Introduction

Intrauterine growth restriction (IUGR), which is defined as less than 10 percent of predicted fetal weight for gestational age, may result in significant fetal morbidity and mortality ***(Bernstein and Gabbe, 1996)***. It is associated with a perinatal mortality rate that is 6 to 10 times higher than that for normally grown fetuses.

The cause of IUGR is multifactorial and complex, including intrinsic fetal conditions as well as maternal and environmental factors ***(Brodsky and Christou, 2004).*** Placental insufficiency is the most common cause and it is associated with raised placental blood flow resistance ***(Baschat and Hecher, 2004).***

Only recently, researchers have focused on the long term morbidity that is associated with this condition. Provocative epidemiologic studies have suggested that IUGR is a risk factor for the development of essential hypertension and hyperlipidemina in later life ***(Godfery and Barker, 2000).*** The actual pathways by which IUGR could lead to hypertension in adult life are unknown but several plausible theories have been put forward ***(Brenner et al., 2006).***

Among the various theories, that of congenital oligonephropathy proposed by ***Brenner et al. (2006)*** is the premise of this study. In 1993, Brenner and Chertow postulated that IUGR may cause congenital oligonephropathy. In essence, this theory proposes that IUGR may lead to impaired renal growth and development, with a subsequent decrease in nephron number and glomerular filtration surface area. Ultimately, this may result in both systemic and glomerular hypertension and acquired glomerular sclerosis with further increase in systemic blood pressure ***(Silver et al., 2003).***

As fetal kidney weight cannot be measured in-utero, renal volume measured by ultrasound is a valid substitute ***(Konje et al., 1997).*** With the latest new developments in the field of three–dimensional ultrasonography, accurate assessment of the fetal organ volume has become feasible and this technique has gained widespread application in different medical fields. Numerous investigators have demonstrated that three-dimensional ultrasonography is superior to two-dimensional ultrasonography in fetal organ measurement ***(Strommen et al., 2004).***

Aim of Work

To compare between fetal renal volume using 3D ultrasound (VOCAL) and fetal renal artery Doppler in intra-uterine growth restricted fetuses and fetuses who have normal growth in order to detect the accuracy of fetal renal volume as a diagnostic test for intra-uterine growth restriction.

Intrauterine Growth Restriction

Intrauterine growth restriction (IUGR) refers to a condition in which a fetus is unable to achieve its genetically determined potential size.

Normal fetal growth

Human fetal growth is characterized by sequential patterns of tissue and organ growth, differentiation, and maturation that are determined by maternal provision of substrate, placental transfer of these substrates, and fetal growth potential governed by the genome.

Lin and Santolaya-Forgas (1998) have divided cell growth into three consecutive phases. The initial phase of hyperplasia is during the first 16 weeks and is characterized by a rapid increase in cell number. The second phase, which extends up to 32 weeks, includes both cellular hyperplasia and hypertrophy. After 32 weeks, fetal growth is by cellular hypertrophy, and it is during this phase that most fetal fat and glycogen deposition takes place. The corresponding fetal growth rates during these three phases are 5 g/day at 15 weeks, 15 to 20 g/day at 24 weeks, and 30 to 35 g/day at 34 weeks.

Fetal growth restriction

Small for gestational age (SGA) fetuses are a heterogeneous group comprising fetuses that have failed to achieve their growth potential (fetal growth restriction, FGR) and fetuses that are constitutionally small. Approximately 50–70% of fetuses with a birth weight below tenth percentile for gestational age are constitutionally small ***(Ott, 1988)*** and the lower the percentile for defining SGA, the higher the likelihood of fetal growth restriction (FGR) ***(Chard et al., 1992).***

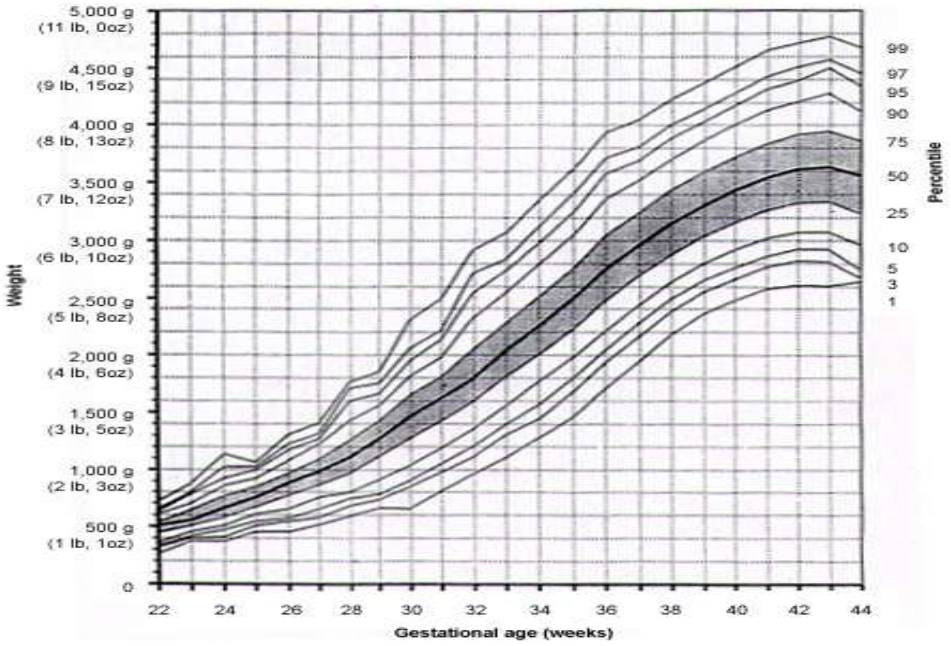

Figure (1): Fetal weight percentiles throughout gestation ***(Peleg et al., 1998).***

Definition of IUGR

The best definition of intrauterine growth retardation is *failure of a fetus to reach its growth potential*. Even this has limitations; e.g., chromosomally abnormal fetuses are difficult to fit into the definition. Currently there is no accurate method of assessing the growth potential of the fetus: the best guide is to establish fetal size early in gestation when the variation in size is least ***(Steer, 1998).***

This definition means that failure to grow along a consistent percentile is more important than absolute size. In other words, a fetus with an abdominal circumference (AC) on the 90^{th} percentile at 28 weeks gestation and the 50^{th} percentile at 36 weeks gestation is more likely to be growth restricted than a fetus which is on the 5^{th} percentile at 28 weeks and again at 36 weeks. Other association of growth restriction is decreased amniotic fluid volume, estimated fetal weight and abnormal umbilical artery waveform may also be incorporated into the definition ***(Nicholas and Richard, 2001).***

Estimated fetal weight (EFW):

There are numerous formulae for calculating the estimated fetal weight (EFW) from ultrasound measurement. Two such examples are that devised by

Warsoff, which uses the biparietal diameter and abdominal circumference ***(Shepard et al., 1982)***, and that of Hadlock, which uses head circumference, abdominal circumference and femur length ***(Hadlock et al., 1982).***

In growth restriction, inclusion of head and femur measurements will lead to an over estimation of fetal weight because growth of this parameters tends to be preserved, whereas abdominal circumference is affected early in growth restriction owing to decrease glycogen storage in the liver. Consequently, EFW is less sensitive than AC at identifying malnourished fetus, but the positive predictive value is greater ***(Hadlock et al., 1982).***

Low birth weight and small for gestational age

Two terms requiring clarification are low birth weight (LBW) and small for gestational age (SGA), LBW is defined by the WHO simply as birth weight <2.5 kg, so does not correct for gestation. SGA is used variably prenatally and postnatally by authors to describe a fetus or neonate with growth parameter(s) (e.g., EFW, AC, birth weight) below a given centile for gestational age. The centiles used are commonly the 2.5^{th}, 3^{rd}, 5^{th}, 10^{th}, and 15th but may be any centile as long as it is specified ***(Hughson et al., 2004)*** or it is EFW less than the mean by two

standard deviation ***(Pollack and Divon, 1992).*** An appropriate definition will depend on the aim of defining a fetus as SGA. The terms IUGR, LBW and SGA are not synonymous there is considerable overlap: some fetuses may meet the criteria for just one of these definitions, whereas others may meet all three ***(Snijders et al., 1993).***

Constitutionally Small Infants:

This group is a different category. Small women typically have smaller babies, if a woman begins pregnancy with a 'weight less than 45kg, the risk of delivering a low for gestational age feteus is increased ***(Cunningham et al., 1993).***

Intrauterine growth retardation (IUGR) complicates up to 10% of all pregnancies. It is associated with a perinatal mortality rate that is 6 to 10 time higher than that for normally grown fetuses and is the second most important cause of perinatal death after preterm delivery.

Causes of Intrauterine Growth Restriction

Maternal causes of IUGR, include the following:

- Chronic hypertension.
- Pregnancy-associated hypertension.
- Class F or higher diabetes.

The above three causes growth restriction by causing vascular disease and they constitute the most common denominator in the causation of IUGR accounting for approximately 1/3 of cases ***(Cunningham et al., 2001).***

- **Cyanotic heart disease:** For example Fallot's tetralogy, Epstein anomaly and Eisenmenger complex result in lower capacity of oxygen transfer to the fetus, thus his growth is retarded ***(Lin, 1985).***
- **Autoimmune disease:** Autoimmune disease e.g., systemic lupus erythromatosis (SLE) is accompanied with premature labour (20-30%), intrauterine fetal death in 10% of cases and significant risk of IUGR, in addition to repeated abortions. IUGR in these cases is ascribed to placental vasculitis and also to corticoids used for treatment, which were shown to decrease fetal head diameters ***(Cunningham et al., 2005).***
- **Protein-calorie malnutrition:** a wasting condition resulting from a diet inadequate in either protein or energy (calories) or both. These inadequacies are major problems for people in developing countries. Also called protein-energy malnutrition (PEM). Symptoms of PEM include generalized muscle wasting and weakness ***(Cetin et al., 2005).***

- **Smoking:** The well-established association between cigarette smoking during pregnancy and IUGR has been reported consistently since 1950. It is the most important single factor causation of IUGR ***(Pollack and Divon, 1992).***

The mechanism involved in this respect involves decreased uteroplacental blood flow which results from:

a) Nicotine activation of catecholamine release resulting in vasoconstriction.
b) Smoking reduces maternal blood pressure for up to 15 minutes, which will reduce the flow of oxygenated blood to the placenta. Smoking is associated with a higher risk for growth restriction. In addition, older pregnant women and those with a previous history of preterm delivery have an increased susceptibility ***(Figueras et al., 2008).***

- Alcohol abuse: Alcohol consumption during pregnancy is a major cause of mental retardation in western countries. Fetal alcohol syndrome (FAS) is mainly characterized by pre- and postnatal stunted growth, neurocognitive disorders, and facial dysmorphism. It compromises the intellectual and behavioral prognosis of the child ***(Seror et al., 2009).***

Fetal alcohol syndrome is estimated to occur in 11% of infants born to moderate drinker mothers (2-3 drinks per day) and 32% of cases of heavy drinkers (5 or more drinks per day) ***(Cunningham et al., 2001).*** Growth retardation is the second classic teratogenic characteristic in Fetus-Alcohol Syndrome; it is of the symmetric**.** 2gm per day was successful in increasing the incidence of pregnancy induced-hypertension & IUGR.

- Uterine malformations.
- Thrombophilias.
- Prolonged high-altitude exposure.

Fetal, placental or umbilical cord causes of IUGR include the following:

Poor placental function is the greatest contributor to FGR, causing placental insufficiency ***(Figueras and Gardosi, 2011).*** Placental insufficiency results in chronic fetal hypoxaemia, and reduced nutrient availability including altered amino acid transfer and fetal hypoglycaemia ***(Cetin and Alvino, 2009).***

- Placental abnormalities: the only common abnormally shaped placenta, which is truly associated with IUGR, is the extrachorial circumvallate placenta,

choriangioma, if large or multiple, can lead to fetal death, malformation or IUGR.

- Chronic abruption: Various degrees of placental separation may be encountered during the second half of pregnancy and are likely to cause IUGR ***(Cunningham et al., 2001).***
- Placenta previa: IUGR was reported to be as high as 16% in cases of placenta previa. The case is ascribed to result maternal anemia and fetal hypoxia ***(Sheinera et al., 2001).***
- Multiple gestations: Twins are likely to develop IUGR in one or both twins more than singleton pregnancy. Growth of twins is usually similar to that of singleton fetuses up to the third trimester after which their rate of growth is much slower than singletons.
- Twin-to-twin transfusion syndrome.
- Chromosomal abnormalities: Fetal aneuploidy is one of the causes of 1UGR. In live births, the incidence of chromosomal aberrations is 0.6%, and less than half of them are clinically significant. It is generally considered that these aberrations operate from early development with the production of symmetric IUGR, however recent observation indicates that this can be asymmetric. The chromosomal aberrations encountered

with IUGR are trisomy 21 i.e. 47 chromosomes with an extra chromosome 21 (Down's syndrome), trisomy 18 (47 with an extra. chromosome 18-Edwards' syndrome), trisomy 13 (47 with extra chromosome 13-Pateau syndrome and Triploidy (69 chromosomes), ***(Cunningham et al., 2005).*** Monosomy of sex chromosomes i.e. 45/XO (Turner syndrome) is associated with some degree of growth retardation Also, trisomy 22 (47 with an extra chromosome 22) has been reported to be associated with IUGR of the fetus.

- Congenital infections:

1- Viral infections: Rubella, cytomegalovirus, herpes simplex hepatitis A and B infections during pregnancy were found to be associated with intrauterine fetal growth restriction ***(Cunningham et al., 2005).***

2- Bacterial infections: Listeriosis, tuberculosis and syphilis have been reported among causes of IUGR ***(Cunningham et al., 2005).*** Syphilis has become extremely rare nowadays, but if it occurs, IUGR is expected to be one of is consequences.

3- Parasitic infections: Parasitic infections most common to be associated with IUGR are toxoplasmosis and malaria.

IUGR occurs when gas exchange and nutrient delivery to the fetus are not sufficient to allow it to thrive in utero. This process can occur primarily because of maternal disease causing decreased oxygen-carrying capacity (eg, cyanotic heart disease, smoking, hemoglobinopathy), a dysfunctional oxygen delivery system secondary to maternal vascular disease (eg, diabetes with vascular disease, hypertension, autoimmune disease affecting the vessels leading to the placenta), or placental damage resulting from maternal disease (eg, smoking, thrombophilia, various autoimmune diseases).

Evaluation of causative factors for intrinsic disorders leading to poor growth may include a fetal karyotype, maternal serology for infectious processes, and an environmental exposure history ***(Severi et al., 2000).***

- ***Morbidity and Mortality:***

IUGR causes a spectrum of perinatal complications, including fetal morbidity and mortality, iatrogenic prematurity, fetal compromise in labor, need for induction of labor, and cesarean delivery.

In a cohort study in Sweden, a 10-fold increase in late fetal deaths was found among very small fetuses. Similarly, ***Gardosi (2006)*** noted in 1998 that nearly 40% of

stillborn fetuses that were not malformed were SGA ***(Gadosi et al., 1998).***

Fetuses with IUGR who survive the compromised intrauterine environment are at increased risk for neonatal morbidity. Morbidity for neonates with IUGR includes increased rates of necrotizing enterocolitis, thrombocytopenia, temperature instability, and renal failure. These are thought to occur as a result of the alteration of normal fetal physiology in utero.

With limited nutritional reserve, the fetus redistributes blood flow to sustain function and to help in the development of vital organs. This is called the brain-sparing effect and results in increased relative blood flow to the brain, heart, adrenals, and placenta, with diminished relative flow to the bone marrow, muscles, lungs, GI tract, and kidneys. The brain-sparing effect may result in different fetal growth patterns ***(Campbell and Thomas, 1985).*** Despite this, it is now apparent that brain-sparing does not ensure normal brain development in growth restricted fetuses. In both humans and animals, neurodevelopmental outcomes are influenced by the timing of the onset of FGR, the severity of FGR, and gestational age at delivery. FGR is broadly associated with reduced total brain volume and altered cortical volume and