INTRODUCTION

Intrauterine growth restriction (IUGR) is a fetal weight that is below the10th percentile for gestational age as determined by ultrasound. This can also be called small for gestational age (SGA) or fetal growth Restriction (FGR) ***(Dasjupta, 2003)**,* while ***(Samangaya et al., 2009)*** defined FGR as one or more of the following: fetal abdominal circumference <5^{th} percentile. Amniotic fluid index < 5^{th} percentile or Doppler umbilical artery pulsatility index > 95^{th} percentile for gestational age. It affects up to 7-8% of all pregnancies ***(NLM, 2002; NVSR, 2004).*** Fetal growth restriction (FGR) complicates 7-15% of pregnant women and in its early and severs form the risk of perinatal morbidity and mortality is increased ***(Baschat et al., 2004).***

Causes of FGR are classified to fetal factor as: chromosomal abnormalities, multiple pregnancies, fetal structural anomalies and fetal infections. Maternal factors as: hypertension anemia, diabetes mellitus, chronic lung diseases and heart. Placental factor as: Chorioangioma, infarction, circumvallate placenta, confined placental mosaicism, obliterative vasculopathy of placental bed ***(Gardosi et al., 2013).***

Umbilical artery Doppler has been the mainstay for diagnosing placental insufficiency for 2 decades. Consequently, fetuses with normal UA Doppler, normally defined as small for gestational age (SGA), have long been considered to be constitutionally small fetuses with a good prognosis ***(Comas et al., 2011).*** Therefore, all Doppler indices of the umbilical artery can be used to distinguish between the high-risk small fetus that is truly growth-restricted and the lower-risk small fetus ***(Ursula and Giancarlo, 2004).***

Several new vasodilator drugs have recently been suggested to augment blood flow to tissues; one of these drugs is sildenafil citrate (Viagra) ***(Wareing et al., 2005)***.

Sildenafil citrate is a selective inhibitor of cyclic guanosine monophosphate (cGMP) formation through inhibition of type 5phosphodiesterase (PDE5) ***(Wareing et al., 2005).*** It increases uterine blood flow and potentiates estrogen-induced vasodilatation ***(Zoma et al., 2004).***

Several studies postulated that Sildenafil citrate may offer a potential therapeutic strategy to improve utero placental blood flow in FGR pregnancies ***(Panda et al., 2014; Dilworth et al., 2013; Dastjerdi et al., 2012).***

AIM OF THE WORK

The aim of this study is to asses the efficacy of sildenafil citrate therapy in prolonging pregnancy in women with fetal growth restriction.

Research hypothesis

Sildenafil citrate may prolong pregnancy in women with fetal growth restriction and abnormal umbilical artery Doppler.

Research Question

Does sildenafil citrate prolong pregnancy in women with fetal growth restriction and abnormal umbilical artery Doppler?

FETAL GROWTH RESTRICTION

Normal fetal growth is a critical component of a healthy pregnancy and influences the long-term health of the offspring. However, defining normal and abnormal fetal growth has been a long- standing challenge in clinical practice and research ***(Zhang et al., 2010).***

Normal fetal growth: Figure (1) ***(David et al., 1998)***

- 14-15 week's gestation "5 gm/day"
- 20 weeks "10 gm/day"
- 32-34 weeks "30-35 gm/day"
    - Mean peaks 230-285 gm/week (32-34 wk).
    - Decreases at 41-42 weeks.
    - Slightly less growth per week for multiples.

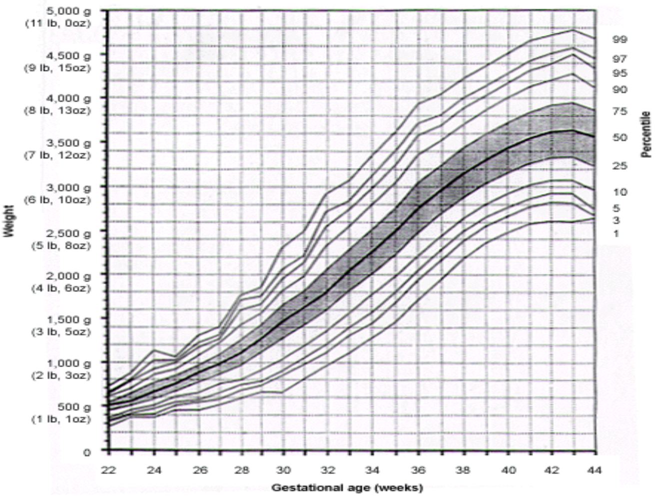

Figure (1): Fetal weight percentiles throughout gestation ***(David et al., 1998).***

Definitions

Small–for–gestational age (SGA) refers to an infant born with a birth weight less than the 10th centile ***(RCOG, 2014).*** Historically SGA birth has been defined using population centiles. But, the use of centiles customized for maternal characteristics (maternal height, weight, parity and ethnic group) as well as gestational age at delivery and infant sex, identify small babies at higher risk of morbidity and mortality than those identified by population centiles ***(Figueras et al., 2008)***. With respect to the fetus, definitions of SGA birth and severe SGA vary. For the purposes of this guideline, SGA birth is defined as an estimated fetal weight (EFW) or abdominal circumference (AC) less than the 10th centile and severe SGA as an EFW or AC less than the 3rd centile ***(RCOG, 2014).***

Fetal growth restriction (FGR) is not synonymous with SGA. Some, but not all, growth restricted fetuses/infants are SGA while 50– 70% of SGA fetuses are constitutionally small, with fetal growth appropriate for maternal size and ethnicity ***(Alberry and Soothill, 2007)***. The likelihood of FGR is higher in severe SGA infants. Growth restriction implies a pathological restriction of the genetic growth potential. As a result, growth restricted fetuses may manifest evidence of fetal compromise (abnormal Doppler studies, reduced liquor volume). Low birth weight (LBW) refers to an infant with a birth weight < 2500 g ***(RCOG, 2014).***

The American College of Obstetricians and Gynecologists (ACOG) defines an FGR fetus as a fetus with an estimated weight below the 10th percentile ***(ACOG, 2013).*** This definition means that failure to grow along a consistent percentile is more important than absolute size. Another 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 Fisk, 2008).***

Not all fetuses measuring less than the 10th percentile are at risk for adverse perinatal outcome; many are just constitutionally small. FGR refers to the fetus that is SGA and displays other signs of chronic hypoxia or malnutrition (***Ville and Nyberg, 2006).***

Incidence:-

Severe early onset fetal growth restriction (FGR) complicates approximately 0.4% 0f pregnancy ***(Von Dadelszen et al., 2011).***

Types of Intrauterine Growth Restriction:-

According to the American Pregnancy Association, they are classified into two types:

Type 1 or symmetric growth restriction:

It represents one-third of cases and results from the effect of noxious agents operating in early fetal life, so the fetus is left with fewer numbers of cells in his organs or the placenta, but yet this limited number of cells can grow. This is seen with congenital or chromosomal defects or exposure of the fetus to early congenital infections. In this type, all organs are small with no organs spared ***(Cunningham et al., 2010).***

Type 2 or asymmetric growth restriction:

It represents two-thirds of cases and results from factors operating later on during pregnancy i.e. when each organ has got its allocated number of cells but their hypertrophy is interfered with the main cause is decreased uteroplacental blood flow or restricting the oxygen and nutrient carrying capacity of blood. The process takes place over a protracted period which would allow the fetus to compensate by redistribution of blood to the most vital organs e.g. brain and heart at the expense of the less vital organs e.g. liver and kidney i.e. this type is brain sparing.

That is why the body circumference lags behind the head circumference, while in type 1 IUGR these two are proportionately reduced ***(Cunningham et al., 2010).***

Etiology:

Normal fetal growth depends on maternal, fetal, placental, and external factors combined with genetically predetermined growth potential ***(Miller et al., 2009).***

1- ***Fetal causes:***

Chromosomal Aneuploidies:

Placentae of fetuses with autosomal trisomies have a reduced number of small muscular arteries in the tertiary stem villi. Depending on which chromosome is extra such as (trisomy 13, 18 and 21, triploidy, uniparental disomy), there may be associated growth restriction ***(Springer et al., 2012).***

Structural anomalies:

Virtually all major structural defects (CNS, CVS, GIT, GUT and musculoskeletal) are associated with an increased risk of having a small fetus. It is not clear whether one predisposes to the other or there is a common cause for both ***(Lau et al., 2011).***

Fetal Infections:

Viral, bacterial, protozoan and spirochetal infections have been implicated in up to 5 percent of cases of fetal growth restriction ***(Comer et al., 2010).***

Multiple Fetuses:

Pregnancy with two or more fetuses is more likely to be complicated by IUGR than singletons ***(Muhlhausler et al., 2011)***.

Dizygotic twins are less affected than monozygotic twins as regard fetal growth restriction. In the latter group, dichorionic variety is at lower risk than the monochorionic one which may suffer twin to twin transfusion**.**

Genetic syndromes:

Systemic lupus erythematosus, antiphospholipid syndrome Thrombophilia (Factor V Leiden heterozygote, Prothrombin gene G20210A heterozygote, MTHFR heterozygote) ***(Lockwood and Schur, 2011).***

2- <u>Maternal causes</u>:

Poor Maternal Nutrition:

In the woman of average or low body mass index (BMI), poor weight gain throughout pregnancy may be associated with fetal growth restriction ***(Yekta et al., 2006).***

Lack of maternal weight gain in the second trimester especially correlates with decreased birth weight ***(Löf et al., 2008).***

Social Deprivation:

The effect of social deprivation on birth weight is interconnected to the effects of associated lifestyle factors such as smoking, alcohol or other substance abuse, and poor nutrition. In a study of 105111 American women ***Farley & colleagues (2006)*** found that the most socially deprived mothers had the smallest infants. Similarly, ***Dejin-Karlsson and Colleagues (2000)*** prospectively studied a cohort of Swedish women and found that lack of psychosocial resources increased the risk of growth-restricted infants.

Teratogens:

Any teratogen is capable of adversely affecting fetal growth. It interferes with normal embryonic or fetal development. Examples include anticonvulsants and anti-neoplastic agents. In addition, cigarette smoking, opiates and related drugs, alcohol, and cocaine may cause growth restriction, either primarily or by decreasing maternal food intake ***(Nigam, 2009).***

Vascular Disease:

Especially when complicated by superimposed preeclampsia, a chronic vascular disease commonly causes growth restriction. Preeclampsia may cause fetal growth failure and is an indicator of its severity, especially when the onset is before 37 weeks ***(Goodwin et al., 2010).***

Chronic Hypoxia:

When exposed to a chronically hypoxic environment, some fetuses have significantly reduced birth-weight. Fetuses of women who reside at high altitude usually weigh less than those born to women who live at a lower altitude ***(Balci et al., 2011).***

Severe hypoxia from maternal cyanotic heart disease frequently is associated with severely growth restricted fetuses ***(Balci et al., 2011).***

Anemia:

In most cases, maternal anaemia does not cause fetal growth restriction. Exceptions include sickle cell disease and some other inherited anemia. Conversely, curtailed maternal blood volume expansion has been linked to fetal growth restriction ***(Makh et al., 2008).***

3- Placental causes:

Placental and Cord Abnormalities:

A number of placental abnormalities may cause fetal growth restriction. They include extensive infarction, chorioangioma, marginal or velamentous cord insertion, circumvallate placenta, or placenta previa. Growth failure in these cases is often presumed to be due to uteroplacental insufficiency. Some women with otherwise unexplained fetal growth restriction and a grossly normal placenta have reduced uteroplacental blood flow when compared with normally grown fetuses ***(Ofelia et al., 2011).***

Abruptio Placentae:

Various degrees of placental separation may be encountered during the second half of pregnancy, and are likely to cause IUGR. Severe placental separation is almost always accompanied by severe anemia, hypovolemia, hypotension or shock with fetal distress or death ***(Siddiqui et al., 2008)***.

Pathophysiology

Deficiency of growth promoting factors:

Insulin and somatomedin appear to be the two important growth hormones for the fetus during intrauterine life. FGR fetuses usually show a degree of deficiency of these two hormones ***(Shimrit et al., 2011).***

Hemodynamic:

When there is reduction or interruption of maternal blood flow, there will be a decrease in the supply of oxygen, glucose and other substrates to the fetus. The fetus will adapt to this condition decrease or cessation of fetal growth, decrease of fetal movement, redistribution of blood flow to the more vital organs (brain– heart – adrenals) on the expense of the others, Recruitment of RBCs from extra-medullary hemopoietic sites leading to polycythemia ***(Drewlo et al., 2006).*** Meanwhile, oxygen supply is defective, so metabolism is reverted to the anaerobic type which leads to lactate accumulation, causing acidosis ***(Blickstein and Green, 2007).***

Organ Changes:

The liver:

In cases of FGR with a defective supply of glucose, glycogen stores in the liver are diminished. This will lead to decrease the size of the liver down to 50% of normal leading to decrease in the abdominal circumference of the fetus ***(Cetin et al., 2008).***

The heart:

Decrease of cardiac glycogen will reduce the ability of the fetus to withstand the stress of labor and delivery. Also, hypoxia will affect the cardiac function. Acute deterioration will not be seen when the uterus is quiescent, but with the onset of uterine contractions which will cause a further decrease in uteroplacental blood flow, oxygen supply is further decreased leading to myocardial depression, which manifests as late deceleration on fetal heart rate monitoring ***(Myrie et al., 2011).***

The kidneys and urine output:

With fetal hypoxia and redistribution of blood to the more vital organs, the fetal kidneys suffer oligemic renal failure which is manifested by decrease or cessation of urine excretion leading to oligohydramnios ***(Myrie et al., 2011).***

The intestine and meconium:

Redistribution of blood will lead to decreased blood flow to the intestine; in addition, there is hypoxia and lactate accumulation. These will result in hyperperistalsis of intestine together with the passage of meconium in the amniotic fluid ***(Rosenberg et al., 2008).***

Immunity in FGR:

Impaired immunity was observed in infants with FGR as evidenced by reduced numbers of circulating T-cells non-specific lymphocytes and lower levels of immunoglobulins in the fetal than in the maternal blood ***(Raghupathy et al., 2011).***

Consequences of FGR

Short term:-

Estimated fetal weight below the 10th percentile is a leading risk factor for fetal death ***(Melamed et al., 2009).*** As birth weight decreases from the 10th percentile to the first percentile, perinatal morbidity and mortality increase markedly ***(Melamed et al., 2009).*** In term infants, the rates of low 5-minutes Apgars, severe acidemia, need for intubation in the delivery room, seizures in the first 24 hours of life, sepsis, and neonatal death increased significantly among infants at or below the third percentile for gestational age ***(Melamed et al., 2009).*** FGR is associated with substantive perinatal morbidity and mortality. Fetal demise, birth asphyxia, meconium aspiration and neonatal hypoglycemia and hypothermia are all increased ***(Zhao and Wu, 2009).***

Long term:-

The problems of the small fetus do not end at birth or soon after birth but continue well into childhood and adulthood. Studies have shown that small children have an increased rate of impaired school performance. One study described significantly higher numbers of children with late entry into secondary school and failure to pass or take the baccalaureate examination in the "small" group as compared with the control group, after controlling for maternal age, maternal educational level, parental socioeconomic status, family size, and gender ***(Selling et al., 2006).***

Another large follow-up study of 14,189 full-term infants from the United Kingdom showed that at 5, 10, and 16 years of age, individuals born with a birth weight less than the fifth percentile had small but significant deficits in academic achievement ***(Strauss, 2000).*** In the United Kingdom, a follow-up study on 2,938 men showed that those with the lowest weight at birth and at 1 year of age had the highest death rate from ischemic heart disease ***(Strauss, 2000).*** The "fetal origins" hypothesis asserts that changes in the intrauterine nutritional or endocrine environment result in permanent alterations in structure, physiology, and metabolism that predispose the affected individual to develop cardiovascular, metabolic, and endocrine disease years later ***(Lau et al., 2011).***