



## PRETERM LABOUR: ROLE OF PROGESTERONE IN PRETERM LABOUR

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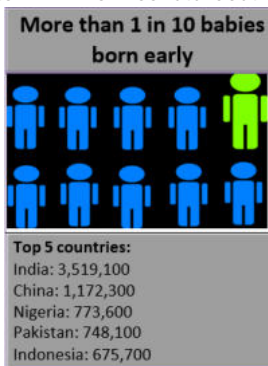
## KEYWORDS :

## WHAT IS PRETERM LABOUR? HOW COMMON IT IS? PRETERMBIRTH: INTRODUCTION

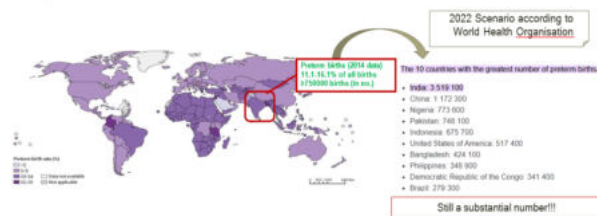
- "Delivery before 37 weeks gestational age"

## World:

- ~15 million preterm births
- Contributes to ~1 million neonatal deaths



## Epidemiology



## Subcategories – Preterm Labour

| Subcategory                         | Duration                                                                 |
|-------------------------------------|--------------------------------------------------------------------------|
| Extremely preterm                   | Less than 28 weeks.                                                      |
| Very preterm                        | 28–32 weeks.                                                             |
| Late preterm                        | 32–37 weeks.                                                             |
| Suspected/threatened preterm labour | Uterine contractions without cervical dilatation                         |
| Diagnosed preterm labour            | Uterine contractions with cervical changes.                              |
| Established preterm labour          | Uterine contractions plus progressive cervical dilatation more than 4 cm |

## What Are The Risk Factors And Complications?

**RISK FACTORS**

**Risk factors for spontaneous preterm birth**

**Modifiable risk factors for spontaneous preterm birth**

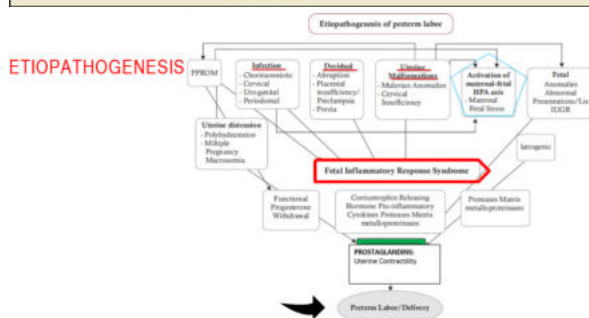
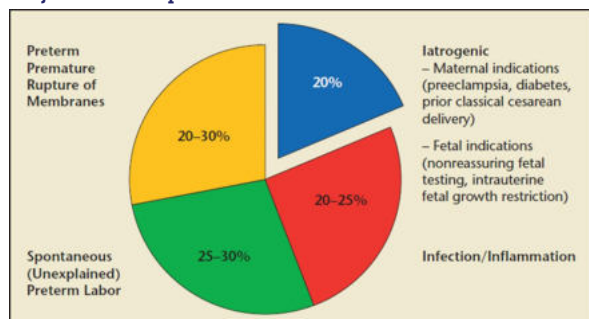
- Cigarette smoking
- Blot drug use
- Anemia
- Bacterial/urinary tract infection
- Gingival disease
- Strenuous work/work environment

**Lower genital tract infections (including bacterial vaginosis, Neisseria gonorrhoeae, Chlamydia trachomatis, Group B Streptococcus, Ureaplasma urealyticum, and Trichomonas vaginalis)**

**Non-modifiable risk factors for spontaneous preterm birth**

- Prior preterm birth
- Age <18 years or >40 years
- Poor nutrition
- Low prepregnancy weight
- Low socioeconomic status
- Absent prenatal care
- Cervical injury or anomaly
- Uterine anomaly
- Excessive uterine activity (7)
- Premature cervical dilation (<2 cm) or effacement (> 80%)
- Overdistended uterus (twins, polyhydramnios)
- Vaginal bleeding

## Major causes of preterm birth



## Complications

**Neonate**

- Necrotizing enterocolitis,
- Intraventricular hemorrhage,
- Bronchopulmonary dysplasia
- Retinopathy of immaturity
- Weak growth
- Presence of congenital anomalies.

**Infant**

- Impaired neurodevelopmental outcome
- Behavioral issues

**Maternal**

- Increased risk for cardiovascular mortality and morbidity typically years after the delivery

## Complications Extending to Adult Life

| Parameter                    | Adverse sequelae in adults born preterm                                                                                                                                                                                                                                                                                |
|------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Neurological                 | <ul style="list-style-type: none"> <li>Significant decrease in brain volume (3).</li> <li>Increased risk of neurological disabilities (4).</li> </ul>                                                                                                                                                                  |
| Cardiovascular and metabolic | <ul style="list-style-type: none"> <li>Low insulin sensitivity and high blood pressure (5).</li> <li>Increased intra-abdominal fat and higher risk of metabolic complications (6).</li> <li>Increased arterial stiffness (7).</li> <li>Reduced ventricular size and volume; impaired systolic function (8).</li> </ul> |
| Bone health                  | <ul style="list-style-type: none"> <li>Significantly lower bone mineral density (9).</li> </ul>                                                                                                                                                                                                                        |
| Others                       | <ul style="list-style-type: none"> <li>Increased risk of social disabilities in adulthood (in terms of educational level attained, income, and establishment of family) (4).</li> </ul>                                                                                                                                |

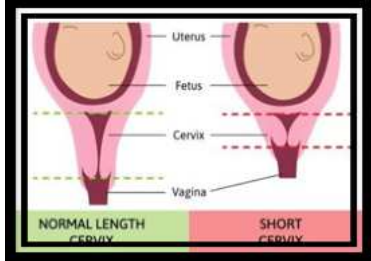
## What Are The Screening And Management Strategies?



## Screening

|                                              |                                                          |
|----------------------------------------------|----------------------------------------------------------|
| History                                      | Modifiable risk factors                                  |
|                                              | Non-modifiable risk factors                              |
| Based on cervical length                     | Ultrasonography for cervical length                      |
| Per speculum examination/vaginal examination | Screening for vaginal infections and bacterial vaginosis |

## Image Of Cervix



## Evaluation- Initial Assessment Of Women Preterm Contractions

| Questions                                                         | Assessment                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
|-------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Is the gestational age less than 37 weeks?                        | Verify dates using clinical history and ultrasonography                                                                                                                                                                                                                                                                                                                                                                                                                                             |
| Are the membranes ruptured?                                       | History of leaking fluid: observed leakage or pooling of fluid from cervical os on sterile speculum examination<br>Positive nitrazine test result<br>Arborization or ferning of fluid on microscopy<br>Positive amniotic protein test result (e.g., placental alpha microglobulin-1 [Amnisure])<br>Ultrasound assessment shows low amniotic fluid<br>Ultrasound-guided transabdominal instillation of indigo carmine dye into the amniotic sac, if available, shows dye outside of the amniotic sac |
| Is the patient in labor?                                          | Observe for regular contractions accompanied by progressive dilation and cervical effacement                                                                                                                                                                                                                                                                                                                                                                                                        |
| Is there an infection?                                            | Evaluate for group B streptococcus carrier status, urinary tract infection, bacterial vaginosis, and sexually transmitted infections (trichomoniasis, gonorrhea, or chlamydia); treat as appropriate                                                                                                                                                                                                                                                                                                |
| What is the likelihood that the patient will deliver prematurely? | Negative fetal fibronectin test results and cervical length of at least 3 cm on ultrasonography have a low likelihood of delivery within 14 days                                                                                                                                                                                                                                                                                                                                                    |

## Fetal Fibronectin(fFN)-

- It is an extracellular glycoprotein secreted by the chorionic tissue at maternal-fetal interface.
- It is present in amniotic fluid, placental tissue and decidua basalis. It acts as a **biological glue** which binds blastocyst to endometrium.
- It can be normally present in cervicovaginal secretions upto 20-22 wks. Around 22 wks chorion fuses completely with underlying decidua. This prevents fibronectin to leak into the vaginal secretions any further, until at term, a few wks before labour when cervix dilates or membranes rupture.
- Therefore presence of fFN between 27 to 34 weeks can provide important marker of preterm labour



rotate swab across posterior fornix



insert swab into tube and break



align swab with cap and seal tube

## Interventions Toprevent Preterm Labour

- Cervical cerclage
- Progesterone supplementation
- Smoking cessation
- The other important interventions that are shown to be beneficial are:
- Fetal fibronectin testing
- Bed rest for hypertension during pregnancy
- Dietary magnesium supplementation in hypertension in pregnancy
- Treatment of clinical hypothyroidism with levothyroxine
- Calcium supplementation In patients with high risk of developing pre-eclampsia



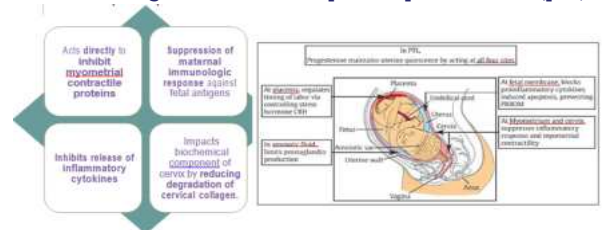
## Progesterones: Commercial preparations

- Natural**
  - Micronized progesterone (oral, vaginal, intra-muscular & subcutaneous)
- Synthetic**
  - Dydrogesterone (Oral)
  - Medrogestone
  - Medroxyprogesterone acetate & other pregnanes
  - Gestonorone & other 17 -OH Progesterone derivatives
  - Norgestrel & other 19-Nortestosterone derivatives
  - Demegestone & other 19-Norprogesterone derivatives
  - Drospirenone

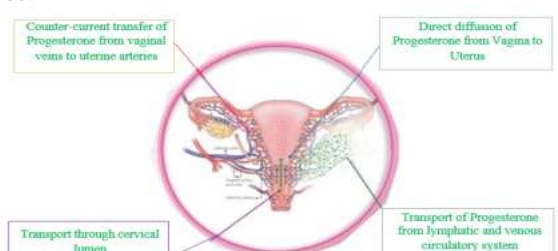


## What Is The Role Of Progesterone In Prevention Of Preterm Labour?

## How Does Progesterone Work Topreventpreterm Birth (ptb)?

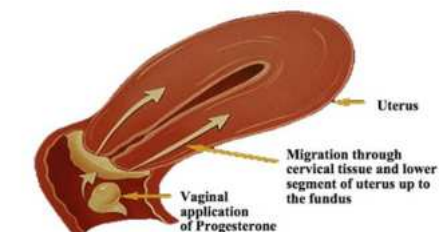


## Vaginalprogesterone – Mechanisms Of Uterine First Pass Effect



## Vaginal progesterone

First uterine pass effect /targeted delivery



Endometrial Diffusion:  
Vaginal Progesterone

One hour after application      Four hours after application



• Progressive diffusion of progesterone from the cervix to the fundus of the uterus

### Main uses of progesterone in obstetrics & gynaecology

- Luteal phase defect
- Threatened abortion
- Recurrent miscarriage/ pregnancy loss
- Preterm labour/birth

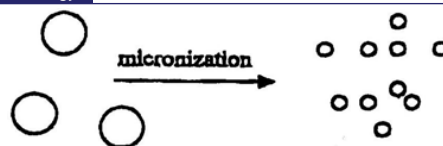


### Advantages Of Vaginal Progesterone Over Other Routes3

| Parameter                  | Vaginal                                                               | Oral                                                                                                               | Intramuscular                                                 |
|----------------------------|-----------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------|
| Plasma concentrations      | Stable plasma concentrations                                          | High interindividual variability<br>Rapid increase followed by a gradual decrease                                  | Supraphysiological plasma concentrations<br>Peaks and valleys |
| First pass metabolism      | First uterine pass effect with targeted delivery into the endometrium | First liver pass effect with several biological active metabolites<br>Specific activity on different target organs |                                                               |
| Endometrium transformation | Mimics more physiological form                                        | Lesser                                                                                                             | Lesser                                                        |
| Adverse effects            | Minimal                                                               | Drowsiness, giddiness                                                                                              | Injections site reactions, allergic reactions                 |

### Natural Micronized Progesterone (NMP)

- **Micronization:**
- Increase half-life of progesterone
- Reduces its destruction in GI tract
- Decreases particle size
- Enhances dissolution
- Maximal serum concentrations are achieved more rapidly with orally administered micronized progesterone than with injected progesterone



### Natural versus synthetic Progesterones

| Micronized natural progesterones                                                                                                                                                                     | Synthetic progesterones                                                                                                                                                                                                                                                                                          |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <ul style="list-style-type: none"> <li>• No effect on mood, HDL-cholesterol &amp; pregnancy outcomes</li> <li>• May cause fatigue &amp; sedation</li> <li>• Fatigue</li> <li>• Somnolence</li> </ul> | <ul style="list-style-type: none"> <li>• Affects mood</li> <li>• Decreases HDL cholesterol levels</li> <li>• Adversely affects pregnancy outcome</li> <li>• May cause fluid retention</li> <li>• Edema</li> <li>• Abdominal bloating</li> <li>• Anxiety</li> <li>• Irritability</li> <li>• Depression</li> </ul> |

### Risk Of Recurrent Preterm Birth

| First birth | Second birth | Subsequent preterm birth (%) |
|-------------|--------------|------------------------------|
| Not preterm |              | 4.4                          |
| Preterm     |              | 17.2                         |
| Not preterm | Not preterm  | 2.6                          |
| Preterm     | Not preterm  | 5.7                          |
| Not preterm | Preterm      | 11.1                         |
| Preterm     | Preterm      | 28.4                         |

### What Do The Guidelines Say About Progesterone Use In Prevention Of Preterm Labour?

Summary Of Recommendations From The Isuog Practice Guideline On The Role Of The Role Of Ultrasound In Spontaneous Ptb In Twin

| Twin pregnancies with short cervix                      |                                                  |
|---------------------------------------------------------|--------------------------------------------------|
| Best test                                               |                                                  |
| Natural progesterone                                    | Recommended                                      |
| Intramuscular 17-Hydroxyprogesterone Caproate (17-OHPC) | Not recommended                                  |
| Cervical pessary                                        | Controversial evidence                           |
| History-indicated cerclage                              |                                                  |
| Ultrasound guided cerclage                              |                                                  |
| Physical examination-guided                             | May be considered in twin pregnancy with dilated |

### Progesterone Preterm Birth Supplementation For The Prevention Of The Recurrent- Acog Practice Advisory Ptb In Twin Pregnancies

1. Vaginal progesterone may be considered as a treatment option for patients with a history of preterm birth, singleton gestation, and a shortened cervix.
2. Intramuscular 17-OHPC is not recommended for the primary prevention of preterm birth in patients with a history of spontaneous preterm birth.
3. Dependent upon cervical length measurement, prior pregnancy history, and past treatment, a discussion of the range of interventions available to prevent a recurrent preterm birth should occur and a collaborative action plan should be developed.



### What Does The Evidence Say About Progesterone Use In Prevention Of Preterm Labour?

## Vaginal progesterone for the prevention of preterm birth: who can benefit and who cannot? Evidence-based recommendations for clinical use

Recommendations for use of vaginal progesterone in women at high risk for preterm birth

- Vaginal progesterone should be offered from 18–24 to 36 wks to women with singleton gestation and a TVS cervical length  $\leq 25$  mm at 18–24 wks, with and without a history of spontaneous preterm birth

Vaginal progesterone should be offered from 18–24 to 36 wks of gestation to women with a singleton gestation and a history of spontaneous preterm birth only if they have a TVS cervical length  $\leq 25$  mm at 18–24 wks of gestation

Vaginal progesterone appears promising to reduce the risk of preterm birth in women with

  - a twin gestation and a midtrimester TVS cervical length  $\leq 25$  mm
  - in women with a singleton gestation conceived by ART

TVS-transvaginal sonographic  
ART-assisted reproductive technologies

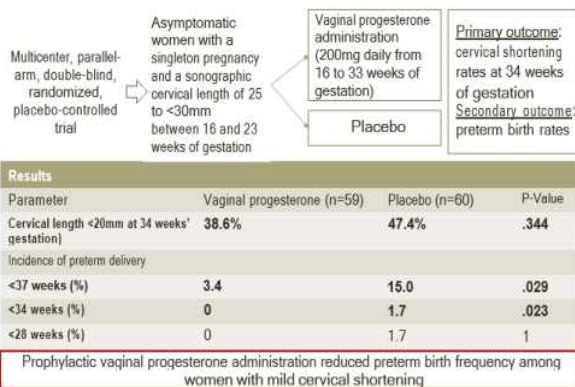
### Preterm Birth Prevention In Twin Pregnancies With Progesterone, Pessary, Or Cerclage: Meta-analysis

- Vaginal progesterone may be beneficial in twin pregnancies In women receiving vaginal progesterone:
- Reduction in risk of preterm birth <34 weeks of gestation
- RR: 0.82

Women who received vaginal progesterone had significantly

- Longer latency (mean difference 13.80 days; 95% CI, 3.97-23.63; 4 trials, 368 women)
- Later gestational age at delivery (mean difference 1.29 weeks; 95% CI, 0.43-2.15; 4 trials, 368 women)
- Lower rate of recurrent PTL (24% vs 46%; RR, 0.51; 95% CI, 0.31-0.84; 2 trials, 122 women)
- Lower rate of neonatal sepsis (2% vs 7%; RR, 0.34; 95% CI, 0.12-0.98; 4 trials, 368 women)

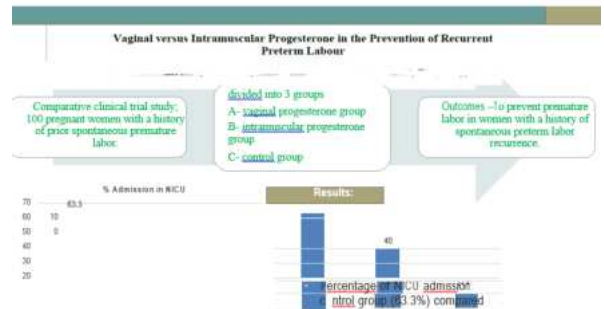
Effects of prophylactic vaginal progesterone administration on mild cervical shortening (TROPICAL study): a multicenter, double-blind, randomized trial



### 2015figo Guideline(international Federation of gynaecology and Obstetrics)

FIGO recommends the following:

1. Sonographic cervical length measurement should be performed in all pregnant patients at 19–23 6/7 weeks of gestation using transvaginal ultrasound. This can be done at the same time as the ultrasound performed for the anatomical survey.
2. Women with a sonographic short cervix (<25 mm) diagnosed in the mid- trimester should be offered daily vaginal micronized progesterone treatment for the prevention of preterm birth and neonatal morbidity.
3. The progesterone formulation to be used is vaginal micronized progesterone (200 mg vaginal soft capsules) nightly or vaginal micronized progesterone gel (90 mg) each morning.
4. Universal cervical length screening and vaginal progesterone treatment (90mg vaginal gel or 200mg micronized vaginal soft capsules) is a cost-effective model for the prevention of preterm birth.



to the progesterone groups (25.2%) (Statistically significant difference)

- Percentage of NICU admission: intramuscular progesterone group (40%) compared to the vaginal progesterone group (11.4%) (Statistically significant difference) Control.IV Vaginal Progesterone



What Is The Status Of Other Progestogens In Prevention Of Preterm Labour?



Today, the U.S. Food and Drug Administration announced the final decision to withdraw approval of Hydroxyprogesterone caproate—a drug that had been approved under the accelerated approval pathway. This drug was approved to reduce the risk of preterm birth in women pregnant with one baby who have a history of spontaneous preterm birth. The decision was issued jointly by the FDA Commissioner and Chief Scientist. Effective today, Makena and its generics are no longer approved and cannot lawfully be distributed in interstate commerce.

### Why did FDA withdraw approval of 17-OHPC?

- 17- hydroxyprogesterone caproate (17-OHPC) are not shown to be effective for reducing the risk of preterm birth in women with a singleton pregnancy who have a history of singleton spontaneous preterm birth
- 17-OHPC also has not shown to be effective for any subgroup of this population, including in women at high risk of preterm birth.
- In addition, there are known risks associated with 17-OHPC

FDA determined that given effectiveness has not been shown, no level of risk is justified.

### CONCLUSION

- Preterm labour has multifaceted etiology
- Progesterone may play a role in preserving ongoing pregnancy, due to both immunological protective effects and its own myorelaxant action
- Using progesterone to prevent preterm labour specially in women with a definitive history of spontaneous PTB in past and those with accidental short cervical length on routine screen can be a useful option

- FDA has withdrawn approval of 17-OHPC, and there are known risks associated with 17- OHPC, dydrogesterone has flagged fetal safety concerns in multiple studies and is not approved for clinical use in regulated markets like US & UK
- Choose the progestogen wisely, for prevention of preterm labour, based on evidence