Introduction

Intrauterine growth restriction (IUGR) represents a variety of conditions and is etiologically associated with maternal, fetal and placental disorders. From a statistical viewpoint, the term "small for gestational age" (SGA) has been used to define newborns whose birth weights falls below the 10^{th} percentile of gestational age specific birth weight standards. This definition has been useful for providing a better understanding of perinatal outcomes. However, the widespread use of ultrasound in obstetrics has changed the traditional way of looking at fetal growth during pregnancy and specific intrauterine growth charts have been developed ***(Carberry et al., 2011).***

From an obstetrician's viewpoint, the term IUGR indicates deviation from the intrauterine growth trajectory, based on intrauterine growth charts derived from formulae which take into account biometrical parameters measured in utero. Considerable differences have been reported between intrauterine and birth weight curves, especially at the lowest gestational ages ***(Gardosi et al., 2004).***

Although premature babies are often defined as low birth weight (LBW), very low birth weight (VLBW) or extremely low birth weight (ELBW), IUGR is often a significant feature for these babies. However, it is important to distinguish babies

who are premature because of spontaneous preterm delivery (most of these neonates are appropriate for gestational age) from babies who are premature because of iatrogenic preterm delivery, since the majority of the most severe IUGR infants will be delivered prematurely for clinical indications. Thus, IUGR represents a risk factor for prematurity and not the opposite. Similarly, in most studies relating maternal malnutrition to IUGR, it is really an association with SGA that is reported ***(Victora et al., 2008).***

Antenatal diagnosis of FGR remains a challenge. Ultrasonography is the best technique, estimating fetal weight and growth velocity using multiple parameters. Body proportionality indices such as ratio of head-to abdominal circumference and Doppler ultrasound studies can provide additional information. Diagnosis is easier at birth because growth-restricted infants show typical changes in body proportionality. Subcutaneous adipose tissue that acts as an energy source and insulator against hypothermia is reduced ***(Beattie et al., 1994).***

Aim of the Work

To evaluate the accuracy and usefulness of measuring femur length to mid-thigh circumference ratio in prediction of growth restricted fetuses by ultrasound.

Fetal Growth Restriction

Pathophysiology

Compared with an average-for-gestational-age (AGA) fetus, the IUGR fetus has altered body composition (including decreased body fat, total protein, whole body DNA and RNA, glycogen, and free fatty acids), altered distribution of weight among organs, and altered body proportions. Approximately 20% of IUGR infants are symmetrically small, with a relatively proportionate decrease in many organ weights. Eighty percent are asymmetrically small, with relative sparing of brain weight, especially when compared with that of the liver or thymus ***(Chernausek, 2012).***

In asymmetric IUGR infants, brain weight is decreased only slightly compared with that of AGA controls, primarily as a result of decreased brain cell size and not to decreased brain cell numbers. Cerebral abnormalities include decreased myelination, decreased utilization of metabolic substrates other than glucose, and altered protein synthesis. Deprivation early in pregnancy is associated with less cerebral sparing and diffusely slowed brain growth ***(Batalle et al., 2012).***

Symmetric IUGR infants have proportionately small brains, usually because of a decreased number of brain cells. Although this may be the result of early, severe nutritional deprivation, the cause is more often a genetic disorder,

infection, or other problem. Usually the thymus is small, with an average decrease of 25%. This decrease may explain in part the decreased cellular immunity seen in IUGR infants ***(Batalle et al., 2012).***

The liver is frequently affected, at least partly because of diminished glycogen deposition. The liver also may have functional (metabolic) abnormalities, as manifested by abnormal cord blood and neonatal serum chemistries. Such abnormalities often reflect the underlying cause of decreased size ***(Yamada et al., 2011).***

Blood flow to the lungs may be decreased, lessening the pulmonary contribution to amniotic fluid volume. This may be partly responsible for the often-encountered oligohydramnios. Decreased pulmonary blood flow may also be associated with accelerated functional pulmonary maturity ***(Pike et al., 2012).***

Renal blood flow frequently is reduced in asymmetric IUGR pregnancies. The resultant diminished glomerular filtration rate may further contribute to oligohydramnios ***(Dicke, 2010).***

Causes and risk factors:

Table (1): Pathogenic classification of IUGR pregnancies ***(Hendrix et al., 2008; Nardozza et al., 2012)***

Fetoplacental causes	
Genetic disorders	Autosomal: trisomy 13, 18, 21; ring chromosomes; chromosomal deletions; partial trisomies,Sex chromosomes: Turner's syndrome, multiple chromosomes (XXX, XXY), Neural tube defects, Skeletal dysplasias: achondroplasia, chondrodystrophies, osteogenesis imperfect,and Abdominal wall defects.
Congenital infections	Viral: cytomegalovirus, rubella, herpes, varicella-zoster. Protozoan: toxoplasmosis, malaria, and Bacterial: listeriosis.
Placental disorders	Placenta previa, placental infarction, chorionic villitis, chronic parital separation, placental malformations (circumvallate placenta, battledore placenta, placenta hemangioma, twin-twin transfusion syndrome)
Multiple gestation	
Maternal causes	
Coexistant maternal disease	Hypertension, anemia (haemoglobinopathy, decreased normal hemoglobin), renal disease (hypertension, protein loss), malnutrition (inflammatory bowel disease "ulcerative colitis, regional enteritis", pancreatitis, intestinal parasites), cyanotic cardiopulmonary disease
Substance abuse/drugs	Alcohol, cigarette smoking, cocaine, heroin, warfarin, folic acid antagonists (methotrexate, aminopterin), anticonvulsants.

Fetoplacental causes

1. Congenital abnormalities:

Genetic disorders account for approximately one-third of IUGR infants. Data from the Metropolitan Atlanta Congenital Defects Program suggest that 38% of chromosomally abnormal infants are IUGR and that the risk of an IUGR infant having a major congenital anomaly is 8–19%. An infant with an autosomal trisomy is more likely to be IUGR ***(Boghossian, 2011).***

The most common trisomy is trisomy21 (Down syndrome), with an incidence of 1.6 per 1000 live births. At term, such infants weigh an average of 350 g less than comparable normal infants and are 4 times more likely to be IUGR. This decrease is most apparent in the last 6 weeks of pregnancy. A similar decrease in birth weight occurs in translocation Down syndrome, whereas mosaic Down syndrome is associated with an intermediate decrease in birth weight ***(Boghossian et al., 2010).***

The second most common autosomal trisomy is trisomy 18 (Edwards' syndrome), which occurs in 1 in 6000–8000 live births. Eighty-four percent of these infants are IUGR. Ultrasound evaluation may reveal associated anomalies. The condition is associated with an increased likelihood of breech presentation, polyhydramnios, fetal neural tube defects, and visceral anomalies. The average birth weight of infants with trisomy 18 is almost 1000 g less than that of controls. In

contrast to the placental weight in infants with trisomies 13 and 21, the placental weight in infants with trisomy 18 also is markedly reduced ***(Sepulveda et al., 2010).***

Trisomy 13 occurs in 1 in 5000–10,000 live births. More than 50% of affected infants have IUGR. Birth weights average 700–800 g less than those of controls ***(Phelan et al., 2001).***

Other rarer autosomal chromosome abnormalities, such as ring chromosomes, deletions, and partial trisomies, are associated with an increased likelihood of IUGR. Sex chromosome abnormalities may be associated with lower birth weight. Extra X chromosomes (> 2) are associated with a 200-g to 300-g decrease in birth weight for each extra X. Turner's syndrome is associated with an average birth weight of approximately 400 g below average. Fetuses with mosaic Turner's syndrome are intermediately affected ***(Boghossian, 2011).***

Fetuses with neural tube defects frequently are IUGR, weighing approximately 250 g less than controls. Anencephalic fetuses are IUGR, even considering the absent brain and skull, with average third-trimester birth weight of approximately 1000 g less than matched controls. Certain dysmorphic syndromes are associated with an increased incidence of IUGR fetuses. Achondroplasia may be associated with low birth weight if either parent is affected but usually is associated with normal birth weight if a spontaneous mutation is the cause. Osteogenesisim perfecta consists of a spectrum of diseases, all of which result in IUGR fetuses ***(Norman et al., 2012).***

Infants born with abdominal wall defects are characteristically IUGR, particularly those with gastroschisis ***(Heydanus et al., 1996).***

Other autosomal recessive syndromes associated with IUGR include Smith-Lemli-Opitz syndrome, Meckel's syndrome, Robert's syndrome, Donohue's syndrome, and Seckel's syndrome. These conditions are rare and are most likely to be diagnosed antepartum in families with a previously affected child. Infants with renal anomalies such as renal agenesis (Potter's syndrome) or complete urinary tract outflow obstruction often have IUGR ***(Nardozza et al., 2012).***

Other congenital anomalies associated with an increased incidence of IUGR outcome are duodenal atresia and pancreatic agenesis ***(Boghossian, 2011).***

2. Congenital infections:

Chronic intrauterine infection is responsible for 5–10% of IUGR pregnancies. The most commonly identified pathogen is cytomegalovirus (CMV). Although CMV can be isolated from 0.5–2% of all newborns in the United States, clinically obvious infection at the time of birth affects only 0.2–2 in 1000 live births. Active fetoplacental infection is characterized by cytolysis, followed by secondary inflammation, fibrosis, and calcification. Only infants with clinically apparent infection at birth are likely to be IUGR. Signs of congenital infection are nonspecific but include central nervous system involvement

(eg, microcephaly), chorioretinitis, intracranial (periventricular) calcifications, pneumonitis, hepatosplenomegaly, and thrombo-cytopenia ***(Cox and Marton, 2009).***

Congenital rubella infection increases the risk of IUGR. Infection in the first trimester results in the most severely affected fetuses, primarily as a result of microvascular endothelial damage. Such infants are likely to have structural cardiovascular and central nervous system defects such as microcephaly, deafness, glaucoma, and cataracts ***(Migilucci et al., 2011).***

Other viruses implicated in causing IUGR are herpesvirus, varicella-zoster virus, influenza virus, and poliovirus, but the number of such cases is small. As expected by virtue of their chronic, indolent nature, protozoan infections are associated with IUGR. The most common protozoan, Toxoplasma gondii, usually is acquired by ingestion of raw meat. Only women with a primary infection are at risk for having an affected infant. The average incidence is 1 in 1000 live births in the United States, but the incidence varies widely among locations and social populations. Approximately 20% of newborns with congenital toxoplasmosis will have IUGR. Malaria is another protozoan infection associated with IUGR ***(Cox and Marton, 2009).***Although bacterial infections occur commonly in pregnancy and frequently are implicated in premature delivery, they are not commonly associated with IUGR. Chronic infection from Listeria monocytogenes is an

exception. Infants usually are critically ill at the time of delivery and often have encephalitis, pneumonitis, myocarditis, hepatosplenomegaly, jaundice, and petechiae ***(Cox and Marton, 2009).***

3. Placental factors:

The placenta plays an important role in normal fetal growth. Placental weight has shown to be less in IUGR infants than in AGA infants irrespective of birth weight, suggesting that appropriate fetal growth may depend on the size or weight of the placenta**.** Several placental abnormalities are associated with an increased likelihood of an IUGR fetus. Placenta previa is associated with an increased incidence of IUGR, probably because of the unfavorable site of placental implantation. Complete placenta previa is associated with a higher incidence of IUGR than is partial placenta previa. Decreased functional exchange area as a result of placental infarction also is associated with an increased incidence of IUGR fetuses. Premature placental separation may occur at any time during pregnancy, with variable effects. When not associated with fetal death or premature labor, premature placental separation may increase the risk of IUGR ***(Vedmedovska et al., 2011).***

Malformations of the placenta or umbilical cord, such as single umbilical artery, velamentous umbilical cord insertion, circumvallate placenta, placental hemangioma, battledore placenta, and twin-twin transfusion syndrome, also are associated

with an increased risk of IUGR. Chronic villitis, chronic inflammation of placental villi, is seen with increased frequency when the placentas of IUGR pregnancies are examined histologically. Finally, uterine anomalies may result in impaired fetal growth, primarily because of the likelihood of suboptimal uterine blood flow ***(Salafia et al., 1992; Heinonen, 2001).***

4. Multiple gestation:

Multiple gestation has long been associated with premature delivery. However, it also is associated with a 20–30% increased incidence of IUGR fetuses, possibly as a result of placental insufficiency, twin-twin transfusion syndrome, or anomalies. Serial ultrasound estimates of fetal weights should be considered in a multiple gestation pregnancy ***(Cleary-Goldman and D'Alton, 2008).***

Maternal factors

Numerous maternal diseases are associated with suboptimal fetal growth. Any woman who has borne 1 IUGR infant is at increased risk for recurrence, with a 2-fold and 4-fold increased risk for IUGR birth after 1 or 2 IUGR births, respectively ***(Ananth et al., 2009).***

1. Hypertension:

Hypertension is the most common maternal complication causing IUGR. Systemic hypertension results in decreased blood flow through the spiral arterioles and decreased delivery of oxygen and nutrients to the placenta and fetus. Hypertension may be associated with placental infarction ***(Bonamy et al., 2011).***

2. Smoking, drug, and alcohol misuse:

Cigarette smoking is much more common among women of childbearing age in the United States than is alcoholism. Smoking causes one-third of IUGR cases and is the single most preventable cause of IUGR pregnancy in the United States today. Women who smoke have a 3 to 4 fold increase in IUGR infants. Birth weight is reduced by approximately 200 g, with the amount of growth restriction proportional to the number of cigarettes smoked per day. Women who quit smoking at 7 months' gestation have newborns with higher mean birth weights than do women who smoke throughout the entire pregnancy. Women who stop smoking before 16 weeks' gestation are not at increased risk for having an IUGR infant. Both habitual drugs and prescribed medications can affect fetal growth. Alcohol use has long been known to be associated with impaired fetal growth. Virtually all infants with fetal alcohol syndrome exhibit signs of growth restriction ***(Romo et al., 2009).***

Heroin and cocaine addicts have an increased incidence of IUGR infants, but confounding variables make determination of a direct cause-and-effect relationship difficult. Methadone use has not been shown to be associated with an increased incidence of IUGR ***(Zhu and Stadlin, 2000).***

Pharmacologic agents have been associated with an increased incidence of IUGR, primarily as a result of teratogenic effects. Warfarin has been associated with an increased incidence of IUGR fetuses, primarily as a result of the sequelae of intrauterine hemorrhage ***(Vitale et al., 1999).***

Folic acid antagonists are associated with an increased risk of spontaneous abortion stillbirth, severe malformations, and IUGR infants ***(Wen et al., 2008).***

IUGR fetuses are more common with maternally administered immunosuppressive drugs (eg, cyclosporine, azathioprine, corticosteroids), but when controlled for the underlying maternal disease, the medications per se probably have little effect on fetal growth ***(Tendron et al., 2002).***

3. Malnutrition and Malabsorption:

Poor maternal weight gain is associated with an increased risk of having an IUGR infant. Studies of infants borne by women who were pregnant during the Siege of Leningrad during World War II showed that daily intake must be reduced to less than 1500 kcal/d before a measurable effect on birth weight becomes evident. Maternal malabsorption may predispose to IUGR pregnancy.The most common clinical situations are inflammatory bowel disease (ulcerative colitis or regional enteritis), pancreatitis, and intestinal parasites ***(Briana et al., 2009; Landis et al., 2009).***

4. Vascular Disease:

Diseases that affect maternal microvascular perfusion can be associated with IUGR. These include collagen vascular disease, insulin-dependent diabetes mellitus associated with microvasculopathy, and preeclampsia ***(Loukavaara, 2004).***

5. Populations and maternal differences:

Mongelli and Gardosi (1996) suggested the use of a customized standard to reduce the false-positive rate for the diagnosis of growth restriction in a normal population.

Maternal Features:

A small woman may have a smaller-than-normal infant because of reduced uterine growth potential. These mothers and infants are completely normal and healthy, but they are small because of genetic variation. The infants are described by the ponderal index (PI), which is calculated using the following formula:

$$\textbf{PI = Birth weight x 1000 / (crown-heel length)}^{3}$$

Asymmetric IUGR infants will have a low ponderal index (ie, they will be long, lightweight infants), whereas small normal infants will have a normal ponderal index. (A normal index at 28 weeks is 1.8. This value increases by 0.2 every 4 weeks to reach 2.4 at 40 weeks) ***(Landmann et al., 2006).***

6. Maternal parity:

Exerts a modest effect on birth weight. First-born infants tend to be smaller and more often categorized as IUGR. This effect decreases with successive deliveries and is not seen beyond the third birth ***(Claas et al., 2011).***

7. Sex of Fetus:

At term, female fetuses are an average 5% (150 g) smaller and 2% (1 cm) shorter than male fetuses. Referring to separate norms for male and female fetuses may increase the power of biometry in assessing IUGR ***(Sheiner, 2004).***