INTRODUCTION

Fetal growth restriction (FGR) is a common and complex clinical problem which confers a considerable risk of morbidity. In addition to infectious causes and congenital malformations, FGR has been identified as a major contributor to perinatal mortality ***(Manning et al., 2013).***

Intrauterine growth failure affects up to 10% of pregnancies and is often referred to as small-for gestational age (SGA), intrauterine growth restriction (IUGR) or fetal growth restriction (FGR) in an inconsistent and confusing manner. Traditionally, an estimated fetal weight (EFW) or abdominal circumference (AC) below the 10th centile raises concerns over suboptimal intrauterine growth, however the distinction between normal and pathologic growth often cannot reliably be made at this arbitrary cut-off. In addition, approximately 70% of fetuses below the 10th centile will have a normal perinatal outcome ***(Lees et al., 2013).*** The risk of adverse outcome is proportional to the degree of growth restriction with those below the 3rd centile and/ or abnormal umbilical artery Doppler measurements at greatest risk of morbidity or mortality ***(Unterscheider et al., 2013).*** In addition, analysis of fetal growth trajectories has been identified as an important factor in the differentiation between physiological SGA and pathological IUGR ***(Unterscheider et al., 2013).***

Vitamin D, a secosteroid hormone known for its classical functions in calcium uptake and bone metabolism, is now well recognized for its non classical actions, including modulation of innate immune response and regulation of cell proliferation ***(Zanetti et al., 2014).*** Vitamin D deficiency is common in pregnant women and is increasingly recognized as a global public health problem. Increasing evidence demonstrates that vitamin D deficiency during pregnancy is linked with gestational diabetes mellitus, pre-eclampsia, and bacterial vaginosis ***(Cho et al., 2013).***

A systematic review of literature highlighted the effect of vitamin D on birth weight ***(Thorne-Lyman and Fawzi, 2012).*** Vitamin D has a key role in fetal growth by its interaction with parathyroid hormone and calcium homestasis.

High prevalence of vitamin D deficiency (about a billion) has been seen among people all over the world ***(Sioen et al., 2012).***

Aim of the Study

The aim of the current study is to investigate the vitamin D status and find if there is an association between maternal vitamin D deficiency and intra uterine growth retardation (IUGR).

Research hypothesis

In pregnant women with IUGR, vitamin D levels may be lower compared to controls.

Research question

Is vitamin D level lower in pregnant women with IUGR than controls?

Chapter 1

INTRA UTERINE GROWTH RETARDATION (IUGR)

Definition:

Intrauterine growth restriction is defined as the pathologic inhibition of intrauterine fetal growth and the failure of the fetus to achieve its growth potential ***(Mandruzzato, 2008).***

Considered by the American College of Obstetricians and Gynecologists (ACOG) "the most common and complex problem in modern obstetrics".

Fetal growth restriction still needs clear criteria because intrauterine fetal growth is not defined by clear parameters but mainly estimated on the basis of multiple factors. Research in this field is trying to find predictive parameters, with the goal of reaching an early diagnosis, which would lead to a better management of the condition ***(American College of Obstetricians and Gynecologists Practice bulletin, 2013).***

Intrauterine growth failure affects up to 10% of pregnancies and is often referred to as small-for gestational age (SGA), intrauterine growth restriction (IUGR) or fetal growth restriction (FGR) in an inconsistent and confusing manner. ***(Green top guideline, 2013).***

Classification:

There are predominately three types of IUGR: symmetrical IUGR, asymmetrical IUGR and mixed IUGR

1. Symmetric IUGR:

The head circumference, height, and weight all are proportionately reduced for GA. And it is due to either decreased growth potential of the fetus (congenital infection or genetic disorders) or extrinsic conditions that are active early in pregnancy ***(Stoll et al., 2010).***

2. Asymmetric IUGR:

Head circumference and height equally affected, but are less affected than weight and all the three measures are below the 10^{th} centile". In these infants, brain growth is usually spared. The usual causes are utero-placental insufficiency, maternal malnutrition, or extrinsic conditions appearing late in pregnancy ***(Stoll et al., 2010).***

3. Mixed IUGR:

Neonates have clinical features of both symmetrical and asymmetrical IUGR at birth. Infants with this type have lesser number of cells and small cell size and it is usually seen in developing countries. This type of IUGR results when early IUGR is affected further by placental causes in late pregnancy.

Table (1): Features of symmetrical and asymmetrical IUGR ***(Sharma et al., 2016).***

Characteristics	Symmetrical IUGR	Asymmetrical IUGR
Period of insult	Earlier gestation	Later gestation
Incidence	20% to 30%	70% to 80%
Etiology	Genetic disorder or infection intrinsic to foetus	Utero-placental insufficiency
Antenatal scan Head circumference, Abdominal circumference, Biparietal diameter and Femur length	All are proportionally reduced	Abdominal circumference- decreased Biparietal diameter, Head circumference, and femur length- normal
Cell number	Reduced	Normal
Cell size	Normal	Reduced
Ponderal Index	Normal (more than 2)	Low (less than 2)
Postnatal anthropometry Weight, length and head circumference.	Reductions in all parameters	Reduction in weight Length and Head circumference- normal (Brain sparing growth)
Difference between head and chest circumference in term IUGR	Less than 3 cm	More than 3 cm
Features of malnutrition	Less pronounced	More pronounced
Prognosis	Poor	Good

Causes:

- Incorrect dating of the pregnancy.
- Constitutionally small size.
- Genetic/chromosomal defects in the fetus.
- Intrauterine infection.
- Intrauterine growth restriction (IUGR) related to an inadequacy in the supply of nutrients and/or oxygen to the fetus through the utero-placental unit.

Risk factors:

The risk factors for IUGR comprise a wide range of conditions and their assessment should be seriously taken into account, as they are easy to perform and are routinely used during pregnancy ***(Gardosi, 2009; Zhong, 2010).***

IUGR is the common end result of maternal, fetal, placental or genetic factors, and it can also result due to a combination of any of these factors.

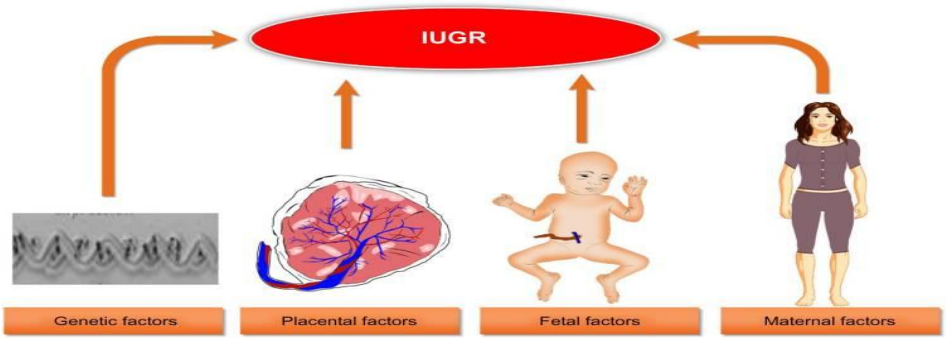

Figure (1): Risk factors of IUGR.

- **Maternal factors**

1. Maternal size

Maternal constitutional factors have a significant effect on fetal growth ***(Sankaran and Kyle, 2009).*** The major risk factors for IUGR include small maternal pre-pregnancy height and weight (BMI less than 20, weight less than 45 kg and more than 75 kg) ***(Zenk et al., 2004; Siza, 2008).***

2. Nutritional status

Maternal nutrition and supply of nutrients to the fetus affect fetal growth. And there is a relationship between maternal nutrition during pregnancy and infant birth weight ***(Martinez and Simmons, 2005).***

3. Maternal illness

Maternal disorders such as pre-eclampsia, eclampsia, antiphospholipid syndrome**,** chronic reno-vascular disease, diabetes mellitus**,** systemic lupus erythematosus(SLE) and chronic hypertensive vascular disease often result in decreased utero-placental blood flow and associated IUGR ***(Tellechea et al., 2015).***

4. Maternal exposure to environmental/extrinsic factors

The fetus may be exposed to chemical agents via the mother, including recreational (drugs of abuse), therapeutic, and occupational exposure (maternal exposure to environmental hazards) ***(Thompson et al., 2009).***

And also there are medications associated with fetal growth restriction (FGR) include anticonvulsants, anticoagulants, and folic acid antagonists ***(Alberry and Soothill, 2007).***

5. Multiple pregnancies:

There is a progressive decrease in placental and fetal weight as the number of fetuses increases in multiple gestations cause of abnormalities with placentation, vascular communications, and umbilical cord insertions ***(Doom et al., 2012).***

- **Fetal factors**

1- Chromosomal disorders:

There is a strong association between IUGR, chromosomal disorders, congenital malformation and genetic abnormalities ***(Puccio et al., 2013).***

Fetal aneuploidy is one of the causes of IUGR. And there are chromosomal aberrations encountered with IUGR such as ***(Cunningham et al., 2005).***

- Trisomy 21 i.e. 47 chromosomes with an extra chromosome 21 (Down syndrome)
- Trisomy 18 i.e. 47 with an extra. chromosome 18 (Edward syndrome)
- Trisomy 13 i.e. 47 with extra chromosome 13 (Pateau syndrome)
- Triploidy (69 chromosomes)

2- Congenital malformations:

Anencephaly, gastrointestinal atresia, potter's syndrome, pancreatic agenesis and hypospadias are examples of congenital anomalies associated with IUGR ***(Puccio et al., 2013).***

3- Congenital infections

Such as TORCH infection (toxoplasmosis, rubella, cytomegalovirus, and herpes simplex virus) is often associated with severe IUGR ***(Brodsky and Christou, 2004)*.**

4- Metabolic disorders

Such as agenesis of pancreas, congenital absence of islets of Langerhans, congenital lipodystrophy, galactosemia**,** hypophosphatasia, fetal phenylketonuria and transient neonatal diabetes mellitus are associated with IUGR ***(Gomella et al., 2013).***

- **Placental factors**

Placental factors are known to influence fetal growth through the transfer of nutrients from the mother to the fetus across the placenta depending on uterine blood flow **(Gaccioli et al., 2013).**

Abnormal placentation that including velamentous cord insertion, vasa previa, placenta previa, and uterine anomalies, such as sub-mucous myomas, synechiae, and septate uterus ultimately comprise utero-placental circulation ***(Ananth and VanderWeele, 2011).***

Premature placental separation may reduce the surface area exchange, resulting in impaired fetal growth ***(Brett et al., 2014).***

- **Genetic factors**

These factors are divided into placental**,**maternal and fetal genes. And IUGR occurs due to defect in the function of these genes for example:

Placental genes:

Table (2): Placental genes associated with IUGR ***(Sharma et al., 2017).***

No.	Genes	Function
1	Homeobox	Control specific aspects of placental growth and differentiation. Play important role in development and maintenance of the blood and lymphatic system
2	Serpin peptidase inhibitor clade A member 3 (SERPINA3)	Regulate wide range of biological processes, including coagulation, inflammation and wound healing. Plays important role in maintaining body homeostasis.
3	Vascular endothelial growth factor (VEGF-A)	Important regulatory protein involved in vasculogenesis and angiogenesis
4	Placental Insulin-like growth factor 1 (IGF1)/Placental Insulin-like growth factor 2 (IGF2)	IGF1 and IGF2 have important role in intrauterine growth IGF-2 action is mediated through endocrine and autocrine stimulation of cellular differentiation

Maternal genes:

Table (3): Maternal genes associated with IUGR ***(Sharma et al., 2017).***

No.	Genes	Function
1	Tumor necrosis factor (TNF)	Produced by macrophages, lymphocytes and trophoblast cells Role in multiple autoimmune and inflammatory diseases
2	Endothelin-1 (ET-1)	Causes placental vasoconstriction
3	Leptin	Produced from human placental trophoblast cells Regulates energy homeostasis, reproductive functions and immune reactions

Fetal genes:

Table (4): Fetal genes associated with IUGR ***(Sharma et al., 2017).***

No.	Genes	Function
1	Urinary protein S100B	Plays role in regulation of several cellular functions (cell-cell communication, cell growth, cell structure, energy metabolism, contraction, and intracellular signal transduction)
2	Nitric oxide	Potent vasodilator released by endothelial cells Role in maintenance of blood pressure Controls vascular tone of feto-placental unit
3	Adrenomedullin	Potent vasodilator Physiologic regulation of blood pressure and vascular homeostasis

Diagnosis or IUGR:

A- Clinical Diagnosis

A) History

- **Previous history of growth restriction**

Women with a previous growth-restricted baby have a 50% increased risk of severe growth restriction in the current pregnancy ***(Figueras and Gardosi, 2011).***

- **Diabetes**

Women with diabetes are at increased risk of having a baby with macrosomia as well as FGR, with increased risk of perinatal morbidity and mortality.

- **Multiple pregnancy.**

Compared with singletons, twin pregnancies have increased risk of mortality and morbidity. Because growth restriction and weight discordance are responsible for a large part of this higher risk of mortality and morbidity ***(Steenhaut et al., 2012).***

B) Examination

Screening for IUGR in the general population relies on symphyseal fundal height (SFH) measurements. This is a routine portion of prenatal care from 20 weeks till term.

The clinician should be aware that the sensitivity of fundal height measurement is limited, and he should maintain a heightened awareness for potential growth-restricted fetuses. In an unselected hospital population, only 26% of fetuses that were SGA were suggested to be SGA based on clinical examination findings ***(Jaiswal et al., 2015).***

SFH should be plotted on a customised chart rather than a population–based chart as this may improve prediction of a SGA neonate. Women with a single SFH which plots below the 10th centile should be referred for ultrasound measurement of fetal size ***(Green top guideline, 2013).***

B- Ultra-Sonographic Diagnosis

1) Biometry

Although no single biometric measurement is completely accurate for helping make or exclude the diagnosis of growth restriction, screening for IUGR is important. Patients may undergo serial sonography during their pregnancies ***(Groom et al., 2007).***

Two systematic reviews have assessed the accuracy of ultrasound biometric measures, both as individual measures, as ratios, and combined (as the EFW). Use of the 10th centile had better sensitivities and specificities than other commonly used centiles.

Fetal abdominal circumference (AC) or estimated fetal weight (EFW) < 10th centile can be used to diagnose a SGA fetus. When using two measurements of AC or EFW to estimate growth velocity, they should be at least 3 weeks apart to minimise false–positive rates for diagnosing FGR. Routine measurement of fetal AC or EFW in the third trimester does not reduce the incidence of a SGA neonate nor improve perinatal outcome. Where the fetal AC or EFW is < 10th centile or there is evidence of reduced growth velocity, women should be offered serial assessment of fetal size and umbilical artery Doppler ***(Green top guideline, 2013).***

2) Ultra-sonographic Doppler Diagnosis

Both arterial doppler and venous doppler have been used to support expectant management or delivery of IUGR fetuses and to identify fetuses at risk. Doppler velocimetry has been shown to contribute to the identification of fetuses at risk of IUGR ***(Alberry and Soothill, 2007).***

Umbilical artery (UA) Doppler is widely accepted as the primary assessment tool in IUGR ***(Alfirevic et al., 2010)*** however there is on-going debate and controversy on the benefit of assessing vessels other than the UA in the setting of IUGR. Several studies have contributed to the understanding of longitudinal Doppler changes occurring in IUGR.