NEW HORIZONS IN PRETERM LABOR

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List of Abbreviations

- **ATP** Adenosine Tri-Phosphate
- **BV** Bacterial Vaginosis
- **cAMP** cyclic Adenosine Mono-Phosphate
- **CNS** Central Nervous System
- **CS** Cesarean Section
- **ECG** ElectroCardioGraphy
- **FDA** Food and Drug Administration
- **GAG** Glucose AminoGlycans
- **GBS** Group B Streptococci
- **HUAM** Home Uterine Activity Monitoring
- **ICU** Intensive Care Unit
- **i.m.** Intra-Muscular
- **IgG** Immunoglobulin G
- **IL** Interleukin
- **IUGR** Intra-Uterine Growth Retardation
- **i.v.** intra-venous
- **IVF** In-Vitro Fertilization
- **IVH** Intra-Ventricular Hemorrhage
- **LBW** Low Birth Weight
- **LMP** Last Menstrual Period
- **LPS** Lipo-Poly-Saccharide
- **LTs** Leukotrienes
- **MCP** Monocyte Chemo-Attractant Protein
- **MIP** Macrophage Inflammatory Protein
- **MFMU** Maternal –Fetal Medicine Units
- **NICHD** National Institute of Child Health and Human Development
- **NIH** National Institute of Health
- **NO** Nitric Oxide
- **NOs** Nitric Oxide Synthetase
- **PAF** Platelet Activating Factor
- **PDE-4** Phosphodiesterase-4
- **PGE2** Prostaglandin Ether 2
- **PGs** Prostaglandins
- **phIGFBP-1** Phosphorylated Insulin-like Growth Factor Binding Protein -
- **PPROM** Preterm Premature Rupture of Membranes
- **PROM** Premature Rupture of Membranes
- **RDS** Respiratory Distress Syndrome
- **ROP** Retinopathy Of Prematurity
- **TAT** Thrombin-Anti-Thrombin III
- **TNF** Tumor Necrosis Factor
- **TRH** Thyrotropin Releasing Hormone
- **UTI** Urinary Trypsin Inhibitor
- **US** Ultrasound
- **WHO** World Health Organization
- **ZAM** Zone of Altered Morphology

Abstract

Preterm labor is a common obstetric problem and a major cause of perinatal mortality. The exact cause of preterm labor remains unclear and there are many risk factors as socioeconomic status and life style factors of the mother. There are many methods of prediction like ultrasound evaluation

The main tools that play an important role in the management of preterm labor are tocolytic therapy, antibiotics and corticosteroids. The prevention of preterm birth depends mainly on identification of women with risk factors and early intervention in order to get better survival outcomes with least possible handicapping.

Keywords:

Preterm labor, tocolytic therapy and corticosteroids.

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Introduction and Aim of Work

Preterm labor means delivery prior to 37 completed week's gestation. It constitutes one of the major health problems as it represents a major cause of perinatal death and long term handicap. Although the incidence of preterm labor has not changed over many years, neonatology has advanced, and the survival of babies has improved. Yet, handicaps continue to occur in babies born at very early gestational ages.

It seems important that prevention of preterm labor is of optimum economic and psycho-social value. Prevention largely depends upon early detection of premonitory symptoms and signs of preterm labor. Recently, investigations as ultrasound and chemical substances as oncofetal Fibronectins, thrombin-anti-thrombin, human chorionic gonadotropin, as well as salivary estriol had been developed.

These tests should be applied for risk group woman and early intervention must be carried out. The failure of arresting of the preterm delivery in most cases is not due ineffective tocolytic therapy but it is due the fact that most women arrive at hospital too late, being in advance progressing labor. This is due to reluctance of women or their ignorance of the warning sign and symptoms of preterm labor, as most of them are common in normal pregnancies.

The main drugs that play an important role in the management of preterm labor are tocolytic therapy [including oxytocin antagonist], antibiotics and drugs to prevent respiratory distress syndrome of the fetus especially corticosteroids.

The aim of this work is to review the subject of preterm labor from all its items especially the prediction and the management.

CHAPTER 1

Pathophysiology Of Preterm Labor

The Cervix

The cervix during pregnancy:

In pregnancy, the uterine cervix serves 2 major functions. First, it maintains its firmness (ie, physical integrity) during pregnancy as the uterus dramatically enlarges. This physical integrity is critical so that the developing fetus can remain in the uterus until the appropriate time for delivery. Second, in preparation for labor and delivery, the cervix softens and becomes more distensible, a process called cervical ripening. These chemical and physical changes are required for cervical dilatation, labor, and delivery of a fetus

The collagen content of the cervix, both type I and type III, undergoes marked changes in pregnancy. The spaces between the collagen bundles become dilated as early as 8 to 14 weeks gestation. Although there is an increase in the total collagen content of the cervix at term, the collagen concentration is reduced by 30 to 50 percent compared with the non-pregnant cervix. This arises because other components of the cervix, the water, and non-collagen proteins are increasing in relatively greater amounts. In addition, the collagen fibrils are reduced in size (**Granstrom et al., 1989)** and **(Kokenyesi et al., 1990).**

Collagen is amenable to breakdown by the action of lytic enzymes. These include collagenase, now called matrix metalloproteinase-1 which is produced by fibroblasts and leukocytes, and leukocyte elastase produced by macrophages, polymorphs, and eosinophils. Collagenase is secreted in a latent form, procollagenase, which is activated by cleavage of the pro-enzyme by plasmin or stromelysin to the active form that specifically breaks down the triple helix of the collagen fibril by hydrolyzing peptide bonds ***(Osmers et al., 1992)****. Radiolabel studies suggest that the cells critically involved in collagen degradation during cervical dilatation are not the cervical fibroblasts but rather polymorphonuclear leukocytes emigrating from blood vessels.*

Elastase breaks down collagen by acting on the telpeptide non-helical domains. This enzyme can degrade not only elastin and collagen but also proteoglycans and it may act synergistically with collagenase on collagen. As the cervical collagen content decreases through pregnancy the leukocyte elastase and collagenase activities increase. In addition, the amount of soluble collagen, reflecting partly degraded collagen, in the tissue increases in parallel with the increased enzyme activities. Mature collagen with many cross links may be broken down during pregnancy and replaced with new collagen that has fewer cross links and is more amenable to rapid breakdown at the time of parturition ***(Osmers et al., 1992)*** *and* ***(Leppert 1995).***

Cervical ripening refers to the increased softening, distensibility, effacement, and early dilatation that can be detected by pelvic examination. These changes are the result of profound alterations in the biomechanical properties of cervical tissue and include a reduction in collagen concentration, an increase, in water content, and .a change in proteoglycan/GAG composition. The predominant change involved in cervical ripening is a re-arrangement and realignment of collagen. **(Calder and Greer, 1992).**

Cervical ripening usually begins prior to the onset of labor contractions and is necessary for cervical dilatation and the passage of the fetus. Cervical ripening is the result of a series of complex biochemical processes that ends with rearrangement and realignment of the collagen molecules. The cervix thins, softens, relaxes, and opens in response to uterine contractions, which pull the cervix over the presenting fetal part.

Control of cervical ripening :

1- Prostaglandins[PGs] :

Physiologically, PGE2 is probably much more important than PGF2 alpha while the role of PGI2 in cervical ripening is uncertain. Amniotic fluid concentrations of PGE2 and PGF2 alpha correlate directly with the cervical score in women at term who are not in labor .In addition receptors for PGE2 and PGF2alpha can be demonstrated in the cervix. Prostaglandins might affect cervical ripening by inducing the breakdown of collagen. PGE_2 treatment will reduce collagen concentration similar to the changes seen in physiologic ripening, but it is uncertain whether this is the result of the breakdown of collagen **(Calder and Greet, 1991).**

Prostaglandins act by altering the ground substance in cervical tissue. PGE_2 can influence cervical fibroblast production of collagen and GAG. The production of these two substances is inversely related such that an increase in GAG production occurs when collagen synthesis is reduced. It was found that PGE2 administration in late pregnancy results in an increase in circulating levels of chondroitin sulfate, similar to those seen in spontaneous labor. Thus, PGE_2-mediated cervical ripening may be explained by alterations in GAG/proteoglycan content that will disperse and destabilize the collagen fibrils, thereby increasing tissue compliance **(Szalay et al., 1989);(Ding et al.,1990)** and **(Calder and Greer, 1991).**

2- Estrogens:

Estrogens such as estradiol have been used to bring about cervical ripening in the clinical situation. The mechanism underlying these effects may be due in part to the induction of prostaglandin synthesis within the tissues. Estradiol might also be responsible for the influx of protease-producing leukocytes that could induce ripening **(Maggan et al., 1995).**

3- Progesterone and antiprogestins:

Progesterone inhibits the effects of collagenase within the uterine corpus, and may have a similar role within the cervix. It has an inhibitory effect on cervical ripening and parturition in those animals in which a decrease in progesterone at term results in ripening and labor. Such a decrease does not occur in the human, but progesterone is a potent anti-inflammatory agent, and could still be an important physiologic inhibitor of the ripening process in vivo by inhibiting neutrophil influx and activation. This is supported by the observation of the cervical softening effect of the antiprogesterones prior to termination of pregnancy, and is associated with a neutrophil influx in animal models. In addition, antiprogesterones might exert their effects through prostaglandins as they appear to stimulate prostaglandin synthesis and reduce catabolism in *vitro*. **(Gupta and Johnson, 1990)** and **(Radestad et al., 1990).**

4-Relaxin:

There is good theoretical evidence that relaxin, a 6-kD dimeric peptide hormone, plays a role in the process of cervical ripening in the human. It has been shown to increase collagenase activity perhaps via a mitogenic effect on fibroblasts, which are known to exhibit relaxin receptors. Pharmacologically, porcine relaxin has been shown to cause cervical ripening in women **(Evans et al., 1983).** While

the specific role of relaxin during human pregnancy is unknown, increased relaxin concentration in the maternal circulation might be associated with preterm labor perhaps by altering cervical connective tissue **(Weiss et al., 1993).**

5- Inflammatory mediators:

Cervical ripening is considered to be a physiologic inflammatory process, characterized by an accumulation of neutrophils in the cervical stroma.Interleukin-8 is an inflammatory cytokine that is capable of producing a selective neutrophil chemotaxis and activation. This cytokine can be produced by fibroblasts in the human cervix and can induce cervical ripening in non-pregnant and pregnant rabbits. Interleukin-8 may have a synergistic interaction with PGE_2 in promoting cervical ripening. Other cytokines, including interleukin-l, and tumor necrosis factor-alpha, have been shown to produce cervical ripening in animal studies **(Barclay et al., 1993)** and **(El Maradny et al., 1994).**

Studies on nitric oxide (NO) production and nitric oxide synthase (NOS) expression in the cervix support the theory that cervical ripening is an inflammatory reaction. It has been demonstrated that the NO- generating system is present in the rat cervix and, in contrast to the uterus is up-regulated during term delivery or preterm labor. The inducible, macrophage-type NOS (iNOS or mNOS), which is the most abundant form in the uterus and cervix in pregnancy, is down-regulated in the uterus and up-regulated in the cervix during term and preterm labor in rats. In addition it has been shown that local application of the NO donor sodium nitroprusside effectively produces cervical ripening without inducing labor in pregnant guinea pigs. These results suggest that NO, which is a known inflammatory mediator, may be involved in the tissue remodeling that occurs during cervical ripening **(Buhimschi et al., 1995)** and **(Ali et al., 1995).**

Other studies have shown that fetal urine and amniotic fluid contain large amounts of a substance called urinary trypsin inhibitor(UTI). UTI, which has been localized in myometrial and cervical cells during pregnancy, has an inhibitory effect on several enzymes,, including elastase, hyaluronidase, and plasmin. It also inhibits many of the cytokines including interleukin-1 and interleukin-8, and one study in rabbits has shown that UTI suppresses premature cervical ripening. Moreover, UTI has been reported to inhibit uterine contractions in patients in preterm labor **(El- Maradny et al., 1994)** and **(Kanayama et al., 1995).**

Similarly interleukin-10 or cytokine synthesis inhibitory factor is a potent natural attenuator of inflammatory cytokine reactions. These substances may have a therapeutic role in suppressing premature cervical ripening when an inflammatory etiology is implicated **(Keirse 1995).**

6- Apoptosis:

Cervical ripening occurs spontaneously in a timely, species-specific manner, suggesting that apoptosis, or programmed cell death, may be involved. Apoptosis is a phenomenon characterized by the shrinkage of cells, compaction of chromatin into uniformly dense bundles, and clear halo nuclei.

One study in pregnant rats showed that, as gestation advanced, the numbers of dying smooth muscle cells in the cervix increased along with DNA degradation fragments and cervical softening **(Leppert and Yu, 1994).**

Evaluation of cervical ripening:

A variety of techniques have been developed to quantify cervical ripening in order to predict the timing of labor and delivery. This quantification is useful for patients at risk for preterm labor and for helping predict which patients will respond to induction of labor for medical reasons or for postdate pregnancy.

The most commonly used methodology to evaluate cervical ripening is the Bishop score because it is simple and has the most predictive value. This score uses cervical dilatation, effacement, consistency, position, and the station of the presenting part. Other methods that have been described in the literature, generally for gauging the risk of preterm labor, include ultrasound assessment of the cervix and detection of fetal fibronectin in cervicovaginal secretions.

Bishop score is calculated as follows:

- **Dilatation**
  - For 0 cm , 0 points are scored.
  - For 1- 2 cm , 1 point is scored.
  - For 3- 4 cm , 2 points are scored.
  - For 5- 6 cm , 3 points are scored.
- **Effacement**
  - For 0-30%, 0 points are scored.
  - For 40-5-%, 1 point is scored.
  - For 60-70%, 2 points are scored.
  - For 80%, 3 points are scored.
- **Station**
  - For -3 station, 0 points are scored.
  - For -2 station, 1 point is scored.
  - For -1 and 0 station, 2 points are scored.
  - For +1 to +2 station, 3 points are scored.
- **Consistency**
  - For firm consistency, 0 points are scored.
  - For medium consistency, 1 point is scored.
  - For soft consistency, 2 points are scored.
- **Position**

- For posterior position, 0 points are scored.
- For mid position, 1 point is scored.
- For anterior position, 2 points are scored.

FETAL MEMBRANES

The fetally derived amnion and chorion are both formed of an epithelial layer (amniotic and cytotrophoblast layers, respectively) that rests on a basement membrane (amniotic and chorionic or pseudo" basement membrane, respectively) that separates the epithelium from a connective tissue layer. The connective tissue layers of the amnion (compact and fibroblast layers) and chorion (reticular layer) are fused together via the intervening spongy layer in a sandwich-like arrangement **(Bell and Malak, l997).**

The connective tissue layers of the amnion and the chorion:

1- Collagens:

Collagens are the main components of the extra-cellular matrix of the connective tissues. The fetal membranes contain different subgroups of fibrillar, filamentous, and basal lamina collagens that are organized into an extensive interacting and continuous network that extends through all the layers of the connective tissue. Collagen types I and III form the main fibrous skeleton of the extra-cellular matrix. Their fibers are arranged parallel to the amniotic epithelium and are tightly packed in the compact layer. However, in the fibroblast and reticular layers, they are less densely packed and organized. The compact layer may therefore play a primary role in maintaining the mechanical integrity of the fetal membranes **(Malak et al., 1993).**

- Stabilization of this fibrous network may be achieved through:

(1) The extensive network of unbanded filaments, ultra-structurally identical to collagen type I, that were identified connecting the large banded fibers together, entrapping the matrix fibers, and anchoring them to the amniotic and chorionic basement membranes.

(2) Interconnection with the electron-dense stromal substance found in the connective tissue, formed of basal lamina components type IV collagen and laminin.

In the basement membranes, collagen type IV and laminin play an important role in attachment of cells to the underlying stroma, and in the connective tissue they may form anchoring spots to connect stromal fibers and filament **(Malak et al., 1993).**