INTRODUCTION

There is no universal agreement on the definition of Intrauterine growth restriction (IUGR). Strictly speaking, any fetus that does not reach his or her intrauterine growth potential is included. Typically; fetuses weighing less than the 10^{th} percentile for gestational age are classified as IUGR. However, many of these fetuses are normal and at the lower end of the growth spectrum (i.e.," constitutionaly small") ***(Wilkins-Haug and Heffner, 2012).***

About 3-10% of all pregnancies are associated with IUGR and 20% of still born infants are growth retarded. The perinatal mortality rate is 5-20 times higher for growth retarded fetuses and serious short or long term morbidity is noted in half of the affected surviving infants. IUGR is estimated to be the predominant cause for low birthweight in developing countries ***(Garite et al., 2004).***

IUGR is associated with low bone mineral content at birth and increased risk for osteoporosis development in later life ***(Namgung and Tsang, 2000).*** However, little is known about the dynamics of fetal bone formation and resorption regarding the normal changes that occur throughout gestation or in clinical situations that result in low bone mass at birth ***(Harrast and Kalkwarf, 1998).***

Osteocalcin, also known as Gla protein, is a marker for bone formation. It is a vitamin K and vitamin D-dependant protein as vitamin K is an essential co-factor for the post translational gamma carboxylation of osteocalcin and it is regulated at the transcripitional level by 1, 25-dihydroxy vitamin D3. It is produced by osteoblasts and has a role in its regulation.

Osteocalcin is 49-residues polypeptide, has a short half life, its gene is located on chromosome 1. The majority of osteocalcin secreted by the osteoblast is deposited in the extracellular bone matrix, serum osteoblast represent the fraction of total osteocalcin that has not absorbed to hydroxyapatite ***(Lee et al., 2000).***

Aim of the Work

To study the bone formation as indicated by osteocalcin level in neonates with asymmetric intrauterine growth restriction.

Chapter (1)

INTRAUTERINE GROWTH RESTRICTION

Definition:

There is no universal agreement on the definition of intrauterine growth restriction **(**IUGR). Strictly speaking, any fetus that doesn't reach his or her intra uterine growth potential is included. Historically, fetuses weighting less than the 10^{th} percentile for gestational age or less than two standard deviations (SD) below the mean for gestational age have been classified as IUGR. However, many of these fetuses are merely constitutionally small. We consider all fetuses less than the 10^{th} percentile for gestational age as small for gestational age (SGA) and restrict the use of the term IUGR for those fetuses in whom corroborative evidence is present ***(Louise et al., 2008).***

In other words, a fetus who has a potential of growth at the 50^{th} percentile but because of maternal, fetal, or placental disorders occurring alone or in combination, become growth restricted (birth weight $<10^{th}$ percentile) is an IUGR fetus and he is at risk for adverse perinatal outcome. A fetus with a potential of growth at the 7^{th} percentile who reaches his potential of growth (7^{th} percentile) is not an IUGR fetus but a SGA fetus. He is a normal small fetus and he is not at risk for adverse perinatal outcome ***(Giancarlo, 2006).***

SGA is a statistically descriptive term that correlates birth length and/or weight with gestational age (G.A.) and is, therefore, a postpartum diagnosis. It does not refer to fetal growth, and is not a synonymous with IUGR although it may be a consequence of diminished fetal growth ***(Hokken et al., 2001).***

It is important to distinguish between infants who experienced in utero growth restriction from infants with normal in utero growth but constitutionally small (i.e. no loss in percentiles throughout gestation) ***(Brodsky and Christou, 2004)***.

In growth clinics in the United Kingdom, SGA is commonly defined as birth weight and/or length two or more standard deviations (SD) below the mean for gender and gestation, which is consistent with the definition of childhood short stature (standing height <-2SD) ***(Johnston & Savage, 2004).***

IUGR describes a decrease in fetal growth rate that prevents an infant from obtaining his or her complete growth potential ***(Hokken et al., 2001)***.

Additionally, in developing countries, there is a direct correlation between the incidence of low birth weight (<2500 g) and IUGR because in developing countries, the high incidence of low-birth-weight (LBW)

infants is almost exclusively due to the incidence of IUGR. Data from developed countries show the opposite, rates of low birth weight being explained almost exclusively by prematurity rates ***(Martinez and Simmons, 2005).***

Some women have a tendency to have constitutionally small babies although both parent's gene affect childhood growth and adult final size, maternal genes mainly influence birth weight. Unfortunately, it can be concluded that a fetus is constitutionally small only after a pathological process has been excluded, which requires examination of new born. Therefore, identification of a constitutionally small baby is usually made in retrospect after the infant is born ***(Peleg et al., 1998).***

The ponderal index arrived at by the following formula, can be used to identify infants whose soft tissue mass is below normal for the stage of skeletal development.

Ponderal index= (Birth weight (gm)/Crown-heel length (cm)^3) ×100.

(Desai and Rao, 2009)

The two components that are necessary to define a SGA fetus are:

a) Birth weight < 10^{th} percentile.

b) Absence of pathogenic process.

(Lin et al., 1991)

To document adequately impaired fetal growth and diminished growth velocity in utero, at least 2 intrauterine size assessments must be performed ***(Hokken et al., 2001).*** Thus, IUGR should be considered a prenatal diagnosis, based primarily on serial measurements of fetal ultrasound parameters including estimates of fetal weight, head circumference, abdominal circumference and femur length ***(Thomas et al., 2000).***

Classification:

1- Symmetric IUGR

It comprises 20 to 30 percent of the IUGR. Symmetric IUGR refers to a growth pattern in which all fetal organs are decreased proportionally due to impairment of early fetal cellular hyperplasia. It begins early in gestation and usually is caused by intrinsic factors such as congenital infections or chromosomal abnormalities However, decreased nutrient supply early in development can restrict growth of all organs ***(Bahado et al., 1999).***

2-Asymmetric IUGR

It comprises 70 to 80 percent of the IUGR. Asymmetric IUGR refers to a growth pattern in which there is reduced body weight and relatively normal length and head growth. It begins in the late second or third trimesters and results from reductions in fetal nutrients that

limit glycogen and fat storage yet allow continued brain growth. It is characterized by a relatively greater decrease in abdominal size (e.g., liver volume and subcutaneous fat tissue) than head circumference.

It is thought to result from the capacity of the fetus to adapt to a hostile environment by redistributing blood flow in favor of vital organs (e.g., brain, heart, and placenta) at the expense of non vital fetal organs (e.g., abdominal viscera, lungs, skin, and kidneys). Mechanisms that spare brain growth are uncertain, but may include increased cerebral blood flow (***Bahado et al., 1999).***

Table (1): Specific Distinctions between Symmetric and Asymmetric IUGR:

	Asymmetric	***Symmetric***
Incidence	70-80%	20-30%
Period of growth restriction	Begins third trimester	Begins first or second trimester
Physical characteristics	Large head size relative to small abdomen	Small head and abdominal size
Pathophysiology	Impaired cellular hypertrophy Decreased cell size	Impaired cellular embryonic division Impaired cellular hyperplasia± hypertropy Decreased cell number±size
Etiology	Mostly extrinsic: placental and maternal vascular factors	Mostly intrinsic . chromosomal abnormalities, congenital malformations, infection, early onset severe preeclampsia, preeclampsia< 30 wk superimposed with chronic hypertention
Outcome	Lower morbidity and mortality	Greater morbidity and mortality

(Resnik, 2004)

Although most infants can be categorized into one of these groups, some infants may have features of both types of IUGR ***(Resnik, 2004).***

Epidemiology

Incidence and significance:

Approximately one-third of low birth weight infants are SGA ***(Lee and Kimberly, 2008).***

In accurately dated pregnancies, approximately 80–85% of fetuses identified as being SGA are constitutionally small but healthy, 10–15% are 'true' IUGR cases, and the remaining 5–10% of fetuses are affected by chromosomal/structural anomalies or chronic intrauterine infection ***(Manning, 2004)***.

IUGR complicates 5% to 8% of all pregnancies. Studies identify a greater percentage (up to 15% of pregnancies), but these reports define IUGR and SGA as equivalent, and 20% of still born infants are growth retarded ***(Aucott et al., 2004)***.

The incidence of IUGR varies according to the reference population with higher rates of IUGR in developing countries ***(Resnik, 2004).***

The perinatal mortality rate is 5-20 times higher for growth retarted fetuses, and serious short or long term morbidity is noted in half of the affected surviving infants ***(Brodsky and Christou, 2004).***

Infants born prematurely who are also severely IUGR have higher neonatal morbidity and mortality when compared to infants of similar GA ***(Bernstein et al., 2000).***

The recurrence risk was found in one study to be 29% if the first pregnancy was affected, and 44% if two pregnancies have been affected ***(Abuzzahab et al., 2003).***

The epidemiology of fetal growth restriction varies internationally. In developed countries, the most frequently identified cause of growth restriction is smoking, while in developing countries, maternal nutritional factors (prepregnancy weight and maternal stature) and infections are leading identified causes ***(Kramer et al., 2000).***

Risk factors and pathophysiology:

Fetal growth is influenced by fetal, placental and maternal factors ***(Brodsky and Christou, 2004).***

A-Maternal factors:

1- Maternal size and nutrition:

Maternal constitutional factors have a significant effect on fetal growth ***(Sascks, 2004)***.

The major risk factors for IUGR include small maternal size (height and prepregnancy weight) and low maternal weight gain. Low body mass index, defined as

(weight [kg]/height [m2]) ×100, is a major predictor of IUGR ***(Desai and Rao, 2009*)**.

Maternal nutrition and supply of nutrients to the fetus affect fetal growth. Evidence shows a relationship between maternal nutrition during pregnancy and infant birth weight. Investigators have found a significant relation between maternal energy intake and placental and infant weights ***(Martinez and Simmons, 2005)***. Maternal nutritional status both before and during pregnancy is associated with fetal growth patterns ***(Doctor et al., 2001).***

The effects of micronutrients on pregnancy outcomes and fetal growth have been less well studied**.** It has been shown that maternal intake of certain micronutrients can affect fetal growth ***(Martinez & Simmons, 2005).***

Zinc deficiency has been associated with fetal growth restriction as well as other abnormalities, such as infertility and spontaneous abortion. Additionally, dietary intake of vitamin C during early pregnancy has been shown to be associated with an increase in birth weight ***(Shah and Sachdev, 2001)***.

Others have shown strong association between maternal intake of folate and iron and infant and placental weight. In developing countries, the effects of nutritional

deficiencies during pregnancy are more prevalent and easier to detect ***(Godfry et al., 1996)***.

2- Multiple pregnancies:

There is a progressive decrease in placental and fetal weight as the number of fetuses increases in multiple gestations. The high risk stems from crowding and from abnormalities with placentation, vascular communications, and umbilical cord insertions ***(Glinianaia et al., 2000).***

3- Maternal illness:

Maternal hypoxia and vascular disease is believed to account for 25-30% of all IUGR infants, it is the most common cause of IUGR in the nonanomalous'infants ***(Resnik, 2004).***

Maternal disorders such as pre-eclampsia, eclampsia ***(Odegard et al., 2000),*** antiphospholipid syndrome ***(Das and Sysyn, 2004),*** chronic renovascular disease, diabetes mellitus and chronic hypertensive vascular disease often result in decreased uteroplacental bood flow and associated IUGR. Impaired delivery of oxygen and other essential nutrients is thought to limit organ growth and musculoskeletal maturation ***(Odegard et al., 2000).***

Mothers with hemoglobinopathies, especially sickle cell disease, often have IUGR infants ***(Desai and Rao, 2009*)*.***

The contribution of thrombophylic disorders to IUGR was also under intensive investigation, and evidence suggests that the prothrombin gene mutation may be the cause. However, it was unclear whether the effect on growth is mediated by placental thrombosis or is secondary to maternal hypertension ***(Martenelli et al., 2001).***

Women with systemic lupus erythematosus (SLE) have a higher prevalence of fetal growth restriction. Some researchers have shown that the majority of adverse fetal outcomes associated with SLE are related to maternal antiphospholipid antibodies ***(Yasmeen et al., 2001).***

4- Maternal exposure to environmental/extrinsic factors:

The fetus may be exposed to chemical agents via the mother from several different avenues, including recreational (drug abuse), therapeutic, and occupational exposure (maternal exposure to environmental hazards) ***(Utpala and Gregory, 2004).***

Maternal medications associated with IUGR include anticonvulsants, anticoagulants, and folic acid antagonists. The two most commonly associated anticonvulsants with IUGR are diphenylhydantoin (phenytoin) and trimethadione ***(Das and Sysyn, 2004).***

5- Infection:

Viruses and parasites (e.g., rubella, toxoplasmosis, cytomegalovirus, varicella-zoster and malaria) may gain access to the fetus transplacentally or across the intact fetal membranes. Infections that develop early in pregnancy have the greatest effect on subsequent growth**.** There is less evidence implicating bacterial infection as an etiology for IUGR, although maternal infections with listeria, tuberculosis, chlamydia and mycoplasma have been reported to increase the risk to IUGR ***(Klein et al., 2006)***.

6- Assisted reproductive technologies:

Singleton pregnancies conceived via assisted reproductive technologies have a higher prevalence of both low birth weight and preterm birth ***(Robinson et al., 2000).***

7- Other maternal factors:

Demographic variables associated with an increased risk of delivering a IUGR neonate include race, pregnancy at the extremes of reproductive life, and previous delivery of a IUGR neonate ***(Fang et al., 1999).***

Women who were born SGA were shown to be at increased risk of giving birth to SGA infants. Parity of the mother also affects fetal size, nulliparous women having a higher incidence of SGA infants ***(Robinson et al., 2000).***