

# **Progesterone & Preterm Birth Prevention: An Evidence Based Appraisal**

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Pre-term birth complicates 7-12% of all pregnancies resulting in 15 million births and 1 million deaths annually worldwide. Out of all preterm births, 25-30% are due to preterm premature rupture of membranes (PPROM), 15-20% are iatrogenic and 50-60% are spontaneous preterm births (sPTB).

Prevention of preterm birth is a challenging task as 80% of the women following PPROM will deliver by the end of one week. Iatrogenic PTBs are on the rise due to increased number of high risk women achieving pregnancy. Hence, spontaneous preterm birth is the only cohort where some prevention strategies might work. Progesterone has been extensively studied as a prevention strategy for PTB since the last three decades.

During pregnancy, corpus luteum secretes progesterone to support pregnancy from 7-9 weeks. Progesterone prevents apoptosis in fetal membranes under both basal and pro-inflammatory conditions, thus protecting the membranes from PPROM. Withdrawal of progesterone results in the onset of labour. Progesterone supplementation enhances these actions through progesterone receptors and alteration in immune response.

## **Progesterone Supplementation**

### **Possible Indications**

- Singleton pregnancy, prior singleton spontaneous PTB (sPTB)
- Singleton pregnancy, prior twin PTB
- Singleton pregnancy, short cervical length, no prior PTB
- Nullipara with short cervical length (CxL)

- Multiple pregnancy, no prior sPTB, normal CxL
- Multiple pregnancy short CxL
- PPROM
- Positive FFN
- After cerclage
- Undelivered after an episode of PTB

### **Singleton Pregnancy with prior sPTB**

In 1990, a meta-analysis by Kierse et al of all the pre-1990 placebo controlled trials, 17 hydroxy progesterone (17HP) led to 50% decrease in PTB in women at high risk of PTB. This was followed by multiple randomized controlled trials (RCT) indicating that the supplementation of 17 HP or micronized vaginal progesterone effectively reduces PTB. In 2013, a Cochrane systematic review also validated these findings.

OPPTIMUM TRIAL (2016) and PROGRESS TRIAL (2017) negated the role of vaginal progesterone for PTB prevention. Further on, PROLONG TRIAL (2020) recruited 1700 women with history of previous PTB and compared 17HP versus placebo. The study did not find any significant difference in PTB <35 weeks. This led to the withdrawal of Makena (17 HP) by the FDA.

#### **Summary of Evidence : Singleton pregnancy prior sPTB**

- Women with previous sPTB - progesterone supplementation, 4 trials effective, 3 trials not effective.

Possible Reasons: difference in study population, race, ethnicity, marital status, smoking, substance abuse, recruitment criteria & background incidence of PTB

- INFERENCE : Use it since no harm

## Short Cervix in Current Pregnancy

In 2007, a Double blind RCT conducted by O'Brien concluded that vaginal progesterone benefitted the women with short cervix  $\leq 25\text{mm}$  as compared to placebo. This was further supported by Fonesca in 2007 and Hasan in 2011. In 2016, Romero gave an update of all previous meta-analysis including OPPTIMUM trial and reported that vaginal progesterone prophylaxis in singleton pregnancies with mid-gestation cervical length  $\leq 25\text{mm}$  decreased PTB  $\leq 34$  weeks by 35%.

A systemic review and meta-analysis of individual patient data from randomized trials (including OPPTIMUM ) conducted by Romero found that vaginal progesterone supplementation reduced the risk of PTB $<34$  weeks, decreased respiratory distress syndrome , neonatal morbidity , NICU admissions, decreased weight  $< 1500$  gram in women with singleton pregnancy with mid-gestational cervical length  $\leq 25\text{mm}$ . At 2 years, no difference was seen in neurodevelopmental outcome.

Two trials (Grobman 2012 and Winer 2015) evaluated 17 HP versus placebo in women with short cervical length and reported no difference in PTB rates.

### **Summary of Evidence : Short cervix in current pregnancy**

Large data supports the use of vaginal progesterone in women with mid-trimester short cervical length.

## Progesterone in other situations

- Singleton pregnancy with previous PTB twin: no study has specifically evaluated this aspect.
- After cervical cerclage : one under-powered trial, 17HP is beneficial
- Positive FFN: little information, OPPTIMUM Trial included this: no benefit
- After PPROM : no benefit , benefit seen if previous PPROM
- Threatened or established preterm labour (PTL) or maintenance therapy after PTL : no difference as compared to placebo .

## **Progesterone in twin pregnancy**

- Unselected twin pregnancies : In 2019, a meta-analysis of 16 trials and 4548 women to compare progesterone supplementation (intramuscular/ vaginal) versus placebo reported, no difference in PTB <28, 34, 37 weeks or neonatal outcomes.
- Twin pregnancy with previous singleton pregnancy with normal cervical length: A trial conducted by Schuit in 2015, no benefit was observed with vaginal progesterone. Data with 17 HP use is not available.
- Twin pregnancy with short cervix: In a 2017 meta-analysis conducted by Romero of individual patient data from 6 randomized trials with twin gestations and mid-trimester cervical length  $\leq 25\text{mm}$ , vaginal progesterone reduced PTB < 33 weeks, neonatal distress, respiratory distress syndrome and birth weight < 1500gm.

**Progesterone in triplet pregnancy** : No benefit seen.

## **Choice of Progesterone**

- Natural Progesterone-Vaginal route: 90 to 400mg; suppository :100-200mg , gel: 90mg. Side effects( S/E): local irritation  
  
Oral route: 400mg, 2-3 studies have used it. S/E: light headedness, fatigue, sleepiness
- 17 HP: 250 mg weekly I/M. S/E: local site reaction, gestational diabetes mellitus(GDM) and intrahepatic cholestasis of pregnancy (IHCP)

## Summary of evidence

CLINICAL SCENARIO	PROGESTERONE	EVIDENCE
Singleton pregnancy previous sPTB singleton	Vaginal progesterone 17 HP	<b>2C</b> <b>2C</b>
Mid-trimester cervical length $\leq$ 25mm, no previous sPTB	Vaginal Progesterone	<b>2B</b>
Multiple Pregnancy: routine use	No Progesterone	<b>1B</b>
Twin Pregnancy , previous preterm birth	Vaginal progesterone /17 HP	+/-
Twin Pregnancy with short CxL	Vaginal Progesterone	+/-
PPROM, +FFN, PTL or after arrested episode	Vaginal Progesterone / 17 HP	<b>No Benefit</b>
After cerclage	Vaginal Progesterone / 17 HP	<b>Unclear</b>

## **Progesterone & PTB prevention: The Last Word**

- If all women with previous PTB receive progesterone prophylaxis, risk of PTB would be reduced by 20% and the absolute PTB rate would reduce by 0.01%.
- If women with short Cx are also identified and treated, an additional absolute risk reduction of 0.02% would be achieved.