INTRODUCTION

Preterm delivery is defined by a birth occurring before 37 weeks of gestation or before 259 days from the last menstrual period. Prematurity is multifactorial and its incidence has increased during the last decade in most developed countries, probably due to increased risk factors responsible for elective prematurity ***(Muglia and Katz, 2010).***

The frequency of preterm delivery contributes a relatively small proportion of total births (5-11%), while it is associated with excess of 70% of the total perinatal mortality in developed countries, when excluding deaths related to congenital anomalies ***(Steer, 2006).***

Preterm birth is responsible for approximately 75% of all neonatal deaths and 50% of childhood neurological morbidities. Preterm birth is also associated with both high immediate and long-term costs after discharge from the hospital ***(Petrou et al., 2003).***

Premature neonates are at increased risk of death and short-term complications such as respiratory distress syndrome, intraventricular hemorrhage, neonatal sepsis and necrotizing enterocolitis. Long-term complications include neurodevelopment disorders such as cerebral palsy, chronic lung disease, blindness and deafness ***(Gotsch et al., 2007).***

Early detection of preterm labor is difficult because of initial symptoms and signs are often mild and may occur in normal pregnancy. Thus, many healthy women will report symptoms during routine prenatal visits, whereas others destined for preterm birth may dismiss the early warning signs as normal in pregnancy. The traditional criteria for preterm labor (persistent contractions accompanied by progressive cervical dilatation and effacement) are most accurate when contraction frequency is six or more per hour, cervical dilatation is three cm or more, effacement is 80% or more, membranes rupture, or bleeding occurs ***(Hueston,2001; Macones et al., 2002).***

In this context, a number of chemical and laboratory biomarkers have been studied for predicting preterm labor. ***(Romero et al., 2010)***

This markers include:

- Fetal Fibronectin (fFN).
- Maternal serum estriol.
- Maternal serum relaxin.
- Alpha Fetoprotein.
- Human chorionic gonadotropin (hCG).
- Prolactin (PRL).
- C-reactive protein (CRP).

A) Human Chorionic Gonadotropin (HCG):

β subunit had been described in the cervicovaginal secretion of pregnant women ***(Anai et al., 1997)***, β-HCG in cervicovaginal secretions mirrors the levels in the maternal serum and AF rising until the beginning of the second trimester and then falling by 18 wks gestation to plateau level for the remainder of the pregnancy ***(Bernstein et al., 1998)***, Quantitative measurement of hCG concentration in the cervicovaginal secretions may be useful in predicting PTB in symptomatic patients. This test has the advantage of being inexpensive and widely available ***(Kashanian et al., 2007).***

B) Prolactin (PRL):

O'Brien and his associates (1994), Guvenal T and his associates (2001) have reported that PRL level in cervicovaginal secretion of preterm labour females was significantly higher than those of normal pregnancy.

AIM OF THE WORK

This study was conducted to assess and compare the accuracy of the β-HCG and prolactin in cervicovaginal secretions for the prediction of preterm labor in women with threatened preterm labor.

Research hypothesis:

In women with threatened preterm labor, β-HCG and prolactin estimation in cervicovaginal secretions may predict the occurance of preterm birth.

Research question:

In women with threatened preterm labor, do β-HCG and prolactin estimation in cervicovaginal secretions predict the occurance of preterm birth accurately?

Chapter 1

PRETERM LABOR (PTL)

Definitions:

Preterm labor:

Preterm delivery is defined by a birth occurring before 37 weeks of gestation or before 259 days from the last menstrual period. Prematurity is multifactorial and its incidence has increased during the last decade in most developed countries, probably due to increased risk factors responsible for elective prematurity ***(Muglia and Katz, 2010).***

The age of viability differs from one country to another and ranges from 20-28 wks of gestations, Regular uterine contractions should be at least 2 every 10 minutes,while cervical changes refer to either dilatation (of 2cm or more) or effacement (cervical length 1 cm or less) ***(Arias, 1993).***

Preterm birth is the leading cause of neonatal mortality and a substantial portion of all birth-related mortality. Preterm delivery accounts for 65% of neonatal deaths and 50% of neurological disability in childhood. Prematurity rates have not changed in recent decades ***(Roy et al., 2006)***, Births before 30 weeks of gestation accounts for most neonatal deaths ***(Chandiramani & Shennan, 2006).***

Aetiology:

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 affect fetal and maternal health often cause preterm delivery. These medically indicated or iatrogenic causes represents about 25% of PTB.
2. Preterm premature rupture of membrane (PPROM), which is followed by preterm delivery causes approximately 25% of PTB.
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).***

Pregnancy complications

Pregnancy complications require a clinical decision to affect preterm delivery rather than to continue pregnancy in a deteriorating intrauterine environment, the most common are maternal hypertension, severe diabetes mellitus, and failure of fetal growth, multiple pregnancies, and abruption placenta ***(Cunningham et al., 2005)***.

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 labour 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)

PTL is multifactorial, it is associated with preterm rupture of membranes, cervical incompetence, polyhydraminos, fetal and uterine annomalies, infections, stress, smoking and heavy work. ***(Haram et al., 2003)*****,** It is also associated with multiple gestation, previous preterm birth,low socio-economic status, maternal/fetal complication,drug use and assisted reproduction all increase the risk of preterm birth.

The mechanisms responsible for these well-established associations are incompletely understood ***(Timothy & Moss, 2006).***

In the amniotic fluid (A.F) of women with spontaneous PTL of infectious aetiology.significantly increased levels of proinflammatory proteins (cytokines) can be detected which is

in contrast to those women in spontaneous PTL of non infectious aetiology. Babies born preterm in the presence of such cytokines are more likely to suffer from lung and brain white matter damage resulting in bronchopulmonary dysplasia and periventricular leukomalacia ***(Yoon & Omero, 2000).***

Neonatal morbidity rates have declined in the recent years largely because of improved neonatal intensive care and better access to these services. With appropriate medical care, neonatal survival dramatically improves as gestational age progresses ***(Tan et al., 2006).***

Table (1): Definitions of PTB using gestational age and birth weight

Gestational age (weeks)	**Birth weight (kg)**
Extremely preterm birth (24wks -28 wks)	Extremely low (<1.0)
Very preterm birth (28 wk-32 wk)	Very low (<1.5)
Preterm birth (32wks-37 wks)	Low (1.5-2.25)

(Chandiramani et al., 2007)

The onset of spontaneous laborat term is associated with the downregulation of placentainterleukin (IL)-10, a major anti-inflammatory cytokine thatprotects pregnancy, and up-regulation of the proinflammatorycytokines IL-1b and tumor necrosis factor (TNF)-a suggestin that IL-10 may be a temporal regulator of gestational length ***(Murphy et al., 2009).***

Threatened preterm labor:

It is usually used to describe pregnancies complicated by episodes of clinically significant uterine activity but without cervical changes.

Arias (1993), Threatened PTL occurs in approximately 2% of pregnancies, However 80% of these pregnancies will proceed to term ***(Parry et al., 2006)*** The diagnosis of threatened preterm labor is difficult.

By definition, regular contractions with cervical effacement or dilatation are required for diagnosing established labor.

Braxton-hicks contractions, which occur after 24 wks gestation, may be painful and can be misdiagnosed as PTL. This will lead to incorrect treatment in up to 80% of cases ***(Haram et al., 2003).***

Preterm infant:

Is the one who is born before 37 weeks gestations of pregnancy ***(ACOG, 1998).***

Extreme premature:

Is the one who is born before 28 completed weeks gestation of pregnancy ***(WHO, 1977).***

Low birth weight (LBW):

Infant who weight less than 2500gm at birth,regardless of gestational age ***(Gabbe et al., 2002 & Cunningham et al., 2001)*.**

Very low birth weight (VLBW):

Infants who weight less than 1500 gm at birth ***(Gabbe et al., 2002)***.

Extremely low birth weight (ELBW):

Infants who weight less than 1000gm at birth ***(Gabbe et al., 2002)***.

Incidence:

It is difficult to quantify the incidence of spontaneous preterm labor, as many studies relating to preterm birth donot discriminate between PTL and iatrogenic therapeutic PTL ***(Vause & Johnston, 2000).***

Signs & symptoms of PTL:

In addition to painful or painless uterine contractions, symptoms such as pelvic pressure, menstrual like cramps, watery vaginal discharge, and pain in the low back have been associated with impending PTB. Such symptoms are thought by some to be common in normal pregnancy and are therefore

often dismissed by patients, clinicians, and nurses ***(Cunningham et al., 2005).***

Because uterine contractions alone may be misleading, the American Collegue of Obstetric &Gynecology has proposed the **f*ollowing criteria*** to ***document PTL between 20 & 37 wks gestation:***

a) Contractions occurring at a frequency of 4 in 20 min plus progressive change in the cervix.

b) Cervical dilatation greater than 1 cm.

c) Cervical effacement of 80% or greater ***(ACOG, 1998).***

Predictive Risk Factors:

A- Maternal characteristics:

1. Age:

There is increased risk of PTL in women under age of 20years and in women over 35 years,they also have a greater risk of adverse perinatal outcomes including low birth weight ***(Schempf et al., 2007).***

2. Race:

There is increased risk for black women independent of the social class ***(Wen et al., 1990)***. The risk of PTB for white

women in the U.S is 11.5% the risk for black women is 17.9% ***(Palomar et al., 2007).***

3. Socioeconomic:

Less education and lower socioeconomic status are also risk factors, although they probably are not independent of one other ***(Goldenberg, 2002).***

4. Cigarete Smoking:

Is associated with excess births under 34 wks of gestations. The greatest risk being to those smoking more than 20 cigarettes per day. Cocaine and opiate users are also risk group have an excess preterm birth among opiate users ***(Volpe, 1992)***, Smoking-related causes of PTB may include spontaneous PTL, PROM, and antepartum bleeding. Solid evidence shows that smoking is associated with PTB. The more the mother smokes, the greater the risk ***(Goffinet, 2005)***.

5. Lack of antenatal care

A risk factor to preterm labour due to failure of detection of women at risk ***(Murray and Bornfield, 1988).***

6. Psychological factors:

Both stress and higher levels of maternal serum cortisol have been associated with spontaneous preterm birth ***(Mercer et al., 2002).***

Neggers and collegues (2004) found a significant risk between LBW and PTL in women injured by physical abuse.

7. Alcohol & coffee abuse:

Alcohol abuse has been linked not only to preterm labour, but also to increased risk of brain injury in preterm infants ***(Holzman et al., 1995)***.

Dose related coffee consumption in the first trimester was associated with 2 fold increase risk of PROM ***(William et al., 1992).***

8. Nutrition:

Women who had total vitamin C intake of <10th percentile preconceptionally had twice the risk of PTL because of PROM ***(Siega-rizet al., 2003).***

B- Past reproductive history:

1. Previous preterm birth:

Is the single best predictor of PTL ***(Wang et al., 1995),*** It is the strongest risk factor for future PTB, although most women who have had a PTB will have subsequent pregnancies of a normal duration ***(Ananth et al., 2006)***.

2. Previous miscarriage:

Previous miscarriage was defined as previous delivery of a conceptous showing no signs of life before 24 wks gestation. Excluding therapeutic abortions, two or more previous miscarriage were more strongly associated with extreme pre term delivery than moderate or mild pre term delivery ***(Smith et al., 2006).***

3. Previous induced abortions:

Induced abortion was associated with an increased risk of idiopathic PTL and PROM ***(Norman, 2007).***

4. Threatened abortion:

Vaginal bleeding in early pregnancy is associated with increased adverse outcomes. ***Weiss & his associates (2004)*** reported data on vaginal bleeding at 6 to 13 wks in nearly 14,000 women.

5. Chorioamnionitis:

Is infection of the membranes and amniotic fluid caused by a variety of microorganisms, a possible explanation of some cases of ruptured membranes, PTL, or both ***(Cox et al., 1996).***

C- Anatomical abnormalities of genital tract:

1) Uterine causes:

Congenital annomalies of the uterus such as infantile, bicornate, septate and arcuate are known causes of preterm birth and spontaneous abortion ***(Paul et al., 1998)***, Asherman's syndrome is associated with increased rate of preterm labour ***(Gonlan & Newman, 1992).***

2) Cervical causes:

Cervical incompetence is responsible for 16-20% of mid trimester abortion and 25% of preterm labour.The high risk group are those with history of traumatic delivery and cervical conization ***(Goldenberg et al., 2000).***

D- Current pregnancy complications:

1. Multifetal pregnancy and poly hydraminous:

Multiple pregnancy and polyhydraminos lead to PTL throught the effects of mechanical strech ***(Terzidou, 2007)***, about half of twins pregnancies will be born preterm ***(Crane et al., 1997).***

2. Bleeding in current pregnancy:

Irrespective the timing, bleeding in pregnancy doubles the risk of subsequent PTL. Threatened abortion in first or early second trimester associated with higher incidence of preterm labour, IUGR, antepartum hemorrage and perinatal death.