0.1	0	0.0	0.56
Wiscot Aldrich syndrome	1	0.1	0	0.0	0.56
Dandy Walker malformation	0	0.0	1	0.2	0.089
Pyloric stenosis	0	0.0	1	0.2	0.089
Tracheal atresia	0	0.0	1	0.2	0.089
UPJ obstruction	0	0.0	1	0.2	0.089
Total	29	2.2	10	2.2	0.99

credible evidence to suggest that bioidentical progesterone was teratogenic or responsible for genital malformations.

In addition, the Prescribing Medicines in Pregnancy database[6] of the Australian Government, Department of Health, Therapeutic Goods Administration, 2018, has classified progesterone as a category A medicine. Conversely, the synthetic progestogens–dydrogesteorone have been assigned category D. The U.S. FDA (Food and Drug Administration)

classified the natural micronized progesterone as a category B drug in 1999.[7]

In pregnancy,[8] it highlights that the retroplacental blood pool, as well as the fetal serum, contains much higher natural progesterone levels as compared with the maternal levels during late pregnancy. Thus, the fetus is already exposed to high concentrations of natural progesterone than that could be accomplished with the exogenous administration of progesterone. The report concludes that progesterone support in pregnancy can be considered completely safe. Notably, in an educational bulletin on progesterone supplementation in early pregnancy,[9] the Practice Committee of the American Society for Reproductive Medicine in collaboration with the Society for Reproductive Endocrinology and Infertility discussed progesterone support in pregnancy. The bulletin recommended that there was no evidence to indicate that maternal supplementation with progesterone increases the risk of birth defects.

Maternal Usage of Oral Dydrogesterone and Neonatal Outcomes

In a randomized, double-blinded placebo-controlled trial reported by Areeruk and Phupong in 2016,[10] 48 pregnant women at 24 to 34 weeks of gestation with preterm labor were either randomized to oral dydrogesterone group (20-mg daily) or placebo. According to the results, the proportions of neonatal birth weight, low birth weight, and Apgar's scores did not differ between the two groups. Additionally, there were no differences between groups regarding neonatal complications, NICU admission, and days of neonatal hospitalization (►**Table 4**).

In the LOTUS II trial[11] reported in 2018, the birth weight, height, head circumference, and Apgar's score were not significantly different between women receiving dydrogesterone and vaginal progesterone. While the incidence of fetal anomalies was 6.3 versus 5.0% in the dydrogesterone and vaginal progesterone groups, respectively.

In another randomized controlled trial that compared the efficacy of oral dydrogesterone and vaginal NMP, Afridi and colleagues[12] reported that several neonatal outcomes were relatively poorer in the dydrogesterone group: NICU admission, head circumference >30 cm, perinatal mortality, oxygen requirement at 28th day of life, intraventricular hemorrhage, and retinopathy of prematurity, suggesting comparatively better outcomes with natural progesterone.

Of note, some recent studies with 17 years of safety data published in 2020 on the fetal safety of dydrogesterone in the first trimester have yielded alarming results. An electronic medical record–based report by Koren and colleagues[13] examined data of 8,508 pregnancies exposed to dydrogesterone during the first trimester in Israel. The study revealed that dydrogesterone exposure was associated with increased risk for hypospadias, overall cardiovascular malformations, spina bifida, and hydrocephalus (►**Table 5**). Moreover, a sensitivity analysis revealed potential additive or synergistic adverse fetal effects of combined dydrogesterone plus assisted reproductive technique, including increased odds of cryptorchidism and congenital dislocation of the hip. The study concluded that the recommended doses of dydrogesterone conferred teratogenic effects in pregnant women. Furthermore, the study suggested that hypospadias and cryptorchidism could be explained by the known effects of dydrogesterone on male genitalia, while the risk for spina bifida could be explained by the accompanying decrease in folic acid levels.

In addition, a recent population-based case control study from Gaza Strip[14] examined data of 202 children with congenital heart disease, and observed an approximately three-time higher risk of congenital heart disease in infants of mothers exposed to dydrogesterone in early pregnancy who received a dosage of 10-mg oral twice daily for the first 12 gestational weeks. The study's findings were considered important enough to be republished later in the *Lancet*.[15]

Table 4 No difference in neonatal outcomes between two groups[5]

Outcome	Dydrogesterone group	Placebo group	*p*-Value
Birth weight (g)	2,812 ± 614.3	2817.2 ± 457.1	0.98
Apgar's score at 1 min < 7	2 (8.3%)	1 (4.2%)	1.00
Median days of hospitalization	5 (3,6)	5 (3,7)	0.57
NICU admission	1 (4.2%)	0	1.00

Abbreviation: NICU, neonatal intensive care unit.

Table 5 Association of dydrogesterone with congenital anomalies[13]

Congenital malformation	Dydrogesterone	Dydrogesterone plus ART
Hypospadias	1.28 (1.06–1.55)	1.56 (1.31–1.85)
Undescended testis	1.0 (0.85–1.19)	1.37 (1.19–1.58)
Congenital hip dislocation	0.9 (0.78–1.04)	1.58 (1.42–1.78)
Fallot tetralogy	1.1 (0.72–1.33)	1.35 (0.5–3.62)
Ventricular septal defect	1.02 (0.91–1.32)	1.07 (0.86–1.34)
Renal dysplasia	1.04 (0.85–1.33)	2.16 (1.22–3.82)
Pylorus stenosis	1.04 (0.84–1.18)	1.25 (0.86–1.82)
Patent ductus arteriosus	1.27 (0.96–1.67)	1.51 (1.17–1.95)
Congenital aortic indufficiency	1.65 (1.008–2.71)	1.96 (1.25–3.1)
Pumlonary stenosis	0.95 (0.81–1.48)	1.21 (0.81–1.81)
Congenital cataract	1.52 (0.84–2.76)	1.52 (0.84–2.76)
Spina bifida	2.29 (1.32–3.97)	2.29 (1.32–3.97)
Congenital hydrocephalus	1.75 (1.03–1.96)	2.04 (1.28–3.25)
TGA	2.03 (0.75–5.4)	2.03 (0.75–5.4)
Overall cardiovascular malformations	1.18 (1.06–1.33)	1.31 (1.12–1.42)

Conclusion

Considering the above evidences, it can be suggested that the maternal usage of NMP may improve clinical neonatal outcomes via prolonging pregnancy, and therefore improving fetal viability and maturity. Currently there are limited good clinical studies supporting the maternal usage of oral dydrogesterone for improving clinical neonatal outcomes via prolonging pregnancy and therefore improving the fetal viability and maturity when used in preterm pregnancies. We feel more high-quality clinical studies are required to conclusively prove the advantages of using oral NMP or oral dydrogesterone.

Conflict of Interest
None declared.

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Future Directions: Natural Micronized Progesterone Sustained Release in Threatened Miscarriage and Preterm Labor

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Am J Perinatol 2021;38:41–42

1. India continues to account for high burdens of threatened miscarriages and preterm births (PTBs) and highly effective treatments for these conditions are needed.
2. Threatened miscarriage and preterm labor could be considered as a continuum of obstetric complications. Women presenting with threatened miscarriage and preterm labor are at an elevated risk of adverse reproductive outcomes. However, if proper treatment is instituted at the proper time, it will likely result in a good outcome for both the mother and the fetus.
3. In patients with threatened miscarriage and preterm labor, it is crucial to assess the clinical history of miscarriage and preterm labor, clinical findings, serum biochemistry, and ultrasound. In such patients, the low maternal serum progesterone levels are strongly associated with adverse outcomes.
4. Natural progesterone supplementation can provide clinically meaningful luteal support throughout the pregnancy. It is inexpensive, easily available, and does not pose any serious threat to either the mother or the fetus. Therefore, clinical supplementation with natural progesterone is recommended for the maintenance of pregnancy, and to ensure fetal viability and maturity.
5. Because of its hormonal and nonhormonal actions on multiple molecular sites, progesterone has been recommended as a cotreatment to prevent preterm labor, especially in women with singleton gestation and a definitive history of PTB in the past, and those with accidental short cervical length on routine screen.
6. Several routes of administration (i.e., oral, vaginal, intramuscular [IM], and transdermal) and various formulations of progesterone have been used in the treatment of threatened miscarriage and preterm labor.
7. Therapeutic compliance and a good safety profile are the prerequisites of long-term progesterone supplementation. The sustained release technologies have achieved once daily dosing, and shown excellent correlation with serum progesterone levels and a high clinical activity. Therefore, the supplementation with sustained-release oral natural progesterone may be preferred for increased compliance.
8. Several recent reports from across the world have recommended oral progesterone treatment for the prevention of threatened miscarriage and preterm labor and the associated morbidity and mortality. Several reports have also observed improved neonatal outcomes with oral progesterone supplementation, such as birth weight, Apgar's score neonatal intensive care unit stay, and neonatal mortality.
9. There is an increasing trend of scientific reports on different formulations of progesterone, and more clinical indications are being researched. However, large-scale multicenter randomized controlled and comparative studies are needed to better evaluate the superiority of different types and routes of progesterones in threatened miscarriage and preterm labor.
10. The fetal safety of progestogens, especially, the synthetic progestogens needs better evaluation through large-scale studies.

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Recommendations snippet

Study (year)	Recommendations
Wani[a] (2020)	With respect to route of administration, it was seen that oral and vaginal routes are equally efficacious for management of Threatened Abortion and Prevention of Preterm labor. Oral NMP SR offers better compliance and convenience to vaginal capsules
Boelig et al[1] (2019)	Oral progesterone appears to be effective for the prevention of recurrent preterm birth and a reduction in perinatal morbidity and mortality rates in asymptomatic singleton gestations with a history of previous spontaneous preterm birth compared with placebo
Palshetkar et al[2] (2019)	The oral progesterone may be preferable in view of patient compliance. Oral supplementation with sustained release progesterone may show improved patient compliance
Piyush and Krishnaprasad[3] (2018)	Oral natural micronized progesterone sustained release (NMP SR) can be suggested for "primary" or "secondary" prophylaxis strategy for high-risk pregnancies. Natural progesterone represents physiological yet safer option for long-term supplementation in these cases while avoiding complications of preterm delivery or infant mortality
Ashoush et al[4] (2017)	Oral micronized progesterone is effective in preventing spontaneous preterm delivery. The additional advantages of oral administration, affordability, and high safety profile make it worth recommending, at least for further research
Malik and Krishnaprasad[5] (2016)	Natural progesterone administered orally as sustained-release (SR) formulation have significant beneficial role in LPD, LPS in ART, bad obstetrics history, and for preterm labor. The monolith dissolution controlled delivery system of oral NMP SR offers improved patient compliance and convenience due to once a day dosing and clinically feasible option as it achieves midluteal "therapeutic" levels of Sr. progesterone ≥14 ng/mL as suggested by MHRA guidelines

[a]Please refer to Discussion section in article "A Prospective Comparative Study of Oral NMP SR Tablets and Vaginal NMP Capsules in Women with Threatened Abortion and Patients at Risk of Preterm Labor" in the supplement.

Conflict of Interest
None declared.

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Notes

Notes

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8 Recommendations and Conclusion

Evidence-Based Clinical Recommendations in the Management of Threatened Miscarriage

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Evidence-Based Clinical Recommendations in the Management of Threatened Miscarriage

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Evidence-Based Clinical Recommendations in the Management of Threatened Miscarriage

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Abstract

Progesterone is an essential hormone that has been widely used in clinical interventions to improve and prevent threatened miscarriage, recurrent miscarriage, and preterm labor. A protein known as the progesterone-induced blocking factor probably acts as an immunological suppressant by inducing production of a T-helper type 2 dominant cytokine and blocking T-helper type 1 activity that mediates the immunological effects of progesterone. It has an essential role in supporting the luteal phase. It has been widely accepted because of its effect on the endometrium and its immunomodulatory and anti-inflammatory actions in the maintenance of pregnancy. Accordingly, women with threatened miscarriage have been treated with the supplementation of progesterone, with varying degrees of success. The purpose of this review is to evaluate the clinical efficacy and safety of natural progesterone for the treatment of threatened miscarriage. Supplementation with natural micronized progesterone has a high bioavailability for cellular and subcellular organelles, and the data support a positive benefit–risk profile by improving live birth rates in those women. The risk factors for threatened miscarriage are polycystic ovary syndrome, smoking, obesity, and a previous history of miscarriage.

Keywords

- progesterone
- threatened miscarriage
- progestogens
- oral natural micronized progesterone capsules
- oral natural micronized progesterone (NMP) sustained release (SR) tablets
- dydrogesterone
- vaginal progesterone
- intramuscular injection

Introduction

Threatened miscarriage, as defined by the World Health Organization (WHO), is pregnancy-related bloody vaginal discharge or frank bleeding during the first half of pregnancy without cervical dilatation. Threatened miscarriage occurs during early pregnancy with vaginal spotting/bleeding and lower abdominal pain. During the first two trimesters, approximately 25% of pregnant women have vaginal bleeding, and approximately 50% of this will eventually suffer an actual threatened miscarriage.[1] Patients with threatened miscarriage are associated with an increased risk of adverse pregnancy outcomes. Therefore, the risk is extensively increased in premature rupture of the membranes, preterm delivery, and neonatal birth weight.[2] Threatened miscarriage is also associated with an increased risk of subsequent pregnancy complications such as antepartum hemorrhage (APH) and intrauterine growth retardation.[3] During the first trimester, the vaginal bleeding is an independent risk factor for pregnancy loss and adverse maternal and perinatal outcomes, which are directly proportional to the amount of bleeding.[4] During the second trimester, bleeding indicates a poor obstetric outcome such as preterm birth and/or congenital malformation and an increased risk of low birth weight infant.[5] First-trimester vaginal bleeding with a visible fetal heart rate associated with threatened miscarriage has a significantly increased risk of subsequent spontaneous abortion compared with normal pregnancy.

The specific objectives of this scientific article are as follows:

- Summarize the current knowledge in threatened miscarriage.
- Analyze the most updated research and clinical usage of progesterone.
- Mechanism and safety aspects for threatened miscarriage to guide future researches and clinical applications.
- To determine the efficacy and the safety of progestogens in the treatment of threatened miscarriage.

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- Clinical safety aspects of natural micronized sustained release (SR) progesterone in the management of threatened miscarriage.

Epidemiology and Etiology of Threatened Miscarriage

Miscarriage or spontaneous abortion is defined as the spontaneous loss of a fetus before the 20th week of pregnancy. The assessment of the epidemiology of abortion is required to help the foundation for research on the safety of abortions performed and the outcome of unsafe abortion.[6] The overall miscarriage rate is reported to be 15 to 20%, which means 15 to 20% of recognized pregnancies result in miscarriage. The frequency and chances of early pregnancy loss decrease with increasing gestational age.[7] According to the WHO data in 2010, abortion is responsible for approximately 8% of maternal mortality worldwide.[8] Approximately 80% of all the cases of early pregnancy loss occurs in the first trimester.[9]

The etiology of threatened miscarriage can be classified into six major categories: genetic, anatomical, metabolic/genetic, infectious, hormonal, and immunological. Approximately half of the cases of threatened miscarriage occur because of chromosomal abnormalities in the fetus. During the second trimester, in pregnancies associated with chromosomally and structurally normal fetuses, the overall risk of miscarriage is relatively low but varies according to the age of mother and ethnicity.[10] However, it is apparent that in many cases, the cause of threatened miscarriage is multifactorial.[11]

Sometimes, maternal factors such as maternal infection, genetic factors, and chronic illness such as hormonal problems and thyroid disease can play a role in threatened miscarriage and also increase the chances of the risk of threatened miscarriage. Other factors associated with an increased risk of threatened miscarriage include women older than 35 years, a previous history of miscarriage, invasive prenatal tests, and weight.[12]

Pathophysiology

During early pregnancy, the pathophysiology of threatened miscarriage represents abdominal/pelvic pain and heavy vaginal bleeding, or both. It is apparent that approximately a fourth of all pregnant women have some level of vaginal bleeding, abdominal cramping, and pain during the first two trimesters. If fetal cardiac activity is present in a patient with threatened abortion, then the risk of spontaneous abortion is less.[1] The endocrine abnormalities, changes in levels of cytokines profile, placental membranes, and maternal immune dysfunction are included in the pathophysiology of histological changes in threatened miscarriage.[13]

Abnormal Cytokine Profiles

During a successful pregnancy, the molecules recognized to play a crucial role are immune-related cytokines that are associated with T-helper type 2 (Th2) immunity.[14,15] The pathophysiology of threatened miscarriage in term of cytokines involves a change in the T-helper type 1 (Th1)/Th2 balance, and thus Th1 activity is responsible for significantly high risk of adverse pregnancy outcome.[16]

The cytokine network has been suggested to be involved in the evolution of threatened miscarriage that results from an increase of uterine Th1 type proinflammatory cytokines and/or a deficiency of Th2/type 3 cytokines. Primarily, the major regulatory function of cytokines is participation in the differentiation of naïve T-helper cells into Th1 cells, or Th2 cells produced by cells of the immune system. Local production of cytokines by uterine and placental cells is considered to influence embryo implantation, decidualization, and placentation. The plasma anandamide (N-arachidonoylethanolamine) is considered to be involved in the positive or negative evolution of subsequent miscarriage. Hence, it is critical for the concurrent development of the blastocyst and preparation of embryo implantation. These changes in the levels of cytokines could help predict the preventive method for the complications and also demonstrate a growing evidence and association between T-helper cells and pregnancy loss.[13] When the maternal serum interleukin (IL)-2 receptor and tumor necrosis factor-α levels were evaluated in patients with threatened miscarriage and compared with normal pregnancies, both the levels were not significantly increased in patients with threatened miscarriage and are equally responsible for good pregnancy outcomes.[17]

Immunological Dysfunction

The maintenance of pregnancy relies on the immunological processes and current immunological therapeutic/preventive strategies of human reproduction and is crucial for early gestations. During the first trimester, in patients with threatened miscarriage, the presence of anti-b2-glycoprotein I antibodies and insufficient recognition of fetal antigens causes an increased risk of pregnancy loss. The circulating levels of chemokines are important components that are involved in the regulation of inflammation and immune response network of the fetoplacental unit. Also, the elevated levels of epithelial cell-derived neutrophil-activating peptide 78 (ENA-78), a chemokine, is involved in the recruitment of leukocyte and promotes angiogenesis which also acts as an indicator of risk of miscarriage.[13,18]

Pinopods and Pregnancy

Pinopods are ultrastructural markers of endometrial receptivity and also known as pinopodes and uterodomes. These are smooth balloonlike projections that appear from the apical epithelial cellular protrusions of the endometrium of the uterus in humans and rats. In humans, structures of pinopods are present in the majority of nonciliated epithelial cells. The frequency of pinopods is dependent and inhibited by increased serum levels of progesterone. At the time of implantation, increased serum levels of progesterone are associated with the development of pinopods. During in vitro fertilization treatment and window of implantation, the function of pinopods is of great importance for increasing serum levels of progesterone and decreasing serum levels of progesterone receptor B expression.[19]

Oxidative Stress

The pathophysiology of threatened miscarriage in terms of oxidative stress involves oxygen free radicals, lipid

peroxidation, and alterations in antioxidant enzyme activities which are known to be a potential teratological threat to the fetal tissues. The early and immense influx of oxygenated maternal blood into the intervillous space may impair this process, resulting in either immediate miscarriage or long-term pregnancy complications as a result of chronic oxidative stress. Furthermore, modified serum nitric oxide (NO) levels might contribute to the pathophysiology of miscarriage because NO in reduced levels may result in endothelial dysfunction, impaired placental perfusion, and subsequently missed abortion. During a miscarriage, a study showed a direct clinical association of the NO mediator in early embryonic development and also confirmed its importance in the uterus and cervix. Hence, any associated factors maintaining and balancing NO metabolism might be useful in the treatment of miscarriage by reducing the substantial morbidity and associated mortality.[13]

Endocrine Disorders

The most common endocrinological factors are obesity and polycystic ovary syndrome (PCOS). Several etiological factors such as endometrial defects, placental thrombosis, and hormonal abnormalities including insulin resistance have been indicated as a developing contributor to miscarriage. A prospective clinical study has demonstrated that plasminogen activator inhibitor activity was a positive independent risk factor of miscarriage in women suffering from PCOS. Furthermore, another review suggested that the hyperinsulinemia is associated with increased levels of plasminogen activator inhibitor-1 and might lead to a decrease in the receptivity of the uterus for implantation window. Thus, it may be indirectly linked to miscarriage.[13]

Risk Factors

Many pregnancies are lost during early gestation, and first-trimester vaginal bleeding is a risk factor for the adverse obstetric outcome and should be taken into consideration when deciding upon antenatal observation.[20] Common risk factors include increased maternal and paternal age,[21,22] environment of living and work, endocrine, a history of miscarriage, obesity,[23-25] low serum progesterone levels,[26] lifestyle factors such as intake of coffee,[27] exercise,[28] stress,[29] exposure to environmental tobacco smoke,[30,31] and alcohol consumption (five or more drinks per week).[12,32,33] During the first trimester of pregnancy, it is important to identify these risk factors and develop an interaction model that will help clinicians to recognize pregnant women who require extra monitoring by therapeutic intervention.[34,35] Numerous researchers have examined and confirmed an association of miscarriage with poor dietary intake of vitamins; therefore, supplementation of vitamins in women either prior to or in early pregnancy may help prevent miscarriage. The evidence has shown that high caffeine consumption of >300 mg/day is an independent risk factor and doubles the risk of miscarriage during pregnancy.[36,37] Periconceptional consumption of supplements that contain 400 µg of folic acid and vitamins before and during early pregnancy reduces a woman's risk for having a baby with neural tube defect.[38-40] However, there was no conclusive evidence for women with a daily intake of supplements of folic acid that influenced the risk of miscarriage before and during pregnancy.[41] Moreover, age is also responsible for the increased incidence of miscarriage as it was revealed that risk of miscarriage in women between 20 and 24 years of age was 8.9% and those aged 45 years or above was 74.7%[42] (►**Table 1**).

There are numerous studies demonstrating an association of endocrine and metabolic diseases with miscarriage. Obesity may lead to an increased risk of miscarriage that has been linked to several adverse reproductive outcomes. Despite the method of conception in pregnancy, obesity and overweight patients have a significantly increased risk of miscarriage, whereas a mild increase in the body mass index does not increase or impact the risk of miscarriage.[43,44] Higher levels of maternal thyroid-stimulating hormone (TSH) concentration and thyroid disorder are also associated with the risk of fetal morbidity. Although, in a group of pregnant women without overt thyroid dysfunction, no association was found between risk of fetal morbidity and maternal free thyroxine (FT4) concentration.[45] In the cases of threatened miscarriage, the presence of low concentrations of FT4 and human chorionic gonadotropin (hCG) and high levels of TSH and gamma globulins indicates a negative outcome for pregnancy.[46]

Special Investigations

The special investigations used to predict the outcome of pregnancy in threatened miscarriage includes an ultrasound examination, and measurement of plasma oestradiol and progesterone levels, β-1-glycoprotein, α-fetoprotein, β-subunit hCG, cystyl aminopeptidase, and human placental lactogen. All these examinations are significantly more accurate in predicting the adverse pregnancy outcome than clinical examination.[47]

Ultrasonography (transvaginal sonography [TVS]) findings include the following:

- A well-formed gestational ring with central echoes from the embryo during pregnancy.
- Observation of fetal cardiac motion and activity:
  - With these TVS findings and observations, there is a 98% chance of continuation of gestations.

Table 1 Tabular representation of miscarriage rates classified by maternal age at conception[13]

Age (years)	Total no. of pregnancies	Miscarriage rate (%)
20–24	350,395	9
25–29	414,149	11
30–34	235,049	15
35–39	93,940	25
40–44	25,132	51
≥45	1,865	75

- Features with an evidence of a blighted ovum represent the loss of the gestational sac, absent fetal echoes, fetal cardiac activity, and smaller mean gestational sac diameter.

The routine clinical investigation features include the following:

- Blood examination for hemoglobin estimation, and ABO and Rh (Rhesus) grouping. There may be a requirement of blood transfusion if miscarriage becomes inevitable, and anti-D gamma globulin has to be given in Rh-negative nonimmunized women.
- A urine analysis can also be obtained for the evaluation of threatened miscarriage.[1]

Diagnosis of Threatened Miscarriage

Vaginal bleeding and uterine cramping are the common indications of early pregnancy loss, but these symptoms are also common in anembryonic gestation, hydatidiform mole or molar pregnancy, ectopic pregnancy, and normal gestation. Hence, an extensive evaluation is needed to make a definitive and confirmed diagnosis of pregnancy. Ultrasonography is the preferred modality to validate the presence of a viable intrauterine gestation. To diagnose the etiology of first-trimester vaginal bleeding, ultrasonography has been the gold standard tool. The first-trimester vaginal bleeding diagnosis is made by medical history, physical examination, measurement of serum β-hCG, and a sonographic finding.[48]

The overall diagnostic accuracy of clinical examination, transvaginal scanning, and serum β-hCG assay as an algorithm has a sensitivity of 99% and a specificity of 100%.[49] TVS is the preferred modality used to evaluate the presence, size, and location of pregnancy. To rule out the possibility of an ectopic pregnancy, serum β-hCG and ultrasound examination are required before treatment.

In TVS findings, a yolk sac is typically seen at 36 days, and a heartbeat is seen on ultrasound at approximately 45 days after the last menstruation. During ultrasound examination, the monitoring of β-hCG is required to determine pregnancy viability, and these levels range from 1,500 to 2,000 IU/mL in association with a gestational sac.[1] The degree of bleeding is usually monitored by assessing hemoglobin and hematocrit. There may be a requirement of suction for the removal of products of conception and blood for better visualization of the cervix. The examination of all tissue is important to determine if it is a clot or products of conception.[13] Bed rest till 48 hours, progesterone, muscle relaxant, and hCG are the commonest and routinely recommended options.

During vaginal examination, the internal cervical os is closed and no cervical motion tenderness is found. Furthermore, the physical examination reveals the presence of a closed internal cervical os with no tissue and there is no passage of tissue during threatened miscarriage. Hence, these findings are important for the diagnosis of different stages of threatened miscarriage.[7]

Management of Threatened Miscarriage

There are a number of options available for the diagnosis of threatened miscarriage, such as clinical history of miscarriage, physical examination, maternal serum biochemistry, and transvaginal scan/findings in different trimesters of pregnancy, and these may also provide valuable information about the prognosis.

In most severe cases, bed rest, supplementation of vitamins and folic acid, hormonal treatment, and progesterone are the better treatment options in threatened miscarriage with or without the presence of subchorionic hematoma. However, meta-analysis has demonstrated the different effects and impact of bed rest on miscarriage during pregnancy. According to recent studies, progesterone can reduce pregnancy loss in women diagnosed with threatened miscarriage, thereby playing a crucial role in the maintenance of pregnancy.[50-54]

Progestogens

There are a variety of progestogens available for therapeutic use.[55] Progestogens can be classified as natural or synthetic.[56,57] Natural progestogens are referred to as the compounds with chemical structures similar/identical to the progesterone of ovarian origin produced by living organisms (►**Fig. 1**).

In contrast, synthetic progestogens (or progestins) are not naturally occurring steroids; these compounds are produced in the laboratory with the modification of their chemical structures (►**Table 2**). Progesterone is a natural progestogen, whereas 17α-hydroxyprogesterone caproate (17OHPC) is synthetic steroid hormone.[56] Even dydrogesterone (6-dehydo-retro-progesterone) is also synthetic progestin and progestationally active retrosteroid[58-60] and was introduced for clinical use in an oral dosage form for the treatment of conditions associated with progesterone deficiency.

Synthetic progestins are associated with androgenic effects, such as fluid retention, decreased high-density lipoprotein, and mood disturbance, that are uncommon.[61,62] The terminology of natural in the context of hormone refers to an agent that has an identical chemical structure to that of the hormone molecules produced by the corpus luteum after ovulation, and levels rise rapidly during the early and midluteal phases of the menstrual cycle.

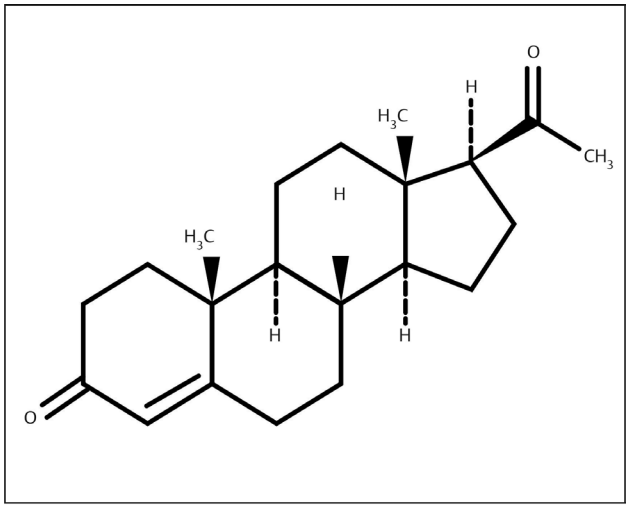

Fig. 1 Structure of progesterone.[108]

Table 2 Tabular representation of comparison between progesterone and 17-α-hydroxyprogesterone caproate[55-57]

Variable	Progesterone	17-α-hydroxyprogesterone caproate
Type of progestogen	Natural	Synthetic
Myometrial activity (in vitro)	Decreases	No effect or increases
Cervical ripening	Prevents	Unknown effect
Primigravida	Yes	No
History of preterm birth	Yes	Yes
Short cervical length	Yes	No
Safety	Safe	Potential safety concern/ signal raised worthy of further investigation[56]
Increased risk of gestational diabetes mellitus	No	Maybe

Source: Adapted from Romero.[102]

The micronized progesterone has a structure identical to endogenous hormones.[63] The micronized progesterone is manufactured in a laboratory from chemicals derived from Mexican wild yams and soy and stimulates the physiological hormone found in the human body.[63] Progesterone can be effectively used as intramuscular (IM) injections or vaginal suppositories[64]; earlier oral administration was not used routinely because it was rapidly metabolized by first-pass effect in the liver and lost its potency, producing irregular blood concentration with poor absorption effects.[65]

However, the micronization process of the natural progesterone reduces the average diameter of the particle size and increases the half-life of progesterone with the metabolites including allopregnanolone by enhancing dissolution of progesterone. When the hormone is taken along with food, the absorption of micronized progesterone is enhanced twofold, demonstrating an indirect stimulatory effect on progesterone receptor.[66]

Route of Administration

Progesterone can be administered through a variety of routes including oral SR tablets, vaginal capsules, IM injection, vaginal suppository, and vaginal gel (►**Table 3**).

Oral Route

The oral route is the most convenient mode of administration in the management of threatened miscarriage. Oral progesterone has a poor bioavailability and is rapidly metabolized by first-pass effects in the liver. Therefore, for a long time, oral progesterone could not be used in clinical applications due to rapid metabolic inactivation by the liver. Synthetic versions are available, which produce adequate plasma and tissue levels. After the discovery of progesterone hormone in 1934, micronized progesterone for oral administration became available in the 1980s, first by a French pharmaceutical company and later by an American firm. The American manufacturer produced capsules of 100 mg of progesterone particles (with a mean diameter of 10 µm) suspended partly in oil and partly in solution.[67] Studies have shown that when progesterone is given orally in this fashion, plasma levels peak at approximately 2 hours and decline to pretreatment levels at approximately 8 hours.[68,69]

Oral Natural Micronized Progesterone Capsules

Micronization process significantly improves and offers greater bioavailability of progesterone. The absorption of oral micronized progesterone is enhanced twofold when taken with food.[70,71] Since 1986, the micronized progesterone started gaining acceptance worldwide.[72] However, this preparation is also associated with complaints of nausea, flushing, and drowsiness due to the metabolites found as a result of hepatic and prehepatic metabolism. There are several side effects due to the requirement of multiple administrations per day as the half-life of this preparation is short.

Oral Natural Micronized Progesterone Sustained Release Tablets

Oral natural micronized progesterone (NMP) SR is a natural and bioidentical progesterone. NMP offers complimentary immunomodulatory and anti-inflammatory actions in various therapeutic conditions including luteal phase support by offering a safety profile for long-term administration. This formulation represents a therapeutic approach by offering "therapeutic compliance" with oral formulation and hence avoiding the side effects related to long-term patient compliance in various reproductive disorders. NMP SR tablet formulation was introduced in India in 2011 and is available in oral formulation. NMP SR formulation releases progesterone gradually, minimizing first-pass metabolism. Currently, NMP SR formulation available in tablet form consists of progesterone in a methylcellulose base. This formulation provides a slow-release matrix for a moderate release of progesterone by hydrating in the gastrointestinal tract.[66] NMP SR tablets have lesser side effects, such as nausea and drowsiness, and better patient compliance. The pharmacokinetic parameters of micronized natural progesterone SR tablets have shown improved bioavailability by representing the average elimination half-life of the SR of progesterone.[73,74] This employs a novel matrix technology for the release of progesterone in small pulses that represents slow SR pattern over 24 hours by demonstrating long elimination half-life of 18 hours with a high protein binding of 90 to 99%.[63] This SR pattern minimizes the hepatic metabolism related side effects such as sedation and drowsiness.[66,73] Hence, many studies have been performed to study the efficacy of oral micronized progesterone as luteal phase support in intrauterine insemination (IUI) cycles.[75]

As a dosage form transits in the small intestine, gradual dissolution and erosion of polymeric matrix result in the release of micron-sized drug particles that undergo micellar solubilization by bile salts that facilitates its absorption through

Table 3 Overview of reviewed clinical efficacy and scientific evidence of progesterone in high-risk pregnancy (threatened miscarriage)

Clinical study	Study population and design	Effects/Results
Turgal et al[76]	Randomized controlled trial A total of 60 women with TA were selected and randomly assigned to one of two groups: oral micronized progesterone group (400 mg/day; *n* = 30) and control group (*n* = 30)	Placental volume difference was significantly higher in the OMP therapy group (336%) than in the control group (141%)
El-Zibdeh and Yousef[103]	Open-label, randomized/threatened miscarriage, viable fetus, *n* = 86, Dydrogesterone + standard supportive care	No adverse effect, one neural tube defect, one heart disease
Prabhat and Korukonda[77]	Retrospective study, 185 patients with high-risk pregnancy at 40 centers OMP SR group was administered in a mean dosage of 271 mg for 18 ± 5 weeks	Long-term administration of oral NMP SR group suggests therapeutic compliance and a safety profile for high-risk pregnancy
Marinov et al [104]	Retrospective study, 68 women were treated for TA with a daily dose of 400-mg MP (orally twice daily)	The preventive treatment with MP in women caused dull pain and weight issues. MP can be recommended in tablet form twice daily with proper indications
Friedler et al[75]	Retrospective study, a total of 64 patients were prospectively randomized into two groups: oral (200 mg × 4 times a day) and vaginal (100 mg × two times a day) requiring intracytoplasmic sperm injection	Higher rate of implantation vaginally as compared with oral administration of MP. Difference in the pregnancy miscarriage patients and ongoing pregnancy rates were not significant statistically. No side effects were reported
Yassaee et al[50]	Single-blind clinical trial study, 60 pregnant women were prospectively divided into two groups: the control group, without any treatment, and the case group, received 400 mg of vaginal progesterone suppository	Rate of abortion in women treated with progesterone suppositories was reduced. Among 60 patients in the case group, the number of abortions (6 cases, 20%) was lower than that in the control group, which had 10 abortions (33.3%)
Wahabi et al[105]	Identification of seven randomized trials, 696 women were recruited to compare the use of natural progestogens in the treatment of threatened miscarriage with either placebo or no treatment	Reduction in the rate of miscarriage with the use of progesterone compared with placebo or no treatment (RR: 0.53; 95% CI: 0.35–0.79) The results suggested that the use of progesterone is effective in the treatment of threatened miscarriage
Czajkowski et al[106]	Randomized, parallel-group, double-blind, double dummy-controlled study, 53 patients with threatened miscarriage and a living embryo, 300 mg of micronized vaginal progesterone or 30 mg of oral dydrogesterone daily supplementation for 6 weeks	Vaginal progesterone administration results in the decrease in the spiral artery pulsatility and resistance index and diastolic ration as compared with oral dydrogesterone treatment

Abbreviations: CI, confidence interval; MP, micronized progesterone; NMP, natural micronized progesterone; OMP, oral micronized progesterone; RR, risk ratio; SR, sustained release; TA, threatened abortion.

lymphatic circulation. Lymphatic absorption limits hepatic first-pass metabolism, and, thus, intact drug reaches the systemic circulation. However, the quantum of drug released in the small intestinal region is not more than 50%, thus reducing the propensity of hepatic first-pass metabolism and eventually minimization of metabolite-related side effects (►**Fig. 2**).[9]

After treatment and hormonal support with oral NMP in the first trimester of pregnancy, the patients with threatened abortion were associated with a positive effect on fetal-placental volume leading to increased placental volume.[76] Also, the Monolith dissolution controlled delivery system of oral NMP SR may offer improved patient compliance and convenience.[76] In the study conducted at 40 centres by Prabhat and Korukonda, clinical supplementation with oral NMP SR can be suggested for primary or secondary prophylaxis approach in high-risk pregnancy[77] and also offers a safety profile for long-term administration.[66,77]

The U.K. MHRA (Medicines and Healthcare Products Regulatory Agency) guidelines recommend supplementation of serum progesterone levels ≥14ng/mL in the midluteal phase for maintaining pregnancy and preventing threatened miscarriage.[78,79] The clinical results of an open-label observational study to determine the success rate of the first IUI cycle with oral NMP SR found that the serum progesterone levels in patients were 46.2 ng/mL with NMP SR 400 mg, 36.1 ng/mL with NMP SR 300 mg, and 20.6 with NMP SR 200 mg.[66,80,81]

Dydrogesterone

Dydrogesterone is a progestationally active stereoisomer and retrosteroid of progesterone available in an oral formulation. Use of dydrogesterone treatment in early pregnancy is suggested to help establish an immune response through inflammatory mediators such as ILs, thereby preventing pregnancy loss. Generally, the systematic analysis suggests that dydrogesterone has a suitable pharmacological profile. Dydrogesterone is a synthetic progestogen agonist, tolerating specific progestogenic effects in relevant cell types. As per clinical studies, there have been benefits of oral dydrogesterone treatment in threatened miscarriage.[59,60]

Omar et al performed a prospective open study to determine the pregnancy outcomes with dydrogesterone therapy in threatened miscarriage in 154 women during the first trimester of pregnancy. A total of 154 women were selected and randomized to either 40 mg dose of dydrogesterone continued by 10 mg twice a day for 7 days or conservative therapy. There was no statistically significant difference between both

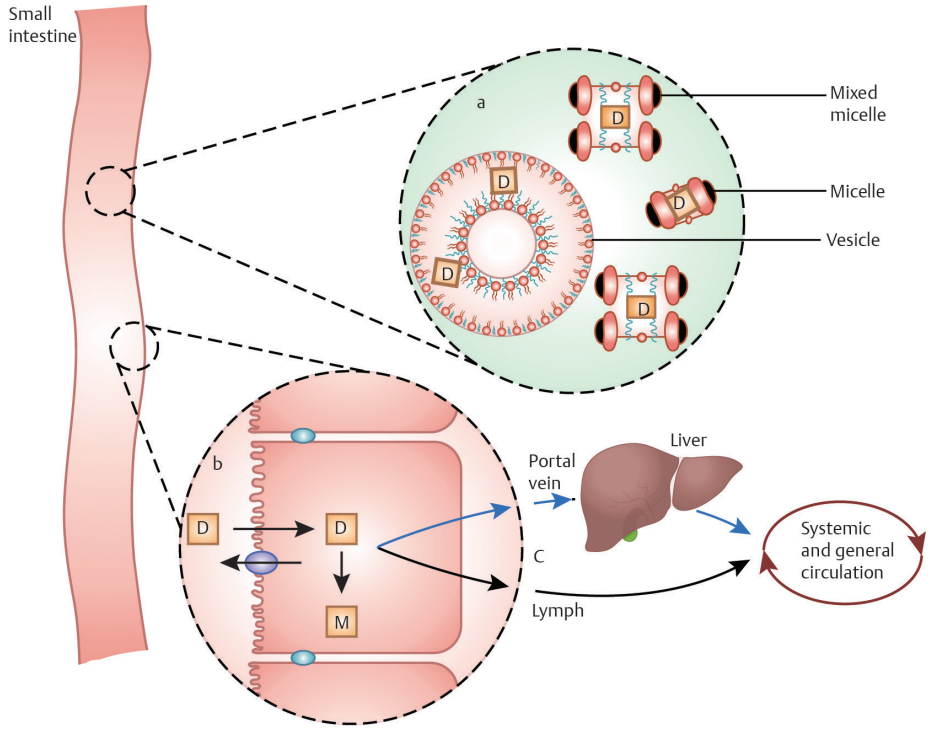

Fig. 2 Potential effect of lipids and lipidic excipients on drug absorption.[109]

groups. This study has shown to reduce the incidence of pregnancy loss in threatened miscarriage in corpus luteal support with dydrogesterone therapy.[82] Recently, a randomized trial showed that dydrogesterone supplementation may prevent miscarriages in pregnant women with threatened abortion. [83]

Intramuscular Injection

An IM injection of progesterone assures reliable absorption by avoiding first-pass metabolism and attains high serum progesterone level up to 72 hours, making it appropriate for threatened miscarriage and maintenance of pregnancy.[84,85] It is used extensively in assisted reproductive techniques due to the assurance of high serum progesterone level. IM progesterone provides optimal blood levels.[67]

Administration of progesterone through an IM injection using oil-based preparation acts as a depot at the site of injection, releasing progesterone gradually over a long period of time. Therefore, longer duration of action with 100/200-mg IM injection preparation results in benefits of alternate day injection and elevates serum progesterone levels. Patients with threatened miscarriage and a history of miscarriage can benefit from longer duration injection as it minimizes injection frequency. When progesterone is administered through the IM route, the plasma levels of progesterone are considered to be most reliable and consistent. Within 2 to 8 hours, a 100-mg injection is rapidly absorbed, producing plasma concentrations of 40 to 50 ng/mL, and up to 72 hours, there is an elevation of plasma progesterone levels. (These data on the administration of IM injection of natural progesterone in oil are in marked contrast to the long-acting physiological effects of the injectable synthetic progestins[67]).

Vaginal Progesterone

The vaginal route of administration of progesterone has numerous advantages, such as bypassing the first-pass hepatic metabolism, rapid absorption, high bioavailability, and local endometrial effect.[86] It is available as vaginal gel, effervescent tablets, and capsules. Vaginal gel contains 90 mg of progesterone with 2% polycarbophil base, which releases progesterone slowly throughout the day, allowing once per day for supplementation. Progesterone gel containing micronized progesterone has increased surface area, decreased particle size, and better absorption rate. These characteristics result in an exponential rise in bioavailability with decreased metabolic and vascular side effects with vaginal moisturizing property.[87,88]

Vaginal Capsule

Vaginal route offers the advantage of first uterine pass effects. For years, progesterone suppositories have been used for the treatment and management of infertility and threatened miscarriage. The formulation of 100-mg progesterone vaginal suppositories produces an elevation in the levels of serum progesterone within a couple of hours between 9.5 and 19.0 ng/mL, whereas there is a gradual fall in plasma progesterone levels over the next 8 hours.[67,85] Overall, the insertion of progesterone vaginal suppositories in vagina is often difficult because they usually liquefy at body temperature, resulting in vaginal discharge. On the first day of treatment with these suppositories, the results show high plasma levels with significant elevation in progesterone but reduced levels with continued administration.[89]

Vaginal Gel

Vaginal gel is available with polycarbophil base, which slowly releases progesterone throughout the day, allowing a day dosing. A nonliquefying vaginal cream containing micronized progesterone was developed to overcome the problems with these suppositories that offer a risk of vaginal irritation, pruritus, vaginal discharge, and monilial infections, whereas this product results in reliable plasma levels of progesterone. An SR vaginal gel with 90 mg of progesterone in 1.1 g of gel with a polycarbophil base has been developed that slowly releases progesterone throughout the day, allowing a single-day application.[90] There are numerous studies of vaginal suppositories gels that suggest the prevention of estrogen-induced endometrial stimulation in relatively low plasma levels of progesterone, indicating a direct uterine effect of vaginal administration at doses that result in lowers plasma levels as compared with other systemic routes of administration.[67,91,92] Absorption is over 48 hours, with a plasma peak of progesterone concentration 6 hours after application.[93] Due to the SR properties of vaginal gel, progesterone absorption is prolonged with an absorption half-life of approximately 25 to 50 hours and an elimination half-life of 5 to 20 minutes.

Progesterone Support during Pregnancy

A study was conducted from 1980 through 2001 on normal pregnancy by evaluating the data on the level of serum progesterone because it relates to a variety of pregnancy-related complications and features of previous reproductive history. Patients with a history of spontaneous abortions had decreased levels of progesterone during their first trimester. During first- and second-trimester spontaneous abortions, the results of this study demonstrated that the level of serum progesterone was significantly and statistically less.[94] Progestogens have been considered as a viable therapeutic option in pregnancy for nearly 60 years, with publications dating back to the 1940s. Progesterone supplementation has been most commonly used in women with recurrent miscarriage and a history of abortion and those undergoing controlled ovarian hyperstimulation. Initially, progesterone administration is suggested in patients who had habitual spontaneous abortion caused by luteal phase deficiency. There is evidence for the safety and tolerability of progesterone treatment in early pregnancy and that progesterone may be useful in some women with recurrent miscarriage. Hence, during early pregnancy, the measurement and evaluation of serum progesterone levels can be considered as an adjunctive marker for the further analysis of pathological pregnancies[94,95] (►**Table 4**).

Safety of Progesterone in Pregnancy

The textbook *The Medical & Surgical Practice of NaProTechnology* elaborates the use of progesterone in early pregnancy. This is the largest single study conducted for 35 years in Pope Paul VI Institute. This includes the report of end result of 933 pregnant patients who received progesterone during pregnancy. The study demonstrated the incidence of fetal abnormalities was actually lower in the population that received progesterone than the population that did not receive progesterone. The conclusion for this extensive study based on naturally occurring progesterone is as follows:

- In this report, there is no substantial evidence to suggest that its use to support pregnancy in early days or months is either teratogenic or responsible for any genital malformations.
- Based on the available evidence, the safety and tolerability of progesterone treatment are also briefly explained, and the study supports a well-established benefit profile for pregnant women.
- The study included more than 2,000 pregnant patients. The use of progesterone treatment was reviewed and reported in each pregnancy. This study supports the use of progesterone during pregnancy, with no increase in birth defects or genital anomalies. Hence, progesterone support in pregnancy can be considered completely safe and well-tolerated.[94]

The 1999 U.S. Food and Drug Administration (FDA) publication has briefly addressed the epidemiological analyses, animal studies, and basic science principles related to the use of micronized progesterone do not cause nongenital malformations. The FDA revoked pregnancy warning labels for the administration of progestational drugs and classified micronized progesterone as a category B drug. It appears that progesterone treatment does not increase the risk of nongenital birth defects.[96,97] The Therapeutic Goods Administration, which is a part of the Health Products Regulation Group, has considered NMP as pregnancy category A drug.[98] Darj et al concluded that micronized natural progesterone is an attractive means of progestogen supplementation in postmenopausal hormone replacement therapy without any liver-related side effects.[99,100]

Table 4 Routes of administration and doses based on the currently available evidence on progesterone in assisted reproduction technology cycles[107]

S. no.	Routes of administration	Doses	Frequency
1	Oral NMP SR	200–300 mg/day[2]	Once daily
2	Intramuscular progesterone	50–100–200 mg/day	Once daily
3	Oral dydrogesterone	20–30 mg/day	Two to three times daily
4	Vaginal micronized progesterone	600–800 mg/day	Two to three times daily
5	Vaginal progesterone gel	8% (90 mg) once daily	Once daily

Abbreviations: NMP, natural micronized progesterone; SR, sustained release.

Recommendations and Conclusion

Women presenting with threatened miscarriage are at an increased risk of adverse reproductive outcomes and under great psychological stress. To diagnose the treatment options for prognosis, it is crucial to determine the clinical history of miscarriage and examination, serum biochemistry of pregnant women, and ultrasound. Bed rest, hCG, and using uterine muscle relaxants have not been shown to be effective in threatened miscarriage. The lower serum progesterone is associated with threatened miscarriage.[101] The clinical supplementation with progesterone is required for the maintenance of pregnancy for early embryonic development, implantation, and fetal development, suggesting therapeutic compliance and a safety profile for long-term administration. Several routes of administration (i.e., oral, vaginal, IM, transdermal) and various formulations of progesterone are available and clinically used in the treatment of threatened miscarriage. The oral progesterone may be preferable in view of patient compliance. Oral supplementation with sustained release progesterone may show improved patient compliance.[77] In conclusion, large-scale multicenter randomized controlled and comparative studies are needed to better evaluate the superiority of different types and routes of progesterones in first-trimester threatened miscarriage.

Conflict of Interest
None declared.

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