Introduction

Preterm birth: defined as any live birth occurring through the end of the last day of the 37th week (259th day) following the onset of the last menstrual period ***(ACOG, 2007)***.

Preterm deliveries are those that occur at less than 37 weeks' gestational age; however, the low-gestational age cutoff, or that used to distinguish preterm birth from spontaneous abortion, varies by location. In the USA, the preterm delivery rate is 12–13%; in Europe and other developed countries, reported rates are generally 5–9% (***Mercer, 2000).***

Preterm birth rate has risen in most industrialized countries, with the USA rate increasing from 9·5% in 1981 to 12·7% in 2005 (***Hamilton, 2006)***.

Preterm births account for 75% of perinatal mortality and more than half the long-term morbidity (***McCormick, 1985)***.

Although most preterm babies survive, they are at increased risk of neurodevelopmental impairments and respiratory and gastrointestinal complications (***Saigal, 2008).***

The obstetric precursors leading to preterm birth are: delivery for maternal or fetal indications, in which labour is either induced or the infant is delivered by prelabour caesarean section. Spontaneous preterm labour with intact membranes, preterm premature rupture of the membranes (PPROM), irrespective of whether delivery is vaginal or by caesarean section **(*Tucker, 1991)***.

Preterm labour is now thought to be a syndrome initiated by multiple mechanisms, including: infection or inflammation, uteroplacental ischaemia or haemorrhage, uterine overdistension, stress and other immunologically mediated processes **(*Goldenberg, 2005)***.

Progesterone, produced by secretion from the corpus luteum and the placenta, is known to be essential for the maintenance of pregnancy early in gestation (***Rebar, 1992).***

In addition, progesterone is known to have actions that maintain pregnancy later in gestation. Progesterone acts to relax smooth muscle in many organs, including the pregnant uterus.

Progesterone has immunosuppressive activity against the activation of T lymphocytes and blocks effects of oxytocin on myometrium (***Stites, 1983).***

Perhaps most importantly, progesterone is a potent inhibitor of the formation of gap junctions between myometrial cells. These intercellular communications are essential for the propagation of coordinated uterine muscle activity leading to labor (***Garfield, 1980).***

Meis et al.,reported the results of a large multicenter trial of 17alpha hydroxyl progesterone. Delivery at less than 37 weeks was reduced from 54.9% in the placebo group to 36.3% in the treatment group. Similar reductions were seen in delivery at less than 35 weeks, from 30.7% to 20.6%, and delivery at less than 32 weeks, from 19.6% to 11.4% (***Meis et al., 2003).***

Low-dose aspirin (LDA) has been noted to reduce the preterm birth (PTB) rate in multiple meta-analyses of the pre-eclampsia (PreE) prevention trials **(*Hauth*, 1993).**

It is unclear if this effect of LDA is entirely due to a reduction in indicated PTB versus reductions in preterm premature rupture of membranes (PPROM) or spontaneous PTB. In the Maternal_Fetal Medicine Unit (MFMU) high-risk Aspirin (HRA) study, a near significant decrease in PTB was found despite no effect on Pre eclampsia. The objective of this study was to assess the impact of LDA on indicated PTB, spontaneous PTB, and PPROM PTB in the MFMU HRA study population ***(Rebecca Jessel, 2015).***

Aim of the work

Research hypothesis:

In pregnant women at risk of PTL, 17 alpha hydroxy progesterone and low dose aspirin may reduce the rate of preterm birth.

Research questation:

In pregnant women at risk of PTL, does 17 alpha hydroxy progesterone and low dose aspirin reduce the rate of preterm birth?

Aim of the study:

This study aim to assess the efficacy of 17 alpha hydroxy progesterone and low dose aspirin in reduction the rate of preterm birth in pregnant women at this risk.

Physiology and Etiology of Preterm Labor

Definitions:

Preterm birth defined as any live birth occurring through the end of the last day of the 37th week (259th day) following the onset of the last menstrual period***(ACOG, 2007)***.

PTB can be further sub-categorized as late preterm delivery- 34 to 36 completed weeks gestation, moderately preterm- 32 to 34 completed weeks, very preterm- less than 32 weeks, and extremely preterm- less than 28 weeks gestation ***(Lockwoodet al., 2011).***

Preterm birth can also be defined by birth weight: low birth weight- less than 2500g, very low birth weight- 1500g, and extremely low birth weight- less than 1000g***(Lockwoodet al., 2011).***

Preterm Labor, also defined by the World Health Organization as: any labor that occurs at less than 37 and more than 20 weeks' gestational age in which there are regular contractions accompanied by cervical changes ***(Goldenberg, 2002).***

Spontaneous pretermbirth (SPB) includes: pretermlabor, pretermspontaneous rupture of membranes (PROM), preterm premature rupture of membranes (PPROM), and cervical weakness***(Ananth and Vintziless, 2006).***

A term birth defined as: a birth occurring between 37 and 42 weeks. Preterm labor defined as the presence of regular uterine contraction of sufficient frequency and intensity to produce progressive effacement and dilatation of the cervix prior to term gestation (before 37 weeks) ***(Sayres, 2010).***

Periviable birthdefined as delivery occurring from 20 0/7 weeks to 25 6/7weeks of gestation ***(Rajuet al., 2014).***

- **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).***

Incidence:

The preterm birth rate (less than 37 weeks) was 9.57% in 2014, down slightly from 2013 and down 8% from 2007. The preterm rate among singleton births has declined 10% since 2007. The 2014 rate of low birth weight (less than 2, 500 grams) was 8.00%, essentially unchanged from 2013, but 3% lower than the 2006 high (8.26%)**(*Hamiltonet al., 2014).***

Preterm birth is the single biggest cause of neonatal mortality and morbidity in the UK, affecting over 52, 000 babies (around 7.3% of live births) in England and Wales in 2012.

There has been no decline in the UK preterm birth rate over the last 10 years***(Costeloeet al., 2012).***

Pathogenesis of preterm labor:

Pathogenesis of premature delivery is assumed to include the following processes:***(Romero and Espinoza, 2007).***

1-Infection.

2-Uteroplacental ischemia.

3-Impaired maternal tolerance of fetus (theory "fetus as an allograft).

4-Allergy.

5-Excessive uterine distension.

6-Cervical incompetence.

1. Infection:

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***(Goncalveset al., 2002).***

It is hypothesized that intrauterine infections trigger preterm labor by activation of the innate immune system. microorganisms elicit release of inflammatory cytokines such as interleukins and tumor necrosis factor 6 (TNF), which in turn stimulate the production of prostaglandin and/or matrix degrading enzymes***(Goldenberg, 2008).***

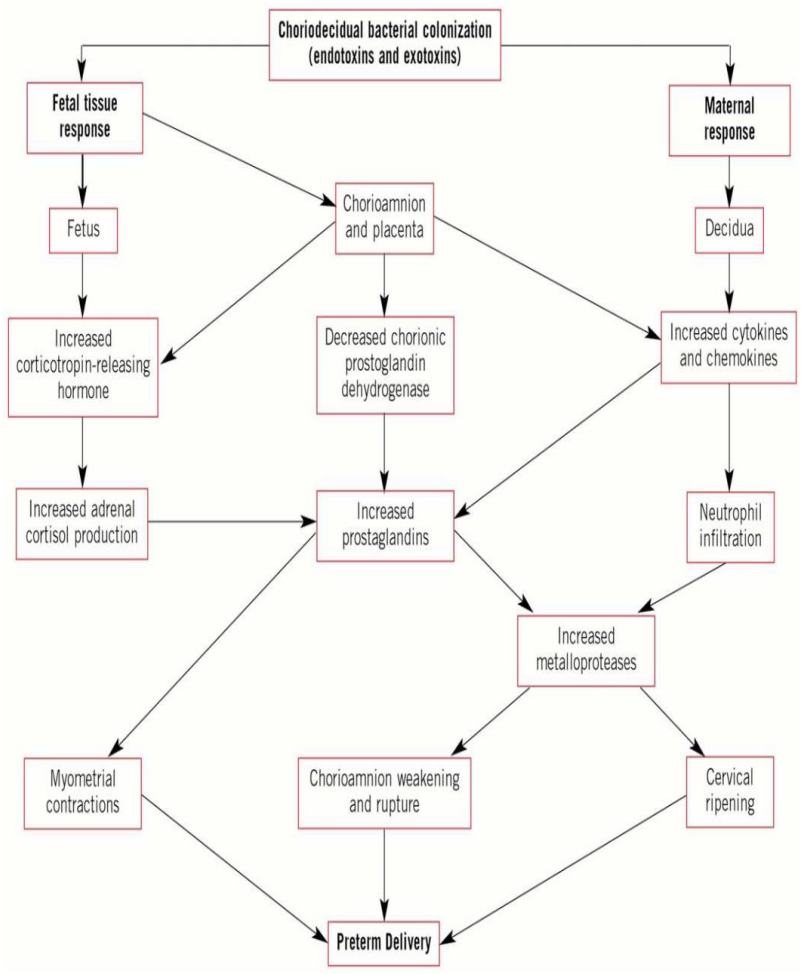

Fig. (1): Pathways leading from choriodecidual bacterial colonization to preterm labor and delivery***(Goldenberg, 2006)***.

Prostaglandins stimulate uterine contractions, whereas degradation of extracellular matrix in the fetal membranes leads to preterm rupture of membranes. It is estimated that 25 to 40 percent of pretermbirths result from intrauterine infection***(Romero, 2007).***

Microbes associated with preterm birth:

Some microorganisms like, Gardnerella vaginalis, Fusobacterium, Mycoplasma hominis, and Ureaplasma urealyticum, are detected more commonly than others in amnionic fluid of women with preterm Labor.

Ureaplasma urealyticum and Mycoplasma hominis,have emerged as important perinatal pathogens ***(Gerber et al., 2003).***

Goldenbergreported that 23 percent of neonates born between 23 and 32 weeks have positive umbilicalblood cultures for these genital mycoplasmas***(Goldenberg, 2008).***

Similar results were reported earlier by the research group at the Perinatology Research Branch of the National Institute of Child Health and Human Development (NICHD). Inone study, amniotic fluid was aspirated by amniocentesis from219 Korean women with prematurely ruptured membranes before 25 weeks.

A positive culture result, primarily for U.urealyticum, was found in 23 percent***(Shimet al., 2004).***

Similarly, Gomez performed amniocentesis in 401 Chilean women and found microbial invasion in 7 percent—the most common organismwas U. urealyticum ***(Gomez et al., 2005).***

Bacterial VaginosisIn this condition, normal hydrogen peroxide-producing, lactobacillus-predominant vaginal flora is replaced with anaerobes that include Gardnerella vaginalis, Mobiluncus species, and Mycoplasmahominis***(Hillier et al., 2003).***

Bacterial vaginosis has been associated with spontaneous abortion, pretermlabor, pretermrupture of membranes, chorioamnionitis, and amnionic fluid infection***(Leitich et al., 2003).***

Environmental factors appear to be important in the development of bacterial vaginosis. Exposure to chronic stress, ethnic differences, and frequent or recent douching have all beenassociated with increased rates of the condition***(Culhaneet al., 2008).***

A gene-environment interaction was identified by (Macones). Women with bacterial vaginosis and a

susceptible TNF- genotype had a nine fold increased incidence of pretermbirth***(Macones, 2004).***

Fromall of these studies, there seems no doubt that adverse vaginal flora is associated in someway with spontaneous pretermbirth. Unfortunately, to date, screening and treatment have not shown to prevent pretermbirth. Indeed, microbial resistance or antimicrobial-induced change in the vaginal flora has reported because of regimens intended to eliminate bacterial vaginosis ***(Carey, 2005).***

2. <u>Uteroplacental ischemia:</u>

There is a rising trend of the relationship between thrombophilias and premature delivery. In these conditions, we assume an excessive coagulation activity with a potential effect on placental microcirculation ***(Czeizela, 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).***

Folic acid metabolism disorder probably in combination with other factors, related to premature delivery. The metabolic transformation of folic acid results in the formation of an active vitamin 4THF-metafoline. One of the enzymes involved in metabolism is methyltetrahydrofolatereductase. Polymorphismis connected with the reduction of their enzymatic activity, particularly in homozygote constitution, resulting in reduced formation of active folic acid metabolite***(Bukowski, 2007).***

4-THF represents a catalyst of the remethylation of methionine into homocysteine. Its lack (MTHFR mutation) causes insufficient homocysteine transformation, followed by its accumulation in the body***(Ozbek, 2007).***

The homocysteine elevation is connected with endothelial impairment Hyperhomocysteinaemia is a significant risk factor for arteriosclerosis. In MTHFR mutation carriers, it is assumed that the above mentioned mechanism might be related to placental micro-circulation impairment to all other consequences of abortion, premature delivery and IUGR ***(Romero, 2007).***

The related endothelial dysfunction initiates a cascade of biochemical processes resulting in premature delivery. The detailed mechanism has not described yet.

The most significant thrombophilias include Leiden Mutation, mutation of coagulation factor II – prothrombin, and anti-phospholipid syndrome***(Czeizel, 2004).***

3. Fetus as an allograft:

A number of autoimmune diseases when uncontrolled connected with a higher risk of premature delivery. The most common ones include ulcerative colitis, lupuserythematosis and thyroid gland immunopathologies***(Romero, 2008).***

Presence of abnormal immunological processes in pathogenesis of premature delivery has already studied for many years. There are various kinds of evidence (at molecular as well as at genetic level) supporting the assumption that premature delivery and/or multiple abortions can occur due to fetus as an allograft***(BloisGarcia, 2007).***

4. Allergy:

The uterus is a rich source of mast cells – one of the "executive" cells of allergic reaction. Pharmacological

degranulation of mast cells results in the induction of uterine activity, particularly prostaglandin release***(Garfield, 2000).***

Another work describes the occurrence of eosinophillic granulocytes in amniotic fluid obtained from women with premature delivery, compared with the control group. The presence of eosinophiles supports the presence of abnormal immune/allergic response as one of the ways to premature delivery***(Garfieled, 2000).***

5. Excessive uterine expansion:

There is no doubt that multifetal pregnancy as well as polyhydramnios lead to an increased risk of preterm birth. Stretching of the myometrium induces the formation of gap junctions, up regulation of oxytocin receptors, and production of prostaglandinE2 and F2 and myosin light chain kinase, which are critical events preceding uterine contractions and cervical dilation ***(Boggess et al., 2005).***

The result of excessive uterine stretch is the premature loss of myometrial quiescence ***(Cunningham et al., 2005).***

Similarly, excessive amniochorial expansion results in mechanical damage of chorions, potentially resulting in PROM. At present, this way to premature delivery is most difficult to control***(Goldenberg, 2006)***.