# ROLE OF PROGESTERONE SUPPLEMENTATION IN PRETERM LABOR

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# ***Abstract***

*Prematurity is the leading cause of neonatal death and handicap. Although all births before 37 weeks of gestation are defined as preterm, most damage and death occurs in infants delivered before 34 weeks. Improvements in neonatal care have led to higher rates of survival among very premature infants, but a major effect on the associated mortality and morbidity will be achieved only by better identification of women at high risk for preterm delivery and by development of an effective intervention to prevent this complication.*

*The prophylactic administration of progesterone beginning in midgestation to women who previously had a preterm birth has been shown to halve the rate of recurrence.*



## ***Keywords:***

*Preterm labor, Progesterone, Tocolytic therapy*

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# *LIST OF* ABBREVIATIONS

| | |
|---|---|
| 17P | 17 α-hydroxyprogeterone caproate |
| ACTH | Adrenocorticotropic hormone |
| ART | Assisted Reproductive Technique |
| BMI | Body Mass Index |
| cAMP | Cyclic Adenosine Mono-phosphate |
| CAP | Contraction-Associated Proteins |
| COX-2 | Cyclooxygenase 2 |
| CREB | cAMP- Response element binding protein |
| CRH | Corticotropin-releasing hormone |
| CS | Cesarean Section |
| DHEAS | Dehydroepiandrosterone Sulfate |
| ER | Estrogen Receptor |
| HPA axis | Hypothalamic-Pituitary-Adrenal axis |
| HUMA | Home Uterine Activity Monitoring |
| IL | Interleukin |
| IM | Intra-muscular |
| IV | Intra-venous |
| IVH | Intra-Ventricular Hemorrhage |
| LBW | Low Birth Weight |
| MMP | Matrix Metalloproteinase |
| NEC | Necrotizing Enterocolitis |
| NF-kB | Nuclear Factor kB |
| NIH | National Institutes of Health |
| PAI | Plasminogin Inhibitor |
| PAR | Protease-Activated-Receptors |
| PGs | Prostaglandins |
| PPROM | Preterm Prelabor Rupture of Membrane |
| PR-A | Progesterone Receptor type-A |
| PR-B | Progesterone Receptor type-B |
| RDS | Respiratory Distress Syndrome |
| US | Ultrasound |
| WHO | World Health Organization |

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# *INTRODUCTION*

Preterm labor is the onset of regular uterine contractions associated with progressive cervical change between viability and 37 completed weeks of gestation. The incidence is between 5% and 10% in most developed nations. In the US, the incidence has increased from 9% to 12% in the past two decades. Preterm delivery can be associated with immediate and long-term neonatal complications. Long-term morbidity includes cerebral palsy, neurodevelopment delay and chronic lung disease. The neonatal outcome is dependent on the gestational age at delivery and associated features such as infection. The lower the gestational age, the higher the risk of mortality and morbidity. The management of preterm labor involves identification of high-risk women, prevention and treatment ***(Jayanta et al, 2007).***

Studies have identified clinical, sonographic, and biochemical markers that help to identify the women at highest risk. Determining cervical length and measuring cervicovaginal fibronectin have been proposed as useful tools for evaluating women at risk of preterm birth and may identify those who might benefit from a timely course of antenatal corticosteroids, but effective interventions to prevent preterm birth remain elusive ***(Spong CY, 2007).***

The most important components of management are aimed at preventing neonatal complications through the use of corticosteroids and antibiotics to prevent group B streptococcal neonatal sepsis, and

avoiding traumatic deliveries. Delivery in a medical center with an experienced resuscitation team and the availability of a newborn intensive care unit will ensure the best possible neonatal outcomes. Obstetric practices for which there is little evidence of effectiveness in preventing or treating preterm labor include the following: bed rest, hydration, sedation, home uterine activity monitoring, oral terbutaline after successful intravenous tocolysis ***(Goldenberg, 2002)***.

Progesterone is a steroid hormone that plays an integral role in each step of human pregnancy. In early pregnancy, progesterone is critical to the maintenance of early pregnancy. The role of progesterone in later pregnancy, however, is less clear. It has been proposed that progesterone may be important in maintaining uterine quiescence in the latter half of pregnancy by limiting the production of stimulatory prostaglandins and inhabiting the expression of contraction-associated protein genes within the myometrium ***(Anna et al, 2006).***

# ***CHAPTER ONE***

# PHYSIOLOGY & BIOCHEMISTRY OF PRETERM LABOR

## *Definitions:*

- Preterm labor, as defined by the World Health Organization, is one that occurs at less than 37 and more than 20 weeks' gestational age ***(Goldenberg, 2002)*.**
- Preterm birth (PTB) refers to a birth that occurs before 37 completed weeks (less than 259 days) of gestation. A very PTB is more variably defined as less than 32, 33, or 34 weeks of gestation, and an extremely preterm birth is a birth at less than 28 weeks of gestation ***(Caughey, 2007).***
- Preterm labor is usually defined as regular contractions accompanied by cervical change occurring at less than 37 weeks' gestation*.* ***(Goldenberg, 2002).***

Although there are many conditions that lead to preterm delivery, one can place most of the causes into three major categories:

1- Complications of pregnancy that severely jeopardize fetal and sometimes maternal health often mandate preterm delivery. These medically indicated or iatrogenic causes represent about 25 percent of preterm births.

2- Preterm premature rupture of the fetal membranes (PPROM), which is followed by preterm delivery, causes approximately 25 percent of preterm births.

3- Spontaneous preterm labor in pregnancies with intact fetal membranes represents the largest cause of preterm delivery,

accounting for about half of preterm births. ***(Cunningham et al, 2005)***

## *-MANDATED PRETERM DELIVERY:*

Commonly, pregnancy complications require a clinical decision to affect preterm delivery rather than continue pregnancy in a deteriorating intrauterine environment. Most commonly, these complications of pregnancy threaten fetal health so that a continued intrauterine existence will likely result in fetal death. Many examples may be cited, but the most common are maternal hypertension, severe diabetes mellitus, and failure of fetal growth, multiple pregnancies, and abruption placenta. ***(Cunningham et al, 2005)***

## *-PRETERM PREMATURE RUPTURE OF MEMBRANES:*

*This is* a spontaneous rupture of the fetal membranes that occurs before 37 completed weeks and before the onset of labor. It is likely that *PPROM* has a variety of causes, but many believe intrauterine infection to be one of the major predisposing events ***(Gomez et al, 1997 & Mercer, 2003).***

Recent studies suggest that the pathogenesis of PPROM relates to increased apoptosis of the cellular components of the fetal membranes as well as an elevation in specific proteases in the membranes and amnionic fluid. Much of the tensile strength of the fetal membranes is provided by the extra cellular matrix within the amnion. Interstitial amnionic collagens, primarily types I and III, are produced in mesenchymal cells and are the structural component most important for its strength ***(Casey & MacDonald, 1996*)**. For

that reason, the degradation of collagens has been a focus of research.

## *-SPONTANEOUS PRETERM LABOR:*

Clinical and laboratory evidence suggest that a number of pathogenic processes can lead to a final common pathway that result in preterm labor and delivery. The four primary processes are:

1- Activation of the maternal or fetal Hypothalamic-Pituitary-Adrenal axis
2- Inflammation
3- Decidual hemorrhage
4- Pathological uterine distention **(*Lockwood & Funai, 2007)***

## 1- Activation of HPA axis

Premature activation of the hypothalamic-pituitary-adrenal (HPA) axis can initiate PTB. Major maternal physical or psychological stress, which can activate the maternal HPA axis, has been associated with a slightly higher rate of preterm delivery **(*Mercer et al, 2005*).** Premature fetal HPA activation can result from the stress of uteroplacental vasculopathy and has a higher correlation with subsequent preterm delivery than maternal stress ***(Salafia et al, 2004).*** In a study done by Henriet and Kaminski they found that placental ischemia in women who delivered preterm was seven times more common than in those delivering at term **(*Henriet & Kaminski, 2001*).** Another study has proved that, severe preeclampsia was associated with a threefold increase in the risk of spontaneous PTB ***(Moreau et al, 2005).***

Corticotropin-releasing hormone plays a role in both term and PTB. The last trimester is marked by rising maternal serum levels of placental-derived CRH. This hormone works with ACTH to increase adult and fetal adrenal steroid hormone production, including the initiation of fetal cortisol biosynthesis. Rising levels of maternal and fetal cortisol further increase placental CRH secretion, which develops a feed-forward endocrine cascade that does not end until delivery. In addition, the rising levels of CRH further stimulate fetal adrenal DHEAS biosynthesis, which acts as substrate to increase maternal circulating estrogens, particularly estriol. It has been hypothesized that a premature rise in cortisol and estrogens causes an early loss of uterine quiescence ***(Cunningham et al, 2005).***

Supporting this hypothesis are numerous studies indicating that spontaneous preterm labor is associated with an early rise in maternal circulating CRH ***(McGrath et al, 2002).*** It appears that levels of CRH in term and preterm women are similar; however, women destined for preterm labor exhibit a rise in CRH that occurs 2 to 6 weeks earlier ***(McLean et al, 1995).*** The rise in CRH has been noted as early as 18 weeks gestation, leading some to suggest that this assay might provide a useful marker for preterm delivery**.** ***(Cunningham et al, 2005).***

CRH also enhances prostaglandin production by amnion, chorion, and decidua ***(Winkvist et al, 1998).*** Prostaglandins stimulate CRH release from the placenta ***(Petraglia et al, 1991*****),** creating a positive feedback loop for CRH secretion. The rise in prostaglandins ultimately results in parturition via the elaboration of proteases (e.g. matrix metalloproteinases) and myometrial contractility. **(*Zeitlin et al, 2004)***

## 2- Inflammation

There is great interest in the role of infection as a primary cause of preterm labor in pregnancies with intact membranes .It has been estimated that as much as 40 percent of preterm labor may be caused by intrauterine infection .This concept has been promoted because of wide spread suspicion that subclinical infection is a common accompaniment and cause of preterm labor. The term subclinical has been used to describe the condition in which intrauterine infection is accompanied by little or no clinical evidence of infection, and at times, microorganisms cannot be recovered from the amnionic fluid ***(Goncalves et al, 2002).***

***(Watts et al, 1992)*** investigated patients in preterm labor and demonstrated that positive amniotic fluid cultures were present in 19% of women with intact membranes with no clinical evidence of intrauterine infection. In women with spontaneous preterm labor, an inverse relationship exists between colonization of the chorioamnion and amniotic fluid and gestational age at delivery. ***(Goldenberg et al, 2000)***

## Sources for intrauterine infection:

It has been suggested that bacteria can gain access to the intrauterine tissues through:

1. Transplacental transfer of maternal systemic infection
2. Retrograde flow of infection from the peritoneal cavity via the fallopian tubes
3. Ascending infection with bacteria from the vagina and cervix.

The lower pole of the fetal membrane-decidual junction embrace the orifice of the cervical canal, which anatomically is patent to

the vagina. This anatomical arrangement provides a passage way for microorganisms to enter intrauterine tissues. For this reason, the ascending route of infection is considered the most common. The intrauterine infection has been categorized into four stages of microbial invasion that include bacterial vaginosis (stage I), decidual infection (stage II), amnionic infection (stage III), and finally fetal systemic infection (stage IV). Progression of these stages is thought to increase the effects on preterm birth as well as neonatal morbidity. ***(Goncalves et al, 2002).***

## The pathogenesis of infection – induced preterm labor:

Microorganisms originating in the vagina or cervix, after ascending, colonize the deciduas and possibly the fetal membranes, where they then may enter the amnionic sac. Lipopolysaccharide or other toxins elaborated by these bacteria induce cytokine production in cells within the deciduas, membranes, or fetus itself. Both lipopolysaccharide and a variety of cytokines that increase due to its presence provoke prostaglandin release from fetal membranes, the deciduas, or both. The rise in cytokines and prostaglandins will then influence both cervical ripening and loss of myometrial quiescence with resultant myometrial stimulation. ***(Challis et al, 2002& Keelan et al and Olson et al, 2003)*** *See Figure (1)*

## Microbes associated with preterm birth:

Some microorganisms, for example, *Gardnerella vaginalis, Fusobacterium, Mycoplasma hominis, and Ureaplasma urealyticum, are* detected more commonly than others in amnionic fluid of women with preterm labor ***(Gerber et al, 2003).***