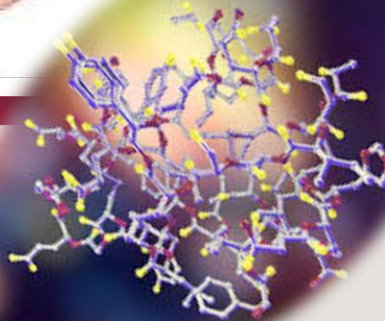


*The role of progesterone
In treatment of
1st trimester bleeding*



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Introduction



- Vaginal bleeding is common in the first half of pregnancy (**25%**) .
- **It results from:**

disruption of blood vessels in the decidua (pregnancy endometrium)

a discrete cervical / vaginal lesion

Introduction



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Threatened
abortion (15-20%)

Introduction



- Bleeding related to threatened abortion is the most common non traumatic cause of 1st -trimester bleeding (15 - 20 % of pregnancies)
- Almost all patients remain hemodynamically stable .
- Only (1 %) of expectantly managed patients require blood transfusion .



Introduction



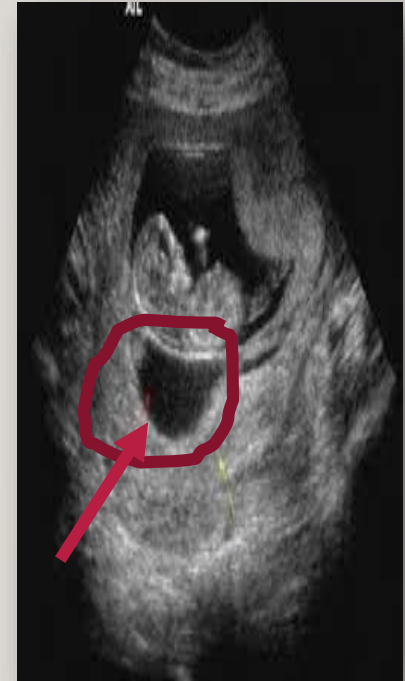
- Pregnancy loss does not always follow vaginal bleeding, even after repeated episodes / large amounts of bleeding.
- **90 - 96 %** of pregnancies with both embryonic/fetal cardiac activity & vaginal bleeding at 7 - 11 weeks are not lost .
- Bleeding in threatened abortion is likely due to disruption of decidual vessels at the maternal-fetal interface.



Introduction



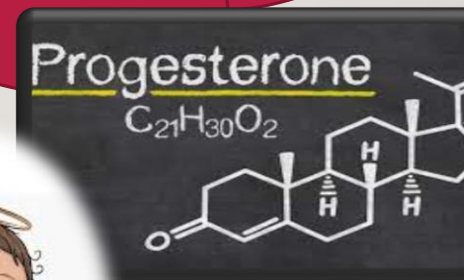
- Disruption of decidual vessels cannot be visualized by ultrasound.
- It may sometimes appear as a subchorionic hematoma.
- Subchorionic hematoma is associated with increased risk of pregnancy loss, When it amounts to $\geq 25\%$ of the volume of the gestational sac.
- No clear association between subchorionic hematoma & risk of preterm birth





Introduction

Possibly ,progesterone
could be live saving
for this pregnancy





• The role of Progesterone in pregnancy :

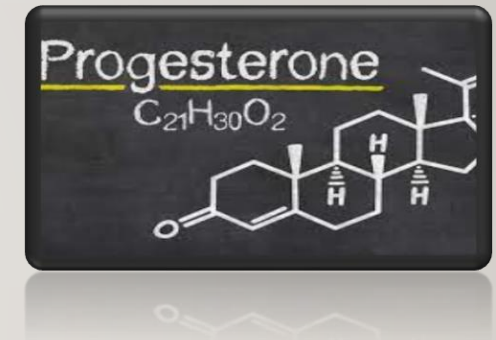
- **Secretory transformation of the endometrium**

- 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**

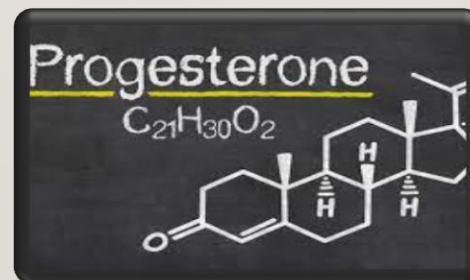
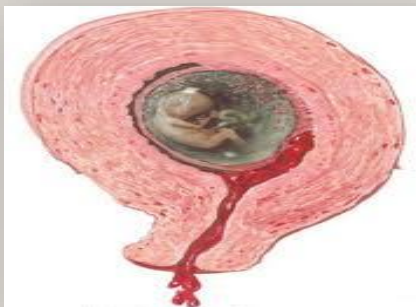
- suppression of T-cell activation & controlling cytokine production during pregnancy
- progesterone may help to establish immune response in early pregnancy & prevent miscarriage





Introduction

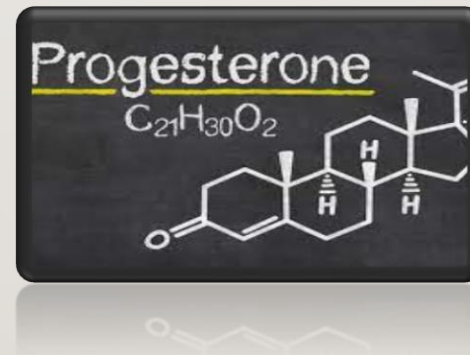
- These progesterone characteristics  use of progesterone in RX of miscarriage .
- Numerous studies have been conducted to assess the use of progesterone in the RX of pregnancy loss .





Introduction

- Available evidence does not support a benefit(live birth rate) of **progesterone** supplementation in patients with threatened abortion & zero / one previous pregnancy loss .



- Management of threatened abortion is expectant .**



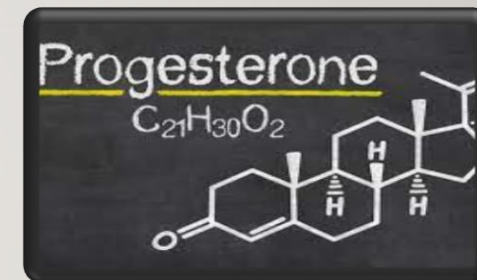


Introduction

- **Progestogens available on the market :**

- **natural type**

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



- **Synthetic type**

- Synthetic progestogens (progestins) are artificially manufactured in a laboratory .

(**medroxy progesterone acetate** , **norethisterone**, **injectable 17-alpha hydroxyprogesterone caproate (17-OHPC)** , **oral dydrogesterone**, **dofamed** , **dophaston**)

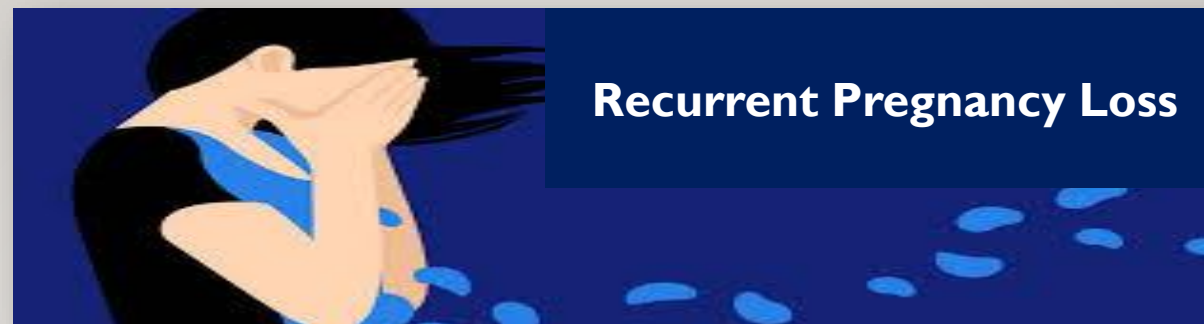


• The rout of administration:

- Oral , oil-filled capsules ; oral micronized progesterone (OMP) / syndetic progesterone
- Vaginal suppositories , gels
- Rectal suppositories
- Oil solutions for IM injection
- Aqueous solutions for sub Q injection

The pharmacokinetics is dependent on route of administration.





consecutive

≥ 2 failed clinical pregnancies
as documented by
ultrasound /
pathologic examination

- biochemical pregnancies for
women undergoing IVF are
acceptable



Recurrent Miscarriage is
defined as the occurrence
of 3 or more consecutive
spontaneous abortions
before
20 weeks

≥ 3 consecutive losses of
clinically recognized pregnancies
prior to the 20th week of
gestation

- ectopic, molar, biochemical
pregnancies (**not included**)

≥ 2

≥ 3

< 20
WEEKS

<24
WEEKS

ESHRE 2017; RPL ≥ 2 pregnancy losses, diagnosed by serum / urine hCG .

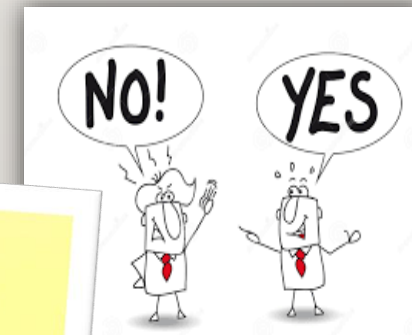
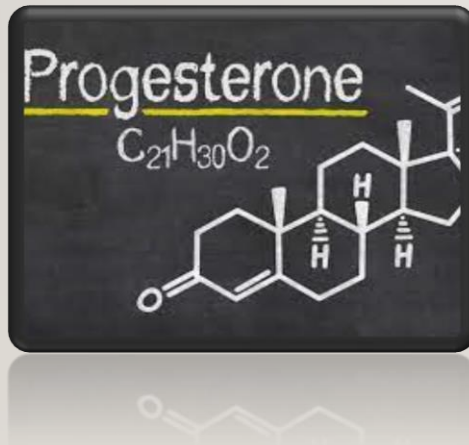
included : biochemical & pregnancies of unknown location but , not included ectopic / molar pregnancies.

ASRM 2020 ; the spontaneous loss of ≥ 2 pregnancies



Unexplained Recurrent pregnancy loss

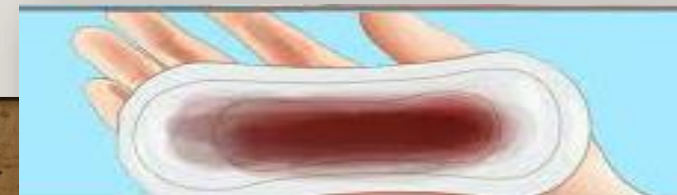
- There is not universal agreement for administration in unexplained RPL .



NICE 2021 Recommendation

- the National Institute for Health Care and Excellence (**NICE**) advises offering vaginal micronized progesterone to individuals who have experienced \geq one prior pregnancy losses & have bleeding early in the current pregnancy .
- progesterone is not advised for individuals with early pregnancy bleeding who have not experienced a prior loss nor for individuals with a HX of prior loss who do not have bleeding in early pregnancy .

\geq one prior pregnancy losses





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RCOG 2023 Recommendation

- Progestogen supplementation should be considered in women with recurrent miscarriage who present with bleeding in early pregnancy (**400 mg micronised vaginal progesterone twice daily** at the time of bleeding until 16 weeks of gestation) . **[Grade B]**

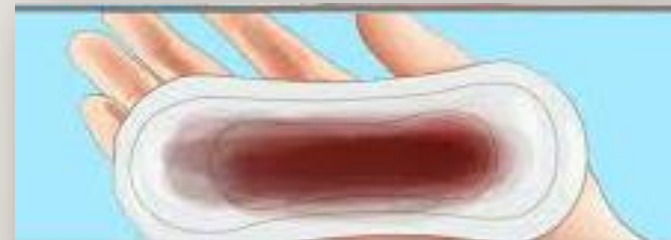
Recurrent pregnancy loss



ESHRE 2023 Recommendation

- Vaginal progesterone may improve live birth rate in women with ≥ 3 pregnancy losses & vaginal blood loss in a subsequent pregnancy (**Conditional**)

Recurrent pregnancy loss



FIGO 2023 Recommendation

Strong
evidence

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

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

FIGO 2023 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 2023 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 .

Recurrent Pregnancy Loss

FIGO 2023 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 & the paucity of studies in this regard should be taken into consideration

FIGO 2023 Recommendation

- 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.
- no evidence that progesterone causes anatomical or physiological abnormalities in the fetus.



**Take
home message*

- Progesterone appears to be essential for maintaining a healthy pregnancy by preparing the endometrium for implantation / decrease in uterine contractility / 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 in threatened abortion .



**Take
home message*

- There seems to be an indication for the use of synthetic oral progesterone / vaginal natural progesterone in :
 - 1- pregnant women with Hx of RPL & vaginal bleeding in 1st trimester
 - 2- pregnant women with \geq one spontaneous abortion & vaginal bleeding in 1st trimester
 - 2- asymptomatic pregnant with HX of RPL
- a strong need for the trials on RX of RPL with progesterone with similar study protocols (route & timing of administration) .



Thanks for your attention

Thanks for your attention

