INTRODUCTION

Preterm labor is the presence of regular uterine contractions in combination with cervical changes and intact membranes before 37 completed weeks ***(Lemons et al., 2001).***

It occurs in 8–12% of all deliveries, and the rate of preterm delivery has increased during the past years in spite of intensive efforts towards early detection and prompt treatment ***(Goldenberg et al., 2008).***

Although it was a goal of U.S. Department of Health and Human Services 2010 to decrease the preterm birth risk to approximately 7%, the incidence of preterm birth remains greater than 12%. This is attributable to both our inability to accurately predict who will deliver preterm and our lack of universal efficient regimens to treat preterm labor and prevent preterm birth ***(Rouse et al., 2008)***.

Therefore despite our inability to significantly decrease the rate of preterm birth, the ability to identify patients at greatest risk for imminent preterm birth nevertheless is valuable to provide medical management that may decrease the adversity associated with prematurity. Specifically, in addition to transfer to a tertiary care center, in patient observation, cerebral palsy prophylaxis and tocolysis ***(Rouse et al., 2008)***.

The American College of obstetricians and Gynecologists recommends the administration of corticosteroids to all women

between 24 and 34 weeks of gestation at risk for delivering "within 7 days" in an effort to reduce the risks of respiratory distress syndrome, perinatal mortality and other morbidities ***(Lyell et al., 2007)***.

However, there is an urgent need for new markers that may be easier and more sensitive than current methods because the majority of women who had undergone a transvaginal ultrasound examination and pelvic examination can experience discomfort ***(Bennett and Richards, 2000).***

Intrauterine infection is one of the most significant causes leading to preterm labor. Numerous studies have focused on markers of intrauterine infection in an effort to find sensitive, less invasive methods for predicting spontaneous preterm delivery. It has been also examined that maternal systemic inflammatory biomarkers, such as C-reactive protein (CRP) and cytokine, play in preterm labor and delivery ***(Romero et al., 2006).***

Now, hematological markers, including leucocytes subtypes and the neutrophil to lymphocyte ratio (NLR), have been proposed as diagnostic and prognostic factors in various diseases ***(Nunez et al., 2008).***

AIM OF THE WORK

The aim of this study is to evaluate the clinical usefulness of systemic inflammatory markers including leucocyte differential counts, CRP and NLR in comparison with cervical length and determined whether these markers, either alone or in combination with cervical length, could be used as a novel predictive and prognostic marker for spontaneous preterm delivery.

PRETERM LABOR

Definition:

Preterm labour is the presence of regular uterine contraction in combination with cervical changes with or without intact membrane before 37 completed weeks ***(Craig et al., 2014).***

Background:

Preterm birth is the major cause of neonatal morbidity and mortality in developed countries. Sequelae of preterm birth are common in the neonatal period, may persist into adulthood and are inversely related to gestational age. Preterm birth may result from either spontaneous developments or medically indicated interventions. Known causes of spontaneous preterm labor include infection (intrauterine or extrauterine), multiple gestation, placental abruption, hormonal disruptions and other factors, though a large proportion of preterm births are 'idiopathic', or without known cause ***(Agrawal and Hirsch, 2012).***

At least 40% of preterm births are associated with intrauterine infection. In individual cases it is often difficult to determine whether infection is the cause or consequence of the processes leading to preterm delivery. However, there is abundant evidence that infection and the inflammation generated by infection, whether within the gestational tissues or elsewhere, are a primary cause of a substantial proportion of preterm births. This evidence includes the following: (a) the

amniotic fluid of patients with preterm labor has higher rates of microbial colonization and levels of inflammatory cytokines than preterm patients not in labor and term patients in labor; (b) intrauterine or systemic administration of microbes or microbial products to pregnant animals can result in preterm labor and delivery; (c) extrauterine maternal infections such as pyelonephritis, pneumonia; and periodontal disease have been associated with premature parturition; (d) subclinical intrauterine infections are associated with preterm labor and delivery; (e) patients with intra-amniotic infection or intrauterine inflammation (i.e. elevation of amniotic fluid cytokines and matrix-degrading enzymes) identified as early as the mid-trimester are at risk for subsequent preterm delivery ***(Ilievski and Hirsch, 2010)***.

Classification and subcategories of preterm birth

By gestational age:

1- World Health Organization reported that ***(WHO, 2015)***.

- Moderate preterm: 32 to <37 weeks
- Late preterm: 34 $^{0/7ths}$ to 36 $^{6/7ths}$ weeks
- Very preterm: 28 to <32 weeks
- Extremely preterm: <28 weeks

2- Another classification reported by ***(Sangkom et al., 2015)***.

- Preterm: <37 weeks
- Late preterm: 34 to 36 weeks
- Early preterm: <34 week

By Birth Weight (Whosis, 2012) showed that

- Low birth weight (LBW): <2500 grams
- Very low birth weight (VLBW): <1500 grams
- Extremely low birth weight (ELBW): <1000 grams

Prevalence and Epidemiology of spontaneous labor in preterm birth

Laughon et al. (2010) evaluated records of 15,136 late preterm births from a population of more than 170,000. Late preterm births comprised 7.8% of all births and 65.7% of preterm births; 29.8% of late preterm births followed spontaneous labor; 32.3% preterm PROM; 31.8% had an obstetrical, maternal, or fetal condition leading to late preterm birth after induction of labor or cesarean delivery in the absence of labor, and 6.1% were unknown.

Worldwide, the preterm birth rate is estimated to be about 11 percent (range 5 percent [parts of Europe] to 18 percent [parts of Africa]), and about 15 million children are

born preterm each year (range 12 to 18 million). Of these preterm births, 84 percent occurred at 32 to 36 weeks, 10 percent occurred at 28 to <32 weeks, and 5 percent occurred at <28 weeks. In the United States in 2010, 11.99 percent of preterm births occurred ***(Blencowe et al., 2012).***

Aetiology of preterm birth

1- Risk factors

2- Causes

A. Risk factors for preterm birth

Preterm birth may follow spontaneous onset of preterm labor or as an obstetric intervention when the risk of continuing the pregnancy, to either the mother or the child is perceived as greater than the risks associated with preterm birth. Much of the increase in preterm births seen in recent years relates to obstetric intervention, sometimes referred to iatrogenic preterm birth, with recent studies from both Europe and North America suggesting that the increase in iatrogenic preterm delivery is associated with a reduction in neonatal mortality ***(Lisonkova et al., 2011).***

Reasons for preterm birth can be classified as ‘maternal’, for example related to a pre-existing maternal medical disorder, such as diabetes; or ‘pregnancy-related’ for example, pregnancy-induced hypertension. While the use of tocolytic drugs may delay delivery following the spontaneous onset of

preterm labor by up to 48 hours ***(Haas et al., 2012),*** there is little evidence to suggest that delaying delivery in this way improves outcomes in terms of either infant mortality or morbidity ***(Alfirevic, 2012).***

About half of the preterm births associated with multiple gestations follow spontaneous onset of labor, with the remaining associated with pregnancy complications such as pre- eclampsia ***(Goldenberg et al., 2008).***

B. Causes of preterm labor

Although preterm birth is recognized to be an adverse outcome of parturition, parturition itself remains incompletely understood. Two compelling principles emerge from the current understanding of pregnancy and parturition. Labor represents a natural continuum of processes that begin at implantation and culminate with the return of the uterus to its non-pregnant state. The continuum involves 5 well-defined phases: implantation, uterine quiescence, activation, stimulation and involution ***(Gravett et al., 2010)*** **(Figure 1).**

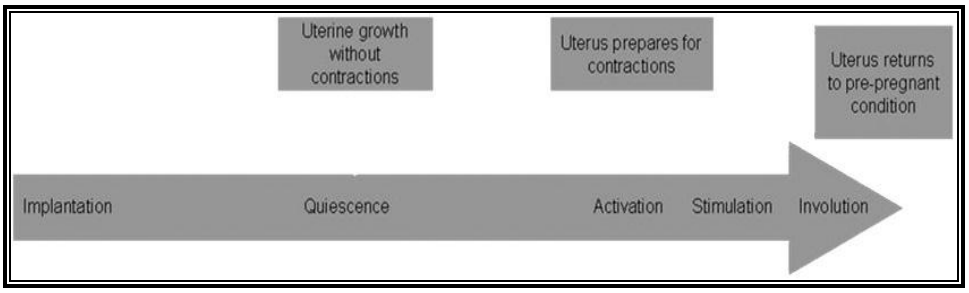

Figure (1): Phases of parturition as a continuum of pregnancy. After implantation, most pregnancy is spent in a state of quiescence, with uterine growth without uterine contractions. Activation is characterized by a biochemical and physiological maturation favoring uterine contractions. Stimulation, or labor, constitutes less than 0.5% of gestation ***(Gravett et al., 2010)***.

Preterm premature rupture of membrane (PPROM) often represents a final common pathway to preterm birth. It has been associated with intrauterine infection, tobacco use, abruption, multiple gestations, previous PPROM, previous cervical surgery or laceration, a short cervix by ultrasound, genetic connective tissue disorders, and vitamin C deficiency. Regional- or ethnic-specific variations in the contribution of specific pathways are not completely understood and reflect the need for further research efforts. Each pathway to prematurity may be influenced by gene environment interactions and by genetic variability ***(Simmons et al., 2010)*** **(figure 2).**

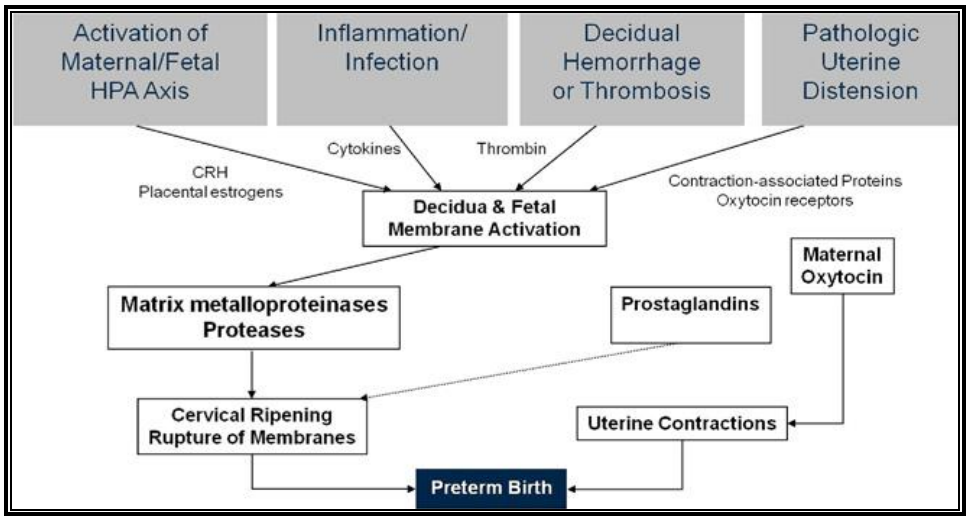

Figure (2): Overview of major pathways leading to preterm labor and delivery. Although there are multiple unique upstream initiators of preterm birth, there a few common downstream effectors. This suggests that interventions targeting unique upstream initiators coupled with interventions targeting common downstream effectors may have enhanced efficacy in treating preterm labor when compared with interventions that target only downstream effectors ***(Simmons et al., 2010)***.

I- Infection/Inflammation

From a global health perspective, infection is one of the most important and potentially preventable causes of early preterm birth. Intrauterine infections are thought to be responsible for up to 50% of extreme preterm births of less than 28 weeks of gestation, where both neonatal mortality and morbidity are high, and are refractory to conventional tocolytic therapy. In addition, extrauterine or systemic infections may play an important role in preterm birth. Observational studies show an association between maternal urinary tract infections, bacterial vaginosis, periodontal disease and both preterm birth and low birth weight ***(Gravett et al., 2010)***.

II- Decidual Hemorrhage/Thrombosis

Decidual hemorrhage may cause either late or early preterm birth. Vascular lesions of the placenta are commonly associated with preterm birth and PPROM. Vascular lesions of the placenta have been reported in 34% of women with preterm delivery, 35% of women with PPROM, and in 12% of term uncomplicated deliveries. The proposed mechanism linking vascular lesions to preterm birth is related to uteroplacental ischemia and thrombin is thought to play a central role ***(Simmons et al., 2010)***.

III- Stress

Stress results in preterm activation of the maternal or fetal hypothalamic-pituitary-adrenal axis and is increasingly recognized as an important cause of late preterm birth. Stress may be simply defined as any challenge, whether physical or psychological that threatens or is perceived to threaten homeostasis of the patient. The authors of several studies have found 50% and 100% increases in preterm birth rates associated with maternal stress, usually defined as a composite of life events, anxiety, depression, or perceived stress. The authors of in vitro and in vivo studies have demonstrated a correlation between hypothalamic corticotropin release, maternal stress and an association to the timing of birth ***(Gravett et al., 2010)***.

IV- Uterine Overdistension

Uterine overdistension plays a key role in the onset of preterm labor associated with multiple gestations, poly-hydramnios, and macrosomia. Multiple gestations, frequently attributable to assisted reproduction technologies, including ovulation induction and in vitro fertilization, is one of the most important causes of late preterm birth in HICs ***(Simmons et al., 2010)***.

V- Cervical insufficiency

Cervical insufficiency has traditionally been associated with second trimester pregnancy losses, but recent evidence suggests that cervical disorders are associated with a wide variety of adverse pregnancy outcomes, including early preterm birth. Cervical insufficiency may be caused by congenital disorders, in utero diethylstilbestrol exposure, loss of cervical tissue after a surgical procedure, traumatic damage, and infection. Cervical length of less than 25 mm measured by transvaginal ultrasonography is correlated with risk of preterm birth ***(Simmons et al., 2010)***.

Cervical insufficiency refers to pathological dilatation and or effacement of the uterine cervix unrelated to labor and leading to pre-viable pregnancy loss, as well as PTB. It may occur with or without coexisting distention of the corpus, and cerclage may be helpful in select instances ***(Maria Siega-Riz, 2001)***.

VI- Environmental Factors

Various environmental exposures have been linked to poor pregnancy outcomes. Maternal serum and umbilical cord blood levels of pesticides, such as dichlorodiphenyl trichloroethane are associated in some, but not all, studies with preterm delivery. Other organophosphate pesticide metabolites are associated with preterm birth at increasing exposure levels in the later part of pregnancy. Air pollution (particulate matter, carbon monoxide, lead, ozone, nitrogen dioxide, and sulfur dioxide) is associated with a variety of poor birth outcomes, including preterm birth ***(Jha et al., 2002)***.

Although there is an association between indoor air pollution and low birth weight. Daily energy needs are often met by burning solid fuels, and women cooking in poorly ventilated homes are disproportionately exposed to air pollution. The harmful effects of smoking during pregnancy are well established and it has been causally associated with preterm delivery and stillbirth ***(Jha et al., 2002)***.

Consequences of preterm birth

A. Infant Mortality

Worldwide, preterm birth is the commonest cause of neonatal death, with about 3.1 million babies per year dying as a direct result of premature birth, although there are dramatically different patterns in survival rates across the

world. In high income countries, about 50% of preterm infants born at 24 weeks survive the neonatal period (the first 28 days of life), rising to 90% at 28 weeks gestation. In contrast, in low-income countries, often less than 10% of those born at 28 weeks survive, and it is only those born at 34 weeks or later that have survival rates of >50% ***(WHO, 2012)***.

Infant death rates are subdivided into neonatal deaths, and post-neonatal deaths, i.e. deaths occurring between 29 days and the end of the first year of life ***(Moser, 2009)***. However survival rates quickly improve, with two-thirds of those born at 24 weeks gestation surviving the first week of life ***(Castanon et al., 2012).***

B. Infant Morbidity

Infants born preterm are at greater risk of problems both in the short and longer term. A greater understanding of the long-term morbidity associated with very preterm birth has come from recent longitudinal follow-up studies. In particular, long-term sequelae in children born before 26 weeks gestation have been demonstrated in the UK ***(Johnson et al., 2009 and Costeloe et al., 2012)*** and in children up to 32 weeks gestation in France ***(Delobel-Ayoub et al., 2009)***. Following delivery, preterm infants are at risk of infectious and non-infectious respiratory problems, with up to 40% of preterm survivors having broncho-pulmonary dysplasia ***(Castanon et al., 2012)***.

This ranges from 67% of the extremely preterm, to 37% among the very preterm ***(Farstad et al., 2010)***. A recent population-based study reported that 7% of surviving neonates were discharged home on oxygen ***(Datta-Nemdharry et al., 2012)***.

Necrotizing enterocolitis is seen almost exclusively in preterm infants. The pathophysiology of this condition is still unclear. Estimates of its incidence range between 4 and 7%, with approximately one third needing surgical management, and case fatality rates between 12 and 30%, with higher case fatality among the more preterm infants ***(Lin and Stoll, 2006)***.

Infants who survive necrotizing enterocolitis are at higher risk of the long term problems associated with preterm birth when compared with other children born at a similar gestational age ***(Pike et al., 2012)***.

Retinopathy of prematurity is seen in up to 3% of very preterm infants (born before 28 weeks gestation) resulting in severe visual impairment in up to 8% of those born before 26 weeks. Further, children born before 28 weeks are at a six-fold risk of myopia and hypermetropia resulting in 25% of this group requiring glasses by the age of six ***(Torloni et al., 2009)***.

Although a smaller proportion (about 3%) of very preterm infants are at risk of a hearing impairment, nevertheless, they are