INTRODUCTION

Preterm labor traditionally includes all deliveries between 24 and 37 weeks gestation. Preterm deliveries should be divided into: mildly preterm births at 32-37 weeks, moderately preterm births at 28-32 weeks, extremely preterm births at 24-28 weeks' ***(Draper et al., 1999).***

The risk factors of preterm labor include major and minor risk factors. The major risk factors include infection of choriodecidual space and amniotic fluid as in bacterial vaginosis, Group B streptococci, pyelonephritis, appendicitis, pneumonia, previous preterm labor, uterine overdistintion as in polyhydramnios, multiple pregnancy, cervical incompetence, uterine abnormalities. The minor risk factors include smoking, low body mass index, maternal age teenage, multiparae, low socioeconomic status, low levels of education ***(Mercer et al., 1999).***

Preterm infants are at risk for specific diseases such as respiratory distress syndrome, intraventricular hemorrhage, bronchopulmonary dysplasia, patent ductus arteriosus, necrotising entericolitis, sepsis, apnea, and retinopathy ***(Mercer, 2003).***

Lipids in the plasma are present as lipoprotein complexes. Plasma lipoproteins contain cholesterol,

triglycerides, phospholipids, free fatty acids, and traces of lipid soluble vitamins and steroid hormones ***(Jackson, 1976).***

Cholesterol exists in two forms free and esterfied forms. Both of which are incorporated in lipoprotein molecules (low density lipoproteins and high density lipoproteins). The normal of total cholesterol is 140-260 mg/dl while the normal range of plasma triglycerides 100-150 mg/dl. The liver is main source of plasma cholesterol. Cholesterol metabolism is divided into two pathways; the first pathway is the exogenous which derived cholesterol from dietary sources, the second is called endogenous or the lipid transporting pathway ***(Myant, 1982).***

Low density lipoproteins are secreted from liver or intestine by receptor mediated process which is taken up into peripheral cells to supply cholesterol ***(Brown and Goldestien, 1977).***

High density lipoproteins are formed in the liver and intestine. It pick up cholesterol from cells and return it back to the liver then excess cholesterol is excreted as bile acids via the gut ***(Tall and Small, 1978).***

Catov et al. (2007) considered that inflammation in women with spontaneous preterm labor might be related to their metabolic profile, such as lipids. Their results indicate the presence of dyslipidemia in women with spontaneous preterm labor.

AIM OF THE WORK

The aim of work is to evaluate the level of C-reactive protein, cholesterol, triglycerides, HDL, LDL in patients with spontaneous preterm labor.

Chapter (1)

PRETERM LABOR

Preterm Labor is defined as the presence of uterine contractions of sufficient frequency and intensity to effect progressive effacement and dilatation of the cervix perior to term gestation between (20-37 wks) ***(Ross and Eden, 2009)***.

Incidence of preterm labor was 12% of all deliveries, and that of preterm deliveries due to PROM 20.4% and infections were the commonest causes of preterm labor ***(Ross and Eden, 2009).***

Etiology

Spontaneous preterm birth is a common outcome of a broad combination of medical and social factors. In fact, it may be said to be a social disease: it happens much more frequently when the mother is poor, has a low educational level, is isolated, single or too young. National data are unequivocal on this major point: preterm birth is closely related to social class.

A wide spectrum of etiologies has been implicated in the delivery of a preterm infant including:

A) Infections and preterm prelabor rupture of membranes

B) Reproductive history. *C) Lifestyle factors.*

D) Sociobiological factors.

(Ross and Eden, 2009)

So, premature labor can be understood as a syndrome with a number of underlying causes including infection, maternal stress, uterine distention, placental hypoxia, bleeding and lack of prostaglandin dehydrogenase. Infection is probably the most important factor at low gestational age, uterine distention and maternal stress increasing in significance further on. In the future, the ability to determine the specific reason in each individual case may be better, which may lead to the development of more effective treatment ***(Goldenberg et al., 2000).***

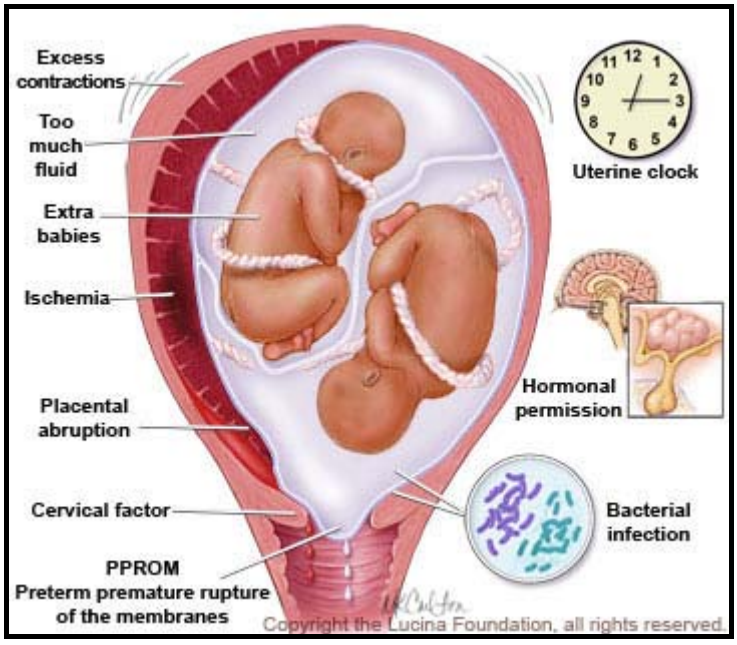

Fig. (1): Pre-term labor: possible causes and risk factors ***(Goldenberg et al., 2000).***

A) Infections and preterm prelabor rupture of membranes

Intrauterine infection is a major cause of preterm labor with and without intact membranes. Intrauterine infection is present in approximately 25% of all preterm birth and preterm PROM and the earlier the gestational age at delivery the higher the frequency of intrauterine infection. Preterm PROM, defined as rupture of membranes at less than 37 weeks' gestation, complicates about 2-3% of pregnancies and is responsible for approximately one third of all preterm births ***(Garland et al., 2002).*** It was straight forward; therefore, to construct a theory to describe the pathogenesis of infection mediated preterm labor. Microorganisms originating in the vagina or cervix colonize in tissues such as decidua and possibly fetal membranes. Lipopolysaccharide (LPS) elaborated by these bacteria induce cytokine formation by phagocytes and thereby preterm labor ***(Athayde et al., 2005).***

Routes of infection:

Most cases of intraamniotic infection are ascending in origin, commonly after prolonged rupture of membranes and labor in patients with multiple vaginal examinations. However, occasionally intraamniotic infection may occur in patients with labor but without membranes rupture. Second route of intraamniotic infection is hematogenous

spread in mothers with bacteremia. Most notably, Listeria monocytogens, which may occur either as an epidemic or in isolated cases, has been reported as a cause of blood borne intraamniotic infection. A third mechanism for development of intraamniotic infection is introduction of bacteria during an invasive procedure. After diagnostic amniocentesis, the risk of acute intraamniotic infection is low. With more extensive manipulations, such as intrauterine transfusion, the risk of acute infection may be estimated as high as 5% ***(Gibbs and Patrick, 1991).***

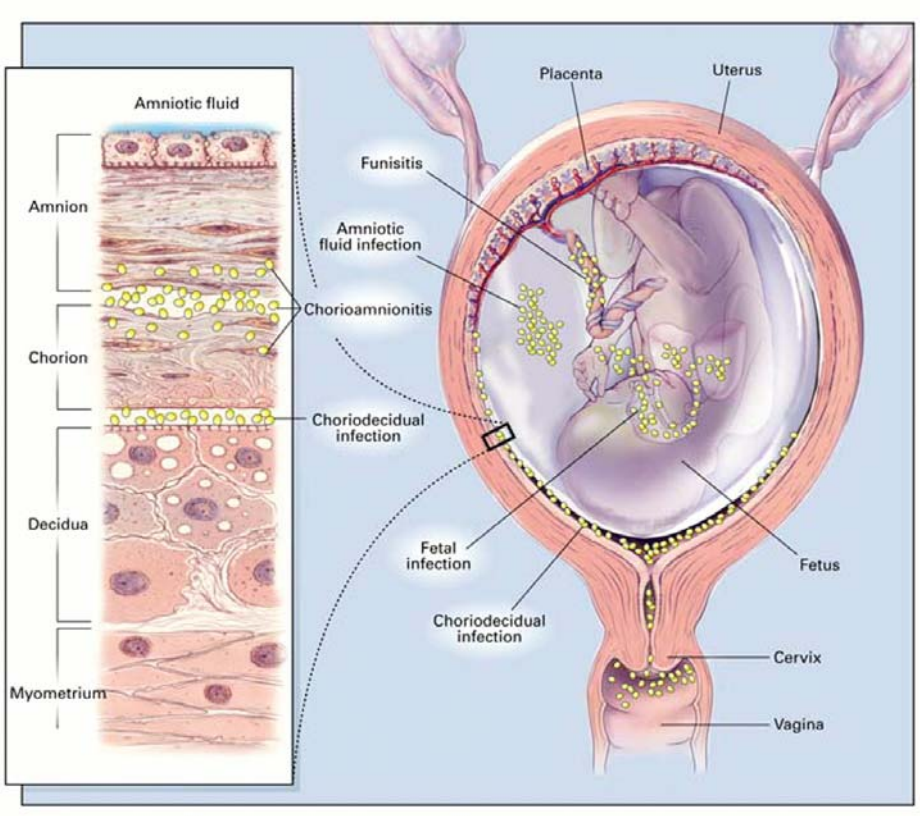

Fig. (2): Potential Sites of Bacterial Infection within the Uterus ***(Goldenberg et al., 2000)***.

A number of maternal bacterial infections are associated with preterm birth including pyelonephritis, asymptomatic bacteriuria, pneumonia, and appendicitis. Also periodontal disease has been shown repeatedly to be linked to preterm birth ***(Jeffcoat et al., 2001)***. In contrast, viral infections, unless accompanied by a significant febrile response, are considered not to be a major factor in relation to preterm birth ***(Goldenberg et al., 2008)***.

Endotoxins released by microorganisms and cytokines stimulate deciduasl responses including the release of prostaglandins which may stimulate uterine contractions. Further the decidual response may include release of matrix-degrading enzymes that weaken fetal membranes leading to premature rupture. Intrauterine infection appears to be a chronic process ***(Goldenberg et al., 2000).***

1- Chlamydia trachomatis:

Chlamydia trachomatis is an obligator intracellular bacterium that has several serotypes, including that cause lymphgranuloma venerum. Genital infection with chlamydia trachomatis is the most common sexually transmitted bacterial disease in women. Cultures from the cervix are positive in up to one fourth of pregnant women. The improved understanding of chlamydia trachomatis pathophysiology in recent years became possible through DNA amplification technique and genome cloning. There is

increasing evidence that chlamydia trachomatis infection may result in a number of adverse pregnancy outcomes, including early and late abortion, infection of the fetus, stillbirth, preterm PROM, prematurity and postpartum endometritis. Ectopic pregnancy is often associated with a previous tubal chlamydial infection. Chlamydia trachomatis infection in newborn feotuses is acquired during vaginal delivery, and it may result in neonatal conjunctivitis and/or neonatal pneumonia ***(Webster et al, 1993).***

El-Shourbagy et al. (1996) performed a case control study in Ain Shams University Maternity hospital to investigate the incidence of genital chlamydial infection among high risk clinical condition in Egyptian women. The study included 501 patients and 192 comparable controls divided into 5 main groups. Group 1 consisted of patients with cervicitis (n = 58) with comparable controls (n = 38) in whom cervix looked clinically normal. Group 2 consisted of patients with abnormal cytology (n = 256) while controls (n = 64) where women with normal smear and colposcopic findings. Group III consisted of patients with tubal factor infertility (n = 85) while controls (n = 50) were infertile women with normal tubes on laparoscopy. Group VI consisted of patients with ectopic pregnancy (n = 22). Group V consisted of patients with preterm labor (n = 80) among which 55 subjects had preterm PROM confirmed by sterile speculum examination. The controls for the last 2 patient groups were 40 women, who were

pregnant at term and had no previous ectopic pregnancy. Active cervical chlamydial infection was diagnosed using direct immunofluorescent test. They found that percentage of positive chlamydial infection was 56.3% among patients with preterm labor, being more frequently found when fetal membranes were ruptured (61.8%) rather than intact (44%). Based on the above results, they stated that empirical treatment is recommended in all patients with preterm labor and preterm PROM as the diagnosis is costly and usually not available.

2- Group B streptococci:

Fortunato et al. (2001) evaluated the effect of peptidoglycan polysaccharide derived from group B streptococcal cell wall on amniochorion cytokine production and compared peptidoglycan polysaccharide effects with lipopolysaccharide. It was concluded that beta peptidoglycan polysaccharide and lipopolysaccharide stimulate cytokine production differently from fetal membranes. Lipopolysaccharide stimulated IL-6 to a greater degree than IL-8, while peptidoglycan polysaccharide stimulated IL-8 to a greater degree than IL-6. This supports the theory that different bacteria may affect the host in contrasting ways which may lead to distinct host response.

3- Bacterial vaginosis:

Camargo et al. (2005) conducted an observational retrospective cohort study on 785 low-risk pregnant women. Three different groups of women were identified: 580 without bacterial vaginosis during pregnancy, 134 with bacterial vaginosis treated using imidazoles during pregnancy, and 71 with bacterial vaginosis not treated during pregnancy. The frequency of prematurity was 5.5% among the women without bacterial vaginosis, 22.5% among those with untreated bacterial vaginosis and 3.7% among those with treated bacterial vaginosis. They concluded that treatment of bacterial vaginosis significantly reduced the rates of prematurity and other perinatal complications among these low-risk Brazilian pregnant women, regardless of the history of previous preterm delivery.

It has been reported that asymptomatic colonization of the decidua occurs in up to 70% of women at term using a DNA probe suggesting that the presence of micro-organism alone may be insufficient to initiate the infectious response. Bacterial vaginosis has been linked to preterm birth raising the risk by a factor of 1.5 – 3. As the condition is more prevalent in black women in the US and the UK, it has been suggested to be an explanation for the higher rate of preterm birth in this population. It is opined that bacterial vaginosis before or during pregnancy may affect

the decidual inflammatory response that leads to preterm birth ***(Goldenberg et al., 2008)***.

4- Ureaplasma urealyticum:

Witt et al. (2005b) studied 207 consecutive women between 23 and 34 weeks of gestation who underwent cesarean delivery. These patients were divided into 3 groups according to the indication for cesarean delivery: patients with preterm labor (group 1), patients with preterm PROM (group 2), and patients with other indications (group 3). Ureaplasma urealyticum was detected in 43.9% (58/132) of the patients of groups 1 and 2, with no significant difference between these 2 subgroups. In group 3, which served as the comparison group, ureaplasma urealyticum was isolated in only 2.7% (2/75) of the patients. Ureaplasma urealyticum as a single pathogen was more frequent than all obligate pathogens together (43.9% vs 39.3%).

5- Candida Albicans:

Zaga-Clavellina et al. (2006) evaluated the secretion of IL-1, TNFα, IL-6, and prostaglandin E_2 (considered as important contributors in pathogenesis of preterm labor and preterm PROM) by the human chorioamnion stimulated with candida albicans. IL-1 was produced in higher amounts in the presence of candida albicans when applied to the choriodecidual side; TNFα and IL-6 secretion did not

change in either the amnion or choriodecidual region. Prostaglandin E_2 synthesis depicted a different pattern, the amniotic tissue was more responsive than the choriodecidual tissue, and this response tended to be higher even when only the amniotic side was stimulated. They concluded that fetal membranes follow different secretion patterns of proinflammatory cytokines depending on the side to which candida albicans was applied.

Aboyeji et al. (2005) performed a prospective case control study in Nigeria to determine the association and the pattern of bacteria/microorganisms in the etiology of PROM. A total of 108 cases of PROM and 98 control cases that presented between 37 completed weeks' and 40 weeks' gestation were analyzed. Pathogens were isolated in 48 patients, giving a recovery rate of 44.4%. The common pathogens include gardnerella vaginalis (29.1%), candida albicans (23.0%) and staphylococcus aureus (18.7%). Others were strep pyogenes (16.6%), coagulase negative staphylococcus (6.3%) and klebsiella (6.3%). Ofloxacin and azithromycin were 100% active against all the isolated pathogens.

Types of cytokines in preterm labor

There are 3 broad classes of cytokines. The lymphokines and monokines, which make up the first class, are produced by cells of the immune system and control

virtually every aspect of immune function. The second and third classes include growth factors and colony stimulating factors; these cytokines control the growth of body tissues and the proliferation of blood cells. Chemokines, a newly recognized category of very small molecular weight proteins, also influence the immune system and may be considered cytokines as well ***(Baggiolini, 1997).***

Mechanism of action of cytokines in preterm labor:

Cytokines bind to specific cell receptors on outside of target cells. Because these receptors are present on many different cell types, cytokines can affect a vast array of cells. Once bound together, the cytokine receptor complex activates an intracellular protein kinase (tyrosine kinase), which in turn leads to the phosphorylation (and activation) of a series of additional intracellular kinases. For most cytokines, activation of these associated kinases turns on a cascade of events that ultimately result in a transcription protein traveling into the nucleus, where it binds to a specific DNA regulatory site, to initiate DNA transcription in the target cell. DNA transcription leads to protein synthesis of the specific proteins that mediate that cytokine's response ***(Yao, 2005).***

Structure and function of cytokines:

A- Proinflammatory cytokines:

1- Interleukin 6:

IL-6 is a 184 amino acid polypeptide. It is produced by various cells, including T and B lymphocytes and other cells. It regulates the growth and differentiation of various cell types with major activities on the immune system, hematopoiesis, and inflammation ***(Le et al., 1989).***

IL-6 induces final maturation of B lymphocytes into antibody producing cells and is a potent growth factor for myeloma and plasmacytoma cells. It stimulates T lymphocyte growth and cytotoxic T lymphocyte differentiation. It promotes megakaryocyte development and synergizes with other cytokines to stimulate the totipotent hematopoietic progenitors. It can also induce differentiation and growth inhibition of some leukemia cell lines ***(Yao, 2005).***

2- Interleukin 8:

IL-8 is a non glycosylated chemoattractant protein for neutrophils. This proinflammatory mediator is secreted by different cells such as monocytes, neutrophils and other cells. The main action of IL-8 is chemotaxis of neutrophils to adhere to endothelium, following which there is diapedesis and recruitment to sites of inflammation. This