



Progesterone Use in Recurrent Pregnancy loss

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INTRODUCTION

- Recurrent miscarriage, affects 1% of couples trying to conceive, is defined as the loss of **≥ 3 consecutive** pregnancies from the time of conception up to 24 completed weeks of gestation.
- Professional bodies differ in their recommendations regarding the definition of recurrent miscarriage, with some requiring **≥ 2 clinical pregnancies** with ultrasound or histological confirmation of pregnancy loss, whereas others require **≥ 3 losses** after a positive pregnancy test with no specification of the need for clinical confirmation.

INTRODUCTION

- **possible causes of RPL :**
- anatomical anomalies
- **endocrine diseases**
- immunological factors
- genetic diseases
- thrombophilia (inherited / acquired) disorders

INTRODUCTION

- **Endocrine abnormalities :**
- thyroid disorders
- polycystic ovarian syndrome
- possibly **progesterone deficiencies**

INTRODUCTION

- **The role of Progesterone in pregnancy :**
- Secretory transformation of the endometrium (necessary for implantation & maintenance of early pregnancy)
(Luteal phase insufficiency is one of the reasons for implantation failure & miscarriage)
- Inhibition of uterine contractility
- An immunomodulatory effect (suppression of T-cell activation & controlling cytokine production during pregnancy)
(progesterone may help to establish immune response in early pregnancy & prevent miscarriage)

INTRODUCTION

- These progesterone characteristics have led to its widespread **use of progesterone in managing recurrent miscarriage.**
- Numerous studies have been conducted to assess the use of progesterone in the management of pregnancy loss .
- There is variation in the **type & dose of progesterone** used and in the methodology of these studies, which has resulted in inconclusive findings.

INTRODUCTION

- **Progestogens available on the market :**

- **natural type**

- The chemical structures ,like those produced by the body ,available as a micronized vaginal gel or pessary (cyclogest) (GEST -TA)

- **Synthetic type**

- (medroxy progesterone acetate , norethisterone, injectable 17-alpha hydroxyprogesterone caproate (17-OHPC) , oral dydrogesterone)
- Synthetic progestogens (progestins) are artificially manufactured in a laboratory.

INTRODUCTION

- The pharmacokinetics of progesterone is dependent on route of administration.
- **The rout of administration:**
- Oral , oil-filled capsules containing micronized progesterone termed oral micronized progesterone (OMP) / syndetic progesterone
- vaginal suppositories , gels
- rectal suppositories
- oil solutions for IM injection
- aqueous solutions for sub Q injection

INTRODUCTION

- **IM progestogens** bypass first-pass metabolism in the intestines & liver .
- IM progestogens achieve very high circulating progesterone levels where the level is maintained for a longer duration compared with vaginally administered progesterone .
- There is no clear evidence to show improvement in pregnancy rate by IM progestogens .

A STUDY RECOMMENDATION

- A systematic review & meta-analysis by Saccone et al. 2017, included 10 trials with a total of 1580 women, concluded that the effect of progesterone in reducing pregnancy loss differs by **the type of progestogen** and that there may be benefit with **synthetic progestogens compared to natural progesterone**.
- This meta-analysis is limited (it included old trials with low quality & small numbers)
- Further direct like-for-like studies need to be conducted to determine the efficacy of progesterone in increasing live births in women with recurrent miscarriage.

INTRODUCTION

- No trial has reported long-term follow-up of progesterone treatment in recurrent miscarriage
- The long-term safety of progesterone supplementation is still not well known.
- There is no evidence that progesterone causes anatomical or physiological abnormalities in the fetus.

FIGO RECOMMENDATION

- Until such evidence is available on the type, timing, and duration of progesterone supplementation, the current recommendations are based on the largest most recent randomized controlled trial available to date.
- FIGO **cannot** address whether progestogens could be more effective if administered during the luteal phase of the cycle, before confirmation of pregnancy.
- There may also be a role for synthetic progestogens in reducing recurrent pregnancy loss.

FIGO RECOMMENDATION

- There is insufficient evidence to recommend the use of progesterone to improve live birth rate in women with recurrent miscarriage.
- Commencing natural vaginal progesterone at positive pregnancy test is not recommended in asymptomatic women with a history of unexplained recurrent miscarriage.
- There may be a role for synthetic oral progesterone, but large placebo-controlled trials addressing timing, dosage, and duration are needed.

FIGO RECOMMENDATION

Strong
evidence

- **Progesterone supplementation during pregnancy in general** is not recommended as no beneficial impact on 1st -trimester recurrent miscarriage has been shown ⊕⊕ ⊕⊕

Weak
evidence

- As there is no clear **evidence of any fetal abnormalities** with progesterone supplementation in pregnancy (oral/injectable/vaginal/rectal type), prescribing it on an empirical basis or as part of research trials is not contraindicated ⊕⊕

Weak
evidence

- As there is no clear **evidence of safety concerns** regarding progesterone supplementation in pregnancy (oral/injectable/vaginal/rectal type), prescribing it on an empirical basis or as part of research trials is not contraindicated ⊕⊕

FIGO RECOMMENDATION

Weak
evidence

- As there is no clear evidence that **a particular progesterone supplementation (dose / type / route)** has a beneficial impact on 1st -trimester recurrent miscarriage, prescribing any (dose / type / route) of progesterone on an empirical basis or as part of research trials is not contraindicated ⊕⊕

Weak
evidence

- It is the authors' view that **injectable progesterone** may not be considered in LRS due to cost & storage requirements ⊕⊕

FIGO RECOMMENDATION

Weak
evidence

- Oral progesterone supplementation during pregnancy can be considered as there seems to be some beneficial impact on 1st -trimester recurrent miscarriage ⊕⊕⊕

Strong
evidence

- Preconception oral progesterone supplementation is not recommended in the management of 1st -trimester recurrent miscarriage as there are no evidence-based published studies ⊕⊕⊕⊕

FIGO RECOMMENDATION

Weak
evidence

- Prescribing a **daily dose of 20 mg oral progesterone** would appear to be optimal, however the limitations of published trials and the paucity of studies in this regard should be taken into consideration ⊕⊕

Strong
evidence

- **Vaginal progesterone supplementation during pregnancy** is not recommended as there is no beneficial impact on 1st -trimester recurrent miscarriage ⊕⊕⊕⊕

Strong
evidence

- **Preconception vaginal / rectal progesterone supplementation** is not recommended in the management of 1ST -trimester recurrent miscarriage as there are no evidence-based published studies ⊕⊕⊕⊕

FIGO RECOMMENDATION

Weak
evidence

- As there is no clear evidence of **safety concerns or fetal abnormalities** regarding the use of vaginal progesterone supplementation in pregnancy, prescribing it on an empirical basis or as part of research trials is not contraindicated ⊕⊕

Weak
evidence

- If prescribing vaginal progesterone on an empirical basis or as part of research trials, a daily **dose of 400–800 mg would appear** to be optimal, however the limitations of published trials and the paucity of studies in this regard should be taken into consideration ⊕⊕

FIGO RECOMMENDATION

Strong
evidence

- **Rectal progesterone supplementation** during pregnancy is not recommended as there is no beneficial impact on 1st-trimester recurrent miscarriage ⊕⊕⊕⊕

Strong
evidence

- **Preconception rectal progesterone supplementation** is not recommended in the management of 1st-trimester recurrent miscarriage as there are no evidence-based published studies ⊕⊕⊕⊕

Weak
evidence

- As there are no published data **on the optimal dose for rectal progesterone supplementation**, no dose is recommended when prescribing on an empirical basis or as part of research trials ⊕⊕

FIGO RECOMMENDATION

Strong
evidence

- **Injectable progesterone supplementation during pregnancy** is not recommended as there is no beneficial impact on 1st-trimester recurrent miscarriage. It is the authors' view that injectable progesterone may not be considered in LRS due to cost & storage requirements ⊕⊕⊕⊕

Strong
evidence

- **Preconception injectable progesterone supplementation** is not recommended in the management of 1st-trimester recurrent miscarriage as there are no evidence-based published studies ⊕⊕⊕⊕

Weak
evidence

- As there are no published data on the optimal dose for injectable progesterone supplementation, **no dose is** recommended when prescribing on an empirical basis or as part of research trials ⊕⊕



**Take
home message*

- Progesterone appears to be essential for maintaining a healthy pregnancy by preparing the endometrium for implantation or modulation of the immune system.
- Its exact role in maintaining a pregnancy is not fully understood.
- Evidence on the use of progesterone suggests no noticeable difference in live birth rates compared to placebo.



**Take
home message*

- There seems to be emerging positive indication for the use of synthetic oral progesterone.
- There is a strong need for the trials on treatment of recurrent miscarriage with progesterone with similar study protocols in terms of route & timing of administration.



Thanks for your attention

