INTRODUCTION

The increasing survival rate of premature infants in developing countries over the past 20 years has created new medical diseases in these infants that did not previously exist. One such disease is osteopenia of prematurity, which occurs in approximately 20-30% of premature infants ***(Ardan, 1951; Çakir et al., 2008).*** Osteopenia of prematurity, also known as bone metabolic disorder, is one of the common diseases in very low birth weight (VLBW) premature infants ***(Kulkarni et al., 1980; Litmanovitz et al., 2007)***.

Osteopenia of prematurity is very common mainly because the period of the greatest bone accretion in pregnancy occurs during the last trimester ***(Forbes, 1979; Ziegler et al., 1976; Litmanovitz et al., 2007)***.

The risk factors of osteopenia include prolonged use of total parental nutrition (TPN), human breast milk feeding without fortifier, and the use of medication enhancing calcium loss, such as diuretics, furosemide, for the treatment of chronic lung disease and the methylxanthines for the treatment of apnea. The other possible causes for osteopenia of prematurity were limited accretion of bone mass in utero and decreased external utero calcium retention ***(Chen et al., 2010).***

Common strategies for the prevention of osteopenia in VLBW infants include calcium and phosphorus supplementation

of human milk/formula ***(Schulzke et al., 2007)***. Despite the use of mineral-enriched special preterm formulas, major improvements in postnatal intensive care, and the reduction in systemic steroids and calcium-wasting diuretics use, these efforts have been only partially successful in improving preterm infant bone mineralization ***(Litmanovitz et al., 2003).***

Diagnostic criteria of osteopenia vary considerably, frequently used biochemical indicators of disturbed bone metabolism are low whole blood phosphate levels, increased urinary calcium/phosphate ratios, and high plasma alkaline phosphatase levels ***(Bishop, 1999; Schulzke, 2010).*** Dual energy X-ray absorptiometry (DEXA) is the most sensitive method, but it is difficult to show acute changes; and reference values are not available for premature infants. Biochemical markers that reflect the skeletal metabolism and growth can be measured in the serum and urine ***(Suzule et al., 2000).***

Mechanical strain is one of the most powerful stimulators of bone formation and growth. Several studies have demonstrated that Regular physical activity programs (range-of-motion exercises), after an initial period of stabilization, might provide a simple intervention for improving bone mineral content and skeletal growth in preterm infants ***(Vicker, 2004; Vignochi et al., 2008).***

More than 90% of organic bone matrix consists of type I collagen, which is primarily synthesized in bone ***(Bergmann et***

al., 2009). Carboxy-terminal telopeptide of type 1 collagen crosslinks is called β-CrossLaps (CTX). It is a specific bone resorption marker for degradation of bone type I collagen by osteoclasts, and it can be measured in the serum ***(Çakir et al., 2008).***

AIM OF THE WORK

The primary aim of this study was to assess whether or not physical activity programs in preterm infants improve bone mineralization as well as growth and reduce the risk of fractures.

The secondary aim was to include other potential benefits of physical activity in terms of length of hospital stay, feeding tolerance and to report adverse events (if any).

PRETERM INFANTS

1) Definition:

Preterm birth is the leading cause of infant morbidity and mortality in the world. The World Health Organization (WHO) defines preterm birth as any birth before 37 completed weeks of gestation or fewer than 259 days since the first day of woman's last menstrual period ***(Beck et al., 2010).***

2) Magnitude of the Problem:

Approximately three-fourths of perinatal deaths occur in fetuses that are delivered at <37 weeks, and about 40% of these deaths occur in those delivered at <32 weeks. In addition to its contribution to mortality, preterm birth has lifelong effects on neurodevelopmental functioning such as increased risk of cerebral palsy, impaired learning, and visual disorders and an increased risk of chronic disease in adulthood ***(Rao et al., 2014).***

The economic cost of preterm birth is high in terms of neonatal intensive care and ongoing health care and educational needs. The social cost is also high, with many families experiencing the sudden loss of a preterm baby or a stressful hospital stay, sometimes for months ***(Shrestha et al., 2010).***

3) Classification of Preterm Births:

Even in developed countries, there is often uncertainty and incomplete recording of estimates of gestation. In most of the

United Kingdom data regarding birth weight but not on gestational age are collected routinely. Although some concordance exists between the categories of birth weight and gestational age, they are not interchangeable ***(Tucker et al., 2004).***

A) There are sub-categories of preterm birth, based on gestational age: as shown in figure (1) ***(Blencowe et al., 2010; Tuker and McGuire, 2004).***

- Extremely preterm (<28 weeks)
- Very preterm (28 to <32 weeks)
- Moderate to late preterm (32 to <37 weeks).

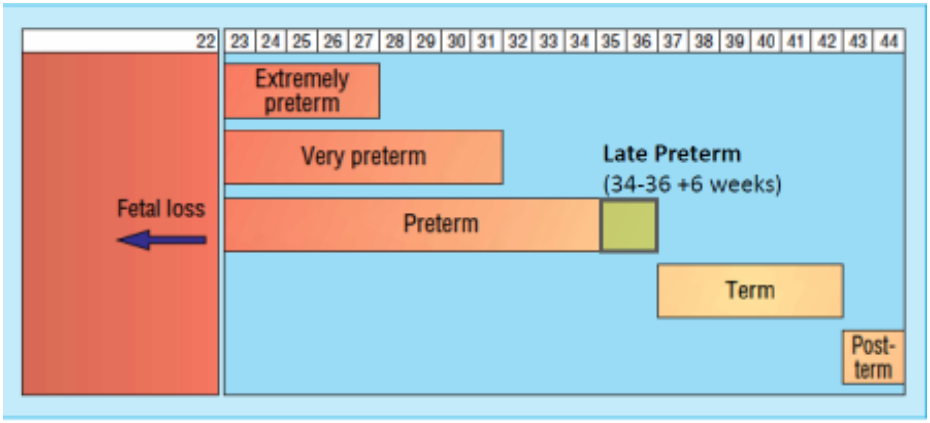

Figure (1): Definitions and classification of infants according to gestational age (post menstrual age) ***(Tucker and McGuire, 2004).***

B) Sub-categories according to weight (irrespective to the period of their gestation): ***(Dandekar et al., 2014)***.

- Low birth weight (<2500gm)

- Very low birth weight (<1500gm)
- Extremely low birth weight (<1000)

4) Epidemiology:

Of 65 countries with reliable trend data, all but three show an increase in preterm birth rates over the past 20 years. Possible reasons for this include better measurement, increases in maternal age and underlying maternal health problems such as diabetes and high blood pressure, greater use of infertility treatments leading to increased rates of multiple pregnancies, and changes in obstetric practices such as more caesarean births before term ***(Blencowe et al., 2010)***.

In developing countries, the main causes of preterm births include infectious diseases and poor availability and accessibility of health care resources ***(Beck et al., 2010).***

In Egypt, despite increased efforts to prevent prematurity, the prevalence of premature birth has significant rate. It may reach approximately to 41,728 each year. These statistic may indicates in some way the highly rate of Neonatal Intensive Care Units (NICUs) admission in hospitals every year ***(EL-Nagger et al., 2013).***

5) Etiology and Risk Factors:

Individual PTBs can be categorized into two major groups demonstrated in figure 2.

A) Spontaneous PTB (accounting for up to 60% of all PTBs), which occur after the spontaneous onset of preterm labor, and in some cases, after spontaneous preterm rupture of the fetal membranes before the onset of labor ***(Gleason and Devarskar, 2012)***.

B) Indicated PTB (accounting for about 40% of PTBs), are those that result from induced preterm labor or preterm cesarean delivery for maternal or fetal indications by the health care team to reduce poor outcomes ***(Gleason and Devaskar, 2012; Moutquin, 2003).***

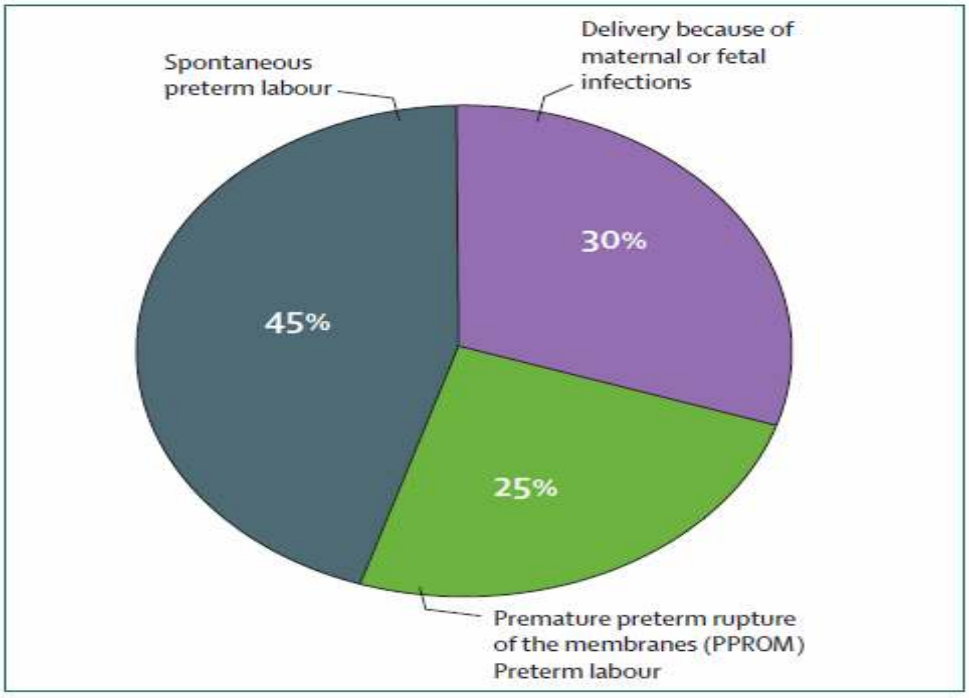

Figure (2): The obstetric precursor of preterm labor ***(Goldenberg et al., 2008).***

A) Spontaneous preterm births

In most spontaneous PTBs, the precise cause for the onset of labor remains unknown; however, a variety of risk factors have been identified ***(Behram and Butler, 2007)*** (Table 1).

Table (1): Risk foctors of prematurity

Variable	Comments
Increasing maternal age at first pregnancy	Number of pregnant women 35-39 years nearly doubled between 1993 and 2003
increasing infertility treatment and multifetal gestation	Number of women seeking infertility treatment increased two fold between 1996 and 2002
Change in practice parameters or guidelines	Improved surveillance and increased medical interventions to prevent still births.
Increased cesarean section rates and decreasing VBAC	-
Increasing maternal overweight and obesity	Errors in estimating gestational age of macrosomic fetus.
Inaccuracy in estimating gestational age	Lack of early ultrasound examination
Iatrogenic or non-medical reasons	Maternal request for early delivery or logistical consideration of patient, family or health care team,

(Gleason and Devaskar, 2012)

In addition the category of spontaneous PB can be differentiated into two subcategories: spontaneous PB with intact membranes and preterm premature rupture of the membranes (PPROM) which is demonstrated in figure 2. In the PPROM category the causes of preterm birth are maternal or

fetal indications in which labor is either induced delivery through vaginal or the newborn is delivered by cesarean sections ***(Goldenberg et al., 2008)***.

Infection is a frequent and important mechanism of disease in preterm delivery. Indeed, it is the only pathologic process. Evidence for causality includes the following ***(Romero et al., 2006):***

(1) Intrauterine infection

(2) Extrauterine maternal infections

(3) Pyelonephritis

(4) Pneumonia

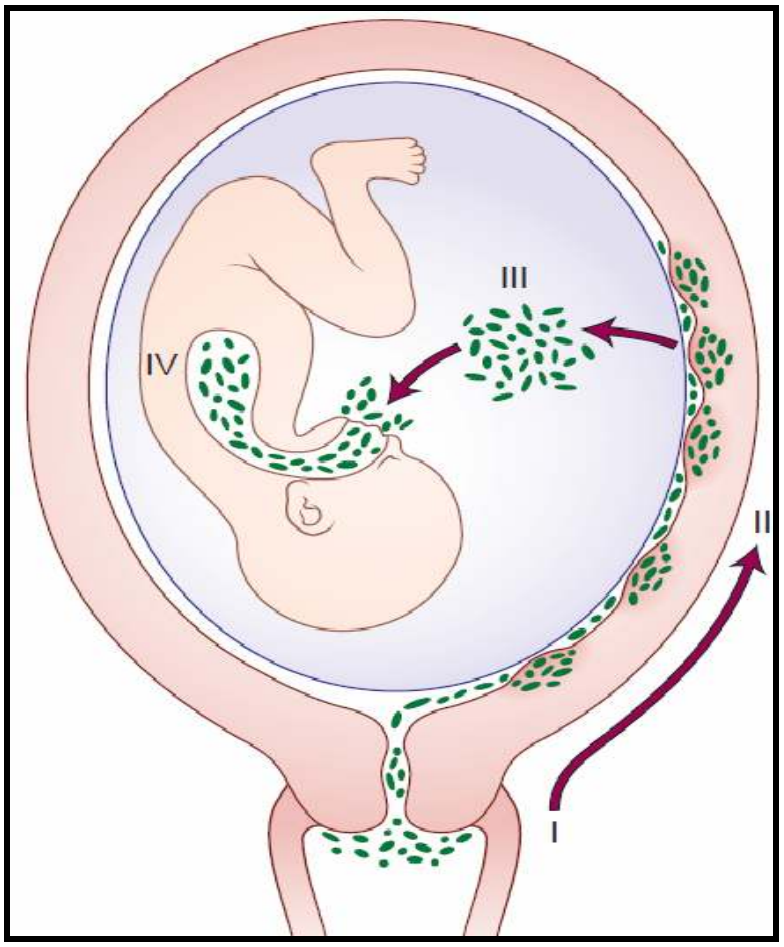

Figure (3): The pathway of ascending infection. Stage I refers to a change in microbial flora in the vagina and/or cervix. In Stage II, microorganisms are located between the amnion and chorion. Stage III represents intra-amniotic infection, and Stage IV is fetal invasion. The most common sites for microbial attack are the skin and the fetal respiratory tract ***(Romero et al., 2006).***

Preterm labour is now thought to be a syndrome initiated by multiple mechanisms, including infection or inflammation, uteroplacental ischemia or hemorrhage, uterine over distension,

stress, and other immunologically mediated processes (figure 3) ***(Romero et al., 2006).***

A precise mechanism cannot be established in most cases; therefore, factors associated with preterm birth, but not obviously in the causal pathway, have been sought to explain preterm labour. An increasing number of risk factors are thought to interact to cause a transition from uterine quiescence toward preterm labour or PPROM ***(Goldenberg and Culhane, 2005).***

Preterm labor and delivery arise from abnormal activation of parturition. No single mechanism describes all cases of PTB; rather, preterm parturition can be viewed as an obstetric syndrome with multiple etiologies, a long preclinical phase, frequent fetal involvement, and genetic factors that modify risk. Contributing pathologic processes may include intrauterine inflammation or infection, uterine ischemia, uterine over distension, abnormal allograft reaction, allergy, cervical insufficiency, and hormonal deregulation ***(Romero et al., 2006).***

Since many of the risk factors result in increased systemic inflammation, therefore increasing stimulation of the infection or inflammation pathway might explain some of the increases in preterm births associated with multiple risk factors demonstrated in figure 4 ***(Goldberg and Culhane***, ***2005).***

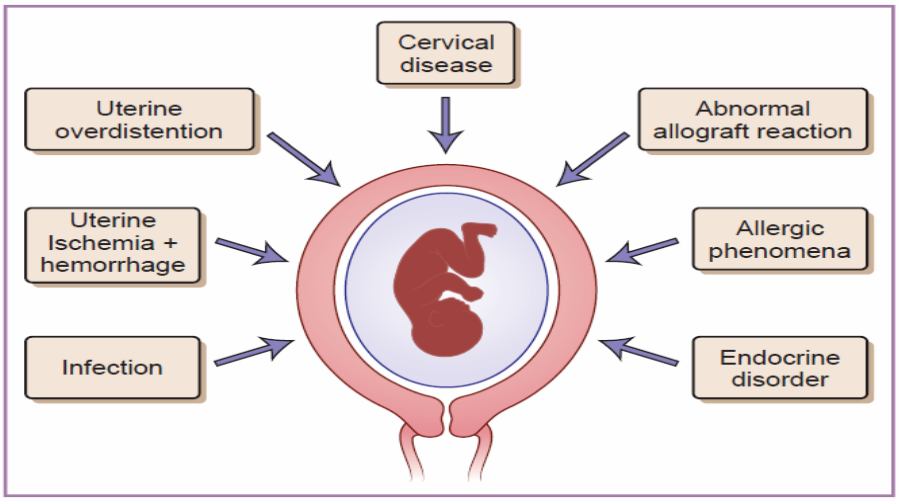

Figure (4): The preterm parturition syndrome ***(Goldenberg et al., 2008).***

Table (2): Causes of increasing preterm birth

Category	Specific Variable	Effect size and comments
Behavirao and physchological contributors	Tobacco and alcohol	Inconsistent effect; these variables may be confounders with lower socioeconomic status
	Other drugs	Cacaine users experience a twofold increase in PTB; other drugs (e.g., marijuana) have inconsistent effects
	Nutrition	Low prepergnancy weight and lower weight gain increase PTB risk; these factors may be confunders with other medical conditions
	Physical activity, employment	Inconsistent effect of employment per se; but long work hours and stress have been associated with increased risk of PTBs
	Douching	Frequent and prolonged vaginal douching during pregnancy can alter vaginal flora and enhance the risk for PTB
	Stress (chronic, acute, life events)	Emotional stress, living conditions, major stressful life events, discrimination and racism, and other forms of stress experiences may act thorough diverse mechanistic pathways, affect many body functions, such as the HPA, immune defense mechanisms, and autonomic nervous system, leading to PTB
Sociodemographic contributors	Maternal age	U-shapted relationship with maternal age and PTB rate, with increased risk in women <17 and > 35 years, in black women, risk seems to increase by age 30
	Marital status	Although unmarried mothers have higher rates of PTB, the protective effects of marital status on the PTB rate may vary across different ethnic groups
	Race and ethnicity	Non-Hispanic black women have high rates of PTB; the causes are likely to multifactorial
	Socioeconomic conditions	Dispartieis in PTB rates by SES (high rates with low SES) are well documented, although the etiologic pathways for such effects are unclear
	Community and neighborhood	Adverse neighborhood conditions influence health outcomes, including PTB rates, through direct and indirect pathways
Medical and pregnancy conditions	Maternal medical illnesses and conditions	Indicated PTBs may occur with chronic hypertension, hypertensive disorders of pregnancy, systemic lupus, hyperthyroidism, pregestational diabetes mellitus, cardiac disease, asthma, renal disorders, and gestational diabetes mellitus
	Underweight and low weight gain	Low prepregnancy weight and lower-than-average increase in weight during pregnancy have been documented with higher rates of PTB
	Fetal conditions	In vitro fertilization, assisted reproductive technology, mulifetal pregnancy, congential anomalies, umbilical cord accidents
	Pregnancy conditions	Placenta previa, first-timester vaginal bleeding, abruption of the placenta, uterine malfomations
	Infections	Maternal-fetal infections, bacterial vaginosis
	Other	Interpregnancy interval of less than 6 months is estimated to increase PTB rate by 30% to 60%; family history of PTB is associated with higher rates of PTB; it is unclear if the effect is caused by genetic factors, environmental factors, or a combination of both
Environmental toxins	Lead, air pollution	Exposures linked to higher PTB rates include lead, tobacco smoke, air pollution (sulfur dioxide, particulates, carbon monoxide), and arsenic in drinking water; however, interactions between such exposures and confounding factors such as SES, race, and ethnicity need to be studied
Gene-environment interactions		Genetic susceptibility and gene environmental interactions is a rapidly evolving field; according to some experts, epigenetic mechanisms are the final common pathway to explain diverse sociodemographic, racial, and ethnic factors an their effects on PTB rates

HPA, hypthalamopituitar axis; PTB, preterm birth; SES, socioeconomic status

* For a comprehensive discussion of various factors noted in this table, please see behraman RE, Bulter As, Preterm birth, causes, consequences, and prevention, Washington, DC, 2007, The National Academics Press.

(Gleason and Devaskar, 2012)

6) Allostatic Load:

Recent studies of the pathophysiology of and biologic responses to stress have uncovered a series of causal pathways for adverse outcomes caused by stresses at multiple levels and from different sources. The biologic responses to stressors have been collectively called allostatic load, a summary measure of major perturbations in the autonomic, endocrine, and immune systems. Allostatic load has been linked to accelerated aging, worsened immunologic tolerance, ineffective defense systems, and increased cardiovascular morbidity. Abnormal allostatic load during the entire life span of a woman can potentially modulate her biologic systems and worsen perinatal outcomes ***(Groer and Burns, 2009; Latendresse, 2009; Herring and Gawlik, 2007; Shannon et al., 2007; McEwen, 2006; Lu and Halfon, 2003).*** Studies are under way to understand the complex relationship between the effects of socio-demographic and biologic stressors on organ systems and their influence on perinatal outcomes.

7) Clinical Assesment of Prematurity:

The newly expanded new Ballard score (NBS) provides valid and accurate assessment of gestational age for extremely premature infants that were not previously available shown in figure 5 ***(Ballard et al., 1991).***