INTRODUCTION

Intrauterine growth restriction (IUGR) refers to a condition in which a fetus is unable to achieve its genetically determined potential size. This definition intentionally excludes fetuses that are small for gestational age (SGA) but are not pathologically small. SGA is defined as growth at the 10^{th} or less percentile for weight of all fetuses at that gestational age. Not all fetuses that are SGA are pathologically growth restricted and, in fact, may be constitutionally small ***(George et al., 2015)*.**

Almost 40% of all fetuses at or below the 10^{th} percentile for growth are at high risk of potentially preventable perinatal death. An0other 40% of these fetuses are constitutionally small. Because this diagnosis may be made with certainty only in neonates, a significant number of fetuses that are healthy but SGA will be subjected to high-risk protocols and, potentially, iatrogenic prematurity ***(Johal et al., 2014).***

The remaining 20% of fetuses that are SGA are intrinsically small secondary to a chromosomal or environmental etiology. Examples include fetuses with trisomy 18, CMV infection, or fetal alcohol syndrome. These fetuses are less likely to benefit from prenatal intervention, and their prognosis is most closely related to the underlying etiology ***(Lopez-Tello et al., 2014)*.**

IUGR may be due to intrinsic (fetal) causes as chromosomal abnormalities (Trisomy 13, 18, 21) and intra-uterine infections (STORCH). Evaluation of such causative factors may include a fetal karyotype, maternal serology for infectious processes and an environmental exposure history ***(Michael et al., 2015)*.**

However, IUGR is actually more commonly due to extrinsic (utero-placental) insufficiency where gaseous exchange and nutrient delivery to the fetus become insufficient to allow it to thrive in utero. This process can occur primarily because of maternal diseases or conditions causing decreased oxygen-carrying capacity (e.g. cyanotic heart disease, hemoglobinopathies, smoking, substance abuse), or due to a dysfunctional oxygen delivery system secondary to maternal vascular disease (e.g. Hypertension, whether chronic or pregnancy associated, DM with vascular disease, autoimmune disease causing vasculopathy, thrombophilias, chronic placental abruption, cord & placental anomalies) or due to twin-to-twin transfusion syndrome ***(Bahlmann et al., 2015).***

Growth-restricted fetuses with severe impairment of umbilical artery (UA) blood flow are at increased risk of adverse outcomes such as intrauterine fetal demise and neonatal death, as well as increased neonatal morbidity, including hypoglycemia, hyperbilirubinemia, hypothermia, intraventricular hemorrhage, necrotizing enterocolitis, seizures, sepsis and RDS ***(Cacciatore et al., 2013).***

Furthermore, epidemiological studies have shown that fetuses with IUGR are predisposed to the development of cognitive delay in childhood as well as metabolic syndrome in adulthood (e.g. Obesity, DM, coronary artery disease and stroke) ***(Trapani et al., 2014).***

Placental abnormalities are considered an early warning sign of a future fetal compromise unless managed properly. Placental dysfunction during pregnancy can result in pregnancy-induced hypertension, fetal growth restriction, or fetal loss. Compromise of fetoplacental circulation is suspected in approximately 20% of stillbirths at the time of autopsy ***(Chan and Gross, 2014).***

During the gestation, plasma levels of several growth factors were found to rise in the maternal blood. These growth factors are thought to participate in the regulation of fetal growth and help maintain normal placental function ***(Salomon et al., 2013; Collins and Jauniaux, 2015).***

The serum levels of PIGF rise gradually during normal pregnancy until the onset of the second trimester and then began to slowly decline. Low PIGF level in the maternal serum has been identified as an independent predictor for preeclampsia ***(Dover et al., 2013).*** Some studies also linked low PIGF levels to intrauterine growth restriction. The data are, however, conflicting on whether

low PIGF is associated with IUGR only in the presence of preeclampsia or this may be an independent association ***(Kurtoglu et al., 2016).***

In this study, we assessed the ability of PlGF to antenatally identify FGR with earlier delivery reflecting the physician's decision to deliver in response to perceived perinatal risks.

Aim of the Work

The aim of our study is to identify the role of Placenta1 growth factor as a biochemical serum marker in the 2nd trimester in predicting IUGR with Doppler study of umbilical artery blood flow in 3rd trimester before delivery.

Chapter (1): Intrauterine Growth Restriction (IUGR)

Definition:

Intrauterine growth restriction (IUGR) is a multicausal pathological condition, that occurs in (10%-15%) of all pregnancies, in which the fetus fails to achieve its genetically determined optimal growth. IUGR is a major clinical and public health issue, mainly in developing countries ***(Lees and Baumgartner, 2013)*** according to the guideline of the American College of Obstetricians and Gynecologists, a fetus with IUGR is a fetus with an estimated weight of less than the 10th percentile for gestational age ***(ACOG, 2013).***

It is important not to confuse IUGR with the term small-for-gestational-age (SGA), as in both conditions the birth weight is below the 10th percentile, but in the case of SGA, not all cases are pathological. Some SGA fetuses are small due to constitutional factors ("small but healthy" fetuses) ***(Figueras and Gratacos, 2014) (Crovetto et al. 2016).*** It is reported that IUGR newborns have a higher risk of perinatal mortality, also a higher tendency to develop short-term and long-term morbidities ***(von Beckerath et al. 2013).***

Antenatal discrimination of fetuses which are small due to placental dysfunction, rather than constitutionally-

small, would improve clinical management, by focusing on the ones that are indeed at-risk of perinatal complications, decreasing unnecessary intervention for pregnancies with constitutionally-small fetuses ***(Benton et al., 2012).***

Placental insufficiency is the major cause of IUGR. Within this common pathogenesis, IUGR presents under two categories; when the onset is early or late in gestation. In general, but not always, there is a correspondence between early onset and the most severe forms of IUGR ***(Lackman et al., 2014).***

The risk of adverse neonatal outcome is always proportional to the degree of growth restriction, with those below the 3rd percentile and/or with abnormal Umbilical artery Doppler measurements being at greater risk of neonatal morbidity or mortality ***(Barker et al., 2014).***

Current antenatal detection rates of IUGR are reported at 25 to 36% ***(Gardosi et al., 2013).*** The incidence of stillbirth in pregnancies with prenatally identified IUGR is 1% (9.7/1,000 births). On the other hand, Pregnancies with unrecognized IUGR have an over 8-fold increased incidence of stillbirth (SB) when compared to pregnancies without IUGR (19.8 versus 2.4/1,000 births). Therefore, preventative strategies and early screening are crucial for better perinatal outcomes in IUGR ***(Chauhan et al., 2013).***

Classification of IUGR:

According to the onset:

1- Early-onset IUGR

Early-onset IUGR represents 20-30% of all IUGR and is highly associated with severe placental insufficiency with abnormal umbilical artery (UA) Doppler resulting in chronic fetal hypoxia ***(Turan et al., 2017).***

If left untreated, the fetal condition usually deteriorates with progression to decompensated hypoxia and acidosis, which is reflected by escalating abnormalities in the Umbilical artery Doppler and increased pulsatility index (PI) in the precordial veins, mainly the ductus venosus (DV) ***(Baschat et al., 2016).***

Sever degree of early-onset IUGR usually results in severe injury and/or fetal death before term in many cases. Management of such cases is challenging and aims at achieving the best balance between the risks of leaving the fetus in-utero and the complication of prematurity 15 ***(Baschat et al., 2016).***

2- Late-onset IUGR

Late-onset IUGR represents 70-80% of all IUGR cases. In this condition, the degree of placental

insufficiency is mild. Thus the umbilical artery Doppler is normal. However, it is usually associated with an abnormal cerebro-placental ratio (CPR). Also an advanced brain vasodilatation, suggesting chronic hypoxia, reflected by the middle cerebral artery (MCA) PI $<5^{TH}$ percentile (p5) may occur in 25 % of late-onset IUGR cases ***(Oros et al., 2013).***

The advanced signs of fetal deterioration with changes in the DV are virtually never observed in cases of the late-onset IUGR. Thus, the cascade of subsequent fetal deterioration, which usually happens in early-onset IUGR, is also not observed ***(Cruz-Martinez et al., 2011).***

3- Mixed IUGR

This case results when a placental insufficiency develops in advanced pregnancy on top of an early-onset IUGR. The affected neonates have clinical features of both the symmetrical and the asymmetrical IUGR at birth ***(Sharma et al., 2016).***

According to the fetal symmetry:

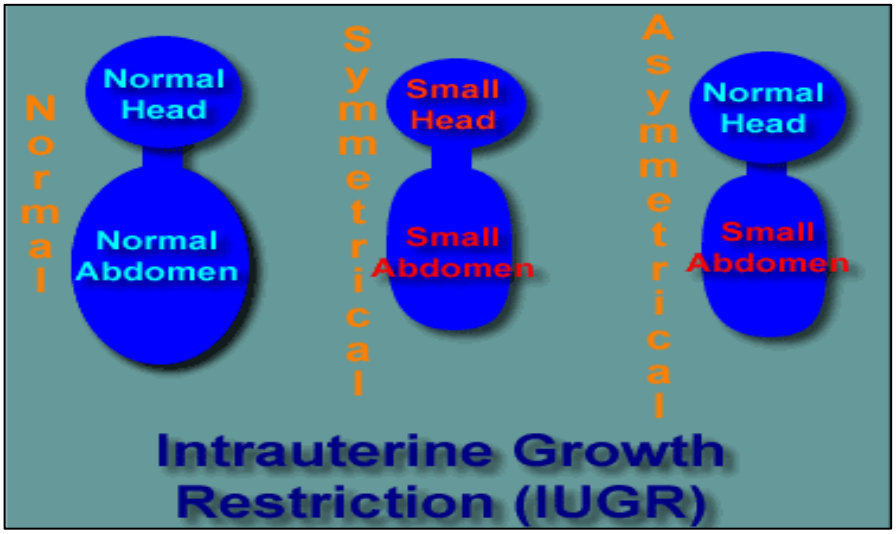

Figure (1): Different types of IUGR ***(Sharma et al., 2016).***

1- Symmetrical IUGR

Symmetrical IUGR refers to fetuses with equally poor growth velocity of the head, abdomen and long bones. It usually results from the early-onset IUGR causes. Antenatal measurements of the head circumference, the abdominal circumference, the biparietal diameter and the fetal length, are proportionally reduced. Postnatal measurements of weight, length and the head circumference are also reduced. Features of malnutrition are less evident, but prognosis is relatively poor ***(Verberg et al., 2015).***

2- Asymmetrical IUGR

Asymmetrical IUGR refers to fetuses with their heads and long bones being spared, compared to their abdomen and viscera. It usually results from the early-onset IUGR causes ***(Verberg et al., 2015).***

With limited nutritional reserve, the fetus redistributes blood flow toward its vital organs, to maintain their functions and development. This is known as the brain sparing effect and results in an increase in the relative blood flow to the brain, the heart, the adrenals and the placenta, with a relatively diminished flow to the bone marrow, the muscles, the lungs, the GIT and the kidneys ***(Bernstein et al., 2016).***

Etiology of IUGR

IUGR could result of maternal, placental, fetal or genetic factors (Figure 2) The incidence of IUGR is six times higher in developing countries when compared to that in developed countries ***(Sharma et al., 2016).***

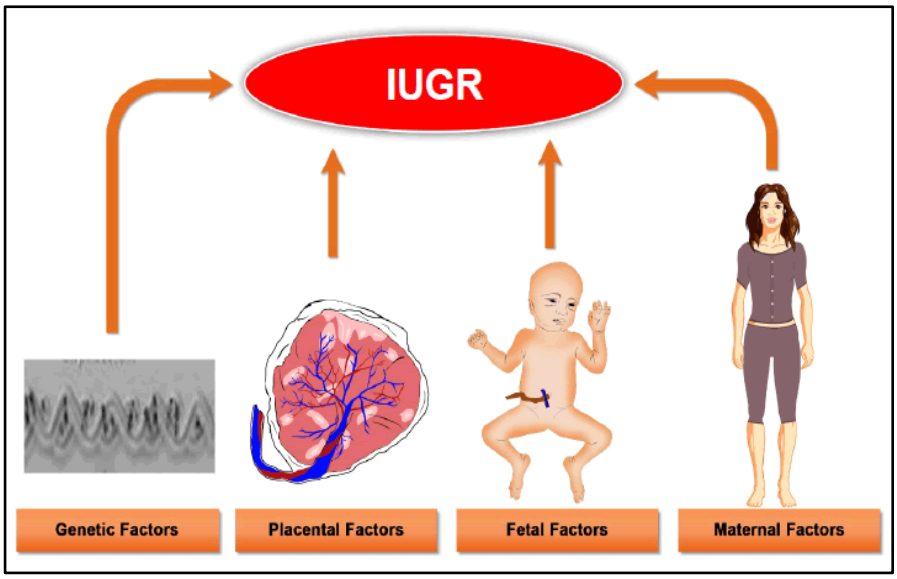

Figure (2): Different causes of IUGR ***(Sharma et al., 2016).***

I. Maternal factors: (Figure 3)

- Maternal age (less than 16 years or more than 35 years).
- Low socio-economic status.
- Parity (none or more than five births).
- Inter-pregnancy interval equal to/ more than 120 months or less than 6 months).
- Previous delivery of an SGA newborn.
- Maternal substance abuse (smoking, alcohol and illicit drugs such as marijuana or cocaine).
- Maternal medications as (warfarin, steroids, anticonvulsants, antineoplastic, antimetabolite, and folic acid antagonists).

- Maternal pre-pregnancy BMI less than 20, weight less than 45 kg or more than 75 kg.
- Assisted reproductive technologies.
- Pregnancy: Moderate to heavy physical work, severe maternal starvation, poor weight gain.
- High-altitude and maternal hypoxia, poor medical care.
- Maternal medical disorders: e.g., asthma, cyanotic congenital heart disease, hypertensive disorders, pre-eclampsia, diabetes associated with vasculopathy, chronic kidney disease, systemic lupus erythematosus, antiphospholipid syndrome, sickle cell disease; acquired thrombophilia (e.g., anti-cardiolipin antibodies and lupus anticoagulant).
- Maternal infection and parasite infestations: TORCH syndrome (= toxoplasmosis, other, rubella, cytomegalovirus, herpes simplex), malaria, tuberculosis, urinary tract infections and bacterial vaginosis

(Sharma et al., 2016).

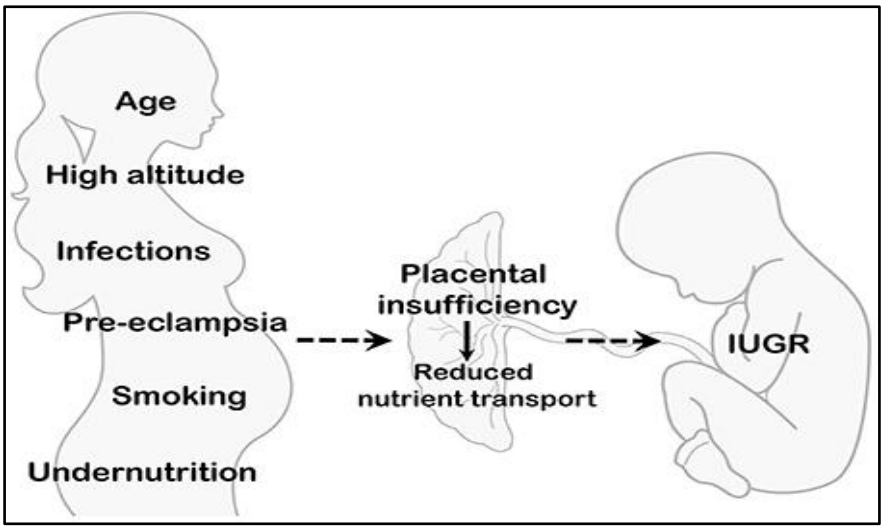

Figure (3): Maternal and environmental conditions associated with IUGR ***(Gaccioli and Lager, 2016).***

II. Fetal factors:

- Chromosomal abnormalities: e.g., trisomies 13, 18, or 21, autosomal deletions, triploidy, ring chromosomes.
- Genetic syndromes: e.g., Russell-Silver syndrome, Rubinstein-Taybi syndrome, Dubowitz's syndrome, Seckel's syndrome and Fanconi's syndrome.
- Major congenital anomalies: e.g., tracheo-oesophageal fistula, congenital heart disease, congenital diaphragmatic hernia, abdominal wall defects (omphalocele or gastroschisis), neural tube defect (e.g., anencephaly) and anorectal malformation.

- Multiple gestations.
- Congenital infections (TORCH syndrome, malaria, congenital HIV infection and syphilis) ***(Sharma et al., 2016).***

III. Placental factors:

Placental insufficiency is the major cause of IUGR. The placental weight of IUGR fetuses is usually smaller by about 24% when compared with the placenta of a normally grown fetus. The pathogenesis of IUGR is not well defined yet. However, it is established that any defect in the placental circulation results in a relative decrease in the placental mass and function and affects the fetal nutrition causing IUGR ***(Baschat et al., 2012).***

The activation of dendritic cells (DCs) at the maternal-fetal interface contributes to the optimal immune response at the level of the decidua to support the fetal-placental development. Reduced number of the circulating inactive DCs in pregnancy could be complicated by IUGR. The number and the activity of DCs can be easily accessed in the peripheral blood ***(Cappelletti et al., 2013).***

Moreover, abnormal implantation, such as placenta previa, can also result in suboptimal fetal nutrition usually through decreasing utero-placental blood flow. Other