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ROLE OF L-ARGININE AND SILDENAFIL IN INTRA UTERINE GROWTH RESTRICTION: A CURRENT REVIEW

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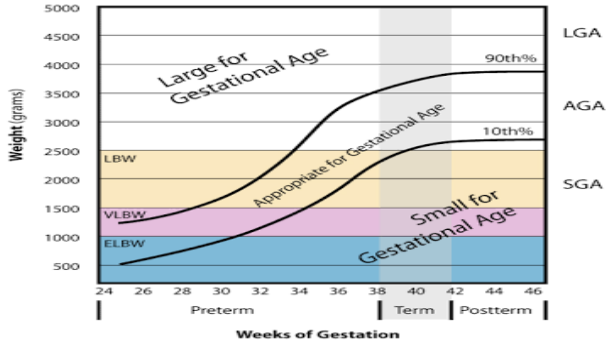
ABSTRACT
IUGR is defined as the birth weight <10 percentile for gestational age. It is the major cause of neonatal morbidity and mortality which affects 8%of pregnancy. IUGR is defined as fetus which fails to reach its normal growth potential. It is referred as fetal growth restrictions or IUGR. Growth restricted babies are often malnourished. IUGR is diagnosed by ultrasound, Doppler, amniocentesis. Several clinical trials have reported L- arginine and sildenafil citrate had effect on IUGR.

L-Arginine, a nutritionally essential amino acid is the precursor synthesis of nitric oxide. It may play a critical role in fetal nutrition oxygenation, resulting in improvement of IUGR pregnancy enhancing birth weight, decreased neonatal morbidity and mortality. Sildenafil is phosphodisterase -5 inhibitor delaying the breakdown of cGMP and enhancing NO-dependent vasodilator. It is used as potential candidate for treatment of IUGR and is also associated with fetal weight gain.

KEYWORDS: L-arginine, sildenafil citrate, intrauterine growth restriction, Birth weight, Gestational age.

INTRODUCTION
Intrauterine growth restriction (IUGR) is a condition in which an fetus is smaller than expected for the number of weeks of pregnancy (gestation age). It is often described as an estimated weight less than the 10th percentile. IUGR can begin at any time during pregnancy, with IUGR the baby does not grow well. IUGR may affect overall size of the baby and the growth of organs, tissues and cells. This can cause many problems.[1] IUGR is one of the major complications of pregnancy affecting 3-10%of all gestations.[2] It is associated with significant increase in morbidity and mortality in perinatal period and infancy. Out of 22 million small for gestation age infants in the world 21 million belongs to developing countries and India's share is substantial, around 7-10 million constituting 30%.[3]



Two standard deviations less than mean is 10%, and greater than mean is 90%. The term IUGR is frequently used or interchangeably but incorrectly with small for gestational age (SGA). IUGR is pathological or counter part of SGA. In other words IUGR is term used by obstetricians to describe a pattern of growth overtime. SGA is used by pediatricians to describe a single point on a growth curve.
The term SGA includes two types
1. Constitutionally small babies
2. IUGR patients.

Approximately 70% of the fetuses with birth weight less than 10% for gestational age are constitutionally small; in the remaining 30% the cause of IUGR is pathologic.[4]

IUGR is defined as fetus which fails to reach its normal growth potential. It is referred as fetal growth restrictions or IUGR. Constitutionally small babies are well proportioned and developmentally normal. Growth restricted babies are often malnourished or dysmorphic.

Types of iugr
1. Intrinsic iugr: is one where fetal growth restriction is caused by intra uterine infection or chromosomal abnormality.

2. Extrinsic iugr: Is one where growth failure is caused by placental or maternal abnormality.

3. Combined or idiopathic iugr: Both intrinsic and extrinsic factors about growth failure.

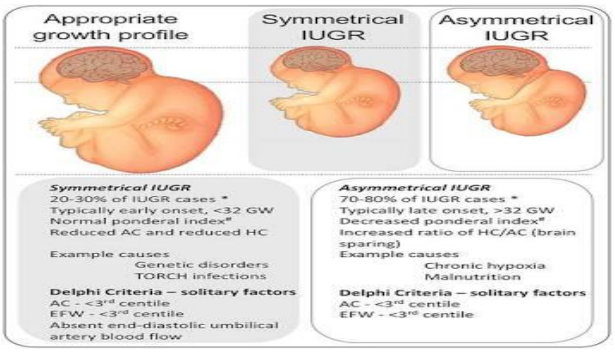
Another classification(as per the population growth charts)[5]

- Moderate : birth weight in the 3 to 10 percentile(or 5th to 10th percentile)
- Severe : birth weight less than 3 percentile(or less than 5th percentile)

Fetal growth occurs in three phases. In phase 1-between 4 to 20 weeks only hyperplasia occurs increasing DNA content, phase 2-between 20-28 weeks. Both hyperplasia and hypertrophy occurs, mytosis starts decreasing whereas cell size starts increasing. In last stage 28-40 weeks only hypertrophy occurs.

Fetuses require glucose oxygen and amino acid for growth. These substrates are derived from placenta and depend on uterine and placenta vascularity.

Fetal growth restriction can be divided into two types, symmetrical when the fetus is small but well proportioned and asymmetrical,[6,7] when the fetus's abdominal growth is restricted. Most of these are linked to placental insufficiency.[8] The human fetoplacental circulation exhibits a low vascular resistance and lacks autonomic innervations. Thus circulating and locally released vasoactive molecules are likely to be involved in control of fetoplacental hemodynamics.[9] The release of local vasoactive molecules such as nitric oxide (NO), from endothelium maintains appropriate placental blood flow, fetal nutrition and oxygenation. Nitric oxide (NO) is constitutively produced in human vein umbilical cells and platelets from conversion of L-arginine to L-citrulline by endothelial NO synthase.[10] It causes cyclic guanosine monophosphate (cGMP) mediated vascular relaxation and inhibits platelet adhesion.[11]



Delayed growth puts the baby at risk of certain health problems during pregnancy, delivery, and after birth. They include:

- Decreased oxygen level[12]
- Hypotension[13]
- Difficulty handling the stresses of vaginal delivery[12]
- Low birth weight[14]
- Type -2 diabetes[15]
- Hypercholesterolemia[16]
- Syndrome X[13]
- Low resistance to infection[12]
- Obesity[17,18]
- Parkinsonism[13]
- Ischemic heart stroke[19,20]
- Low Apgar scores (a test given immediately after birth to evaluate the newborn's physical condition and determine need for special medical care)[12]
- Meconium aspiration (inhalation of stools passed while in the uterus), which can lead to breathing problems[12]
- Trouble maintaining body temperature[12]
- Abnormally high red blood cell count[12]

In the most severe cases, IUGR can lead to stillbirth. It can also cause long-term growth problems.

Causes of Intrauterine Growth Restriction

IUGR has many possible causes. A common cause is a problem with the placenta. The placenta is the tissue that joins the mother and fetus, carrying oxygen and nutrients to the baby and permitting the release of waste products from the baby.[12] IUGR is the common end result of maternal, placental, fetal, or genetic factors, and IUGR can also result due to a combination of any of these factors. Various maternal factors such as mother age, inter-pregnancy interval (less than 6 months or 120 months or more), maternal health, behavioral habits, and maternal infection affects the growth of the fetus and are responsible for causing IUGR.[21,22]

IUGR can also occur as the result of certain health problems in the mother, such as:

- Advanced diabetes
- high blood pressure or heart disease
- Infections such as rubella, cytomegalovirus, toxoplasmosis, and syphilis
- Kidney disease or lung disease
- Malnutrition or anemia
- Sickle cell anemia
- smoking, drinking alcohol, or abusing drugs

Other possible fetal causes include chromosomal defects in the baby or multiple gestations (twins, triplets, or more).[12] IUGR commonly related to reduced uteroplacental blood flow, reduced oxygen-carrying capacity, or decreased nutrition supply to the fetus. Women at extremes of reproductive age, especially young maternal age, are at increased risk for IUGR.[22,23] Similarly advanced maternal age has been associated with low birth weight.[22,24]

Symptoms

The main symptom of IUGR is small for gestation age baby or look malnourished, thin and pale and have loose,dry skin. The umbilical cord is often thin and dull instead of thick and shiny.[12] Fetus weight less than

expected for the gestation age, decreased skeletal mass, long finger nails.[25]

Diagnosis

Doctors have many ways to estimate the size of fetus during pregnancy. One of the simple and most common method is measuring the distance from the mothers fundus(top of the uterus) to the pubic bone.[26] After 20th week of pregnancy, usually the measure in centimeters corresponds with the number of weeks of pregnancy. Lower than expected measurement may indicate IUGR.

Other test procedure to diagnose IUGR and assess the baby's health includes the following:

Ultrasound: ultrasound involves using sound waves to create picture of the baby. In ultrasound the doctor see the baby in the uterus with an instrument that is moved over the mothers abdomen. It can also used to measure the baby's head and abdomen. The doctor compares those measurements to growth charts to estimate the baby's weight. It can also used to determine how much amniotic fluid is in the uterus. A low amount of amniotic fluid could suggest IUGR.[27]

Doppler flow: Doppler flow is one of the test that uses sound waves to measure the amount and speed of blood flow through the blood vessel. This test is used to check the blood flow in the umbilical cord and vessels in the baby's brain.[28,29,30,31,32,33,34,35]

Weight checks: It is routinely used test to check mother's weight at every prenatal checkup. If a mother is not gaining weight, it could indicate a growth problem in her baby.[12]

Fetal monitoring: This test involves placing sensitive electrodes on the mother's abdomen. The electrodes are held in place by a lightweight stretchable band and attached to a monitor. The sensors measure the rate and pattern of the baby's heartbeat and display them on a monitor or print them.[36]

Amniocentesis: In this procedure, a needle is placed through the skin of the mother's abdomen and into her uterus to withdraw a small amount of amniotic fluid for testing. Tests may detect infection or some chromosomal abnormalities that could lead to IUGR.[12]

Prevention of iugr

Although IUGR can occur even when a mother is perfectly healthy, there are things mothers can do to reduce the risk of IUGR and increase the odds of a healthy pregnancy and baby.

- Keep all of your prenatal appointments. Detect problems early that allow your treatment early.
- Be aware of baby's movements. If you notice changes in baby's movement, inform your doctor immediately.
- Balanced energy protein.[37]
- Calcium supplementation.[38]
- Multiple micronutrient supplementation[39]
- Preventive strategies for malaria in pregnancy[40]
- Get plenty of rest. Rest will help you feel better and it may even help your baby grow and try to get 8 hours of sleep or more each night. An hour or 2 of rest in the afternoon is also good.
- Practice healthy lifestyle habits. If you drink alcohol, take drugs and smoke, stop for the health of baby.
- Check your medications. Sometimes a medication a mother is taking for another health problem can lead to problems with her unborn baby.

Treatment of iugr

Role of L-Arginine in Pregnancy and Fetal growth L-Arginine is a versatile amino acid with a wide range of biological functions. The "L" in the name refers to the left-handed configuration of the molecule. It serves as a precursor not only to proteins but also nitric oxide which has been identified as endothelium-derived relaxing factor. There are several proposed mechanisms by which Arginine supplementation might improve fetal growth.[41]

a. Increasing utero placental perfusion and fetal nutrient delivery by increasing local nitric oxide (NO) concentrations.
b. A second mechanism is Arginine mediated stimulation of maternal growth hormone secretion.
c. A third potential mechanism is enhancement of placental growth and development via the promotion of polyamine synthesis.
d. Arginine, in modest to high amounts, is a potent fetal insulin secretagogue, and insulin is a major anabolic hormone in the fetus.
e. Finally, Arginine has been shown to stimulate skeletal muscle protein synthesis.

Role of sildenafil

Sildenafil citrate (SC) is a phosphodiesterase-5 (PDE5) inhibitor. It acts by preventing the degradation of the second messenger cyclic guanosine 3 ′,5 ′ - monophosphate by the enzyme PDE-5. This results in increased nitric oxide production and consequent vascular smooth muscle relaxation and an increase in vasodilatation.[42] Due to its preferential vasodilatory effects on pelvic vasculature, SC is now a well-established treatment for erectile dysfunction in males[43] and this remains its most common indication for use. It has also been trialled in children.[44,45,46] and pregnant women[47,48,49] with pulmonary hypertension (PH). The vasodilatory effects of SC also manifest on uterine and myometrial vessels[50,51,52] which results in increased uterine flow[53,54] and endometrial thickening[52,55] putatively promoting an increase in fetal weight.[56] Its use in human pregnancy has largely been restricted to a few specific maternal indications, including severe PH[57-63] or preeclampsia (PET).[64,65] and as an adjunct to presumed inadequate uteroplacental perfusion[54,66] and severe early-onset fetal growth restriction (FGR).[53,67-70] This in turn has led to a current ongoing multicentre

randomised controlled trial (RCT) of SC for the treatment of severe FGR.[71] To date, the use of SC in human pregnancy has been confined to relatively small RCTs and case series and reports.

Data sources

An online database search for all relevant publications from the past 30 years was undertaken by the authors and institutional research librarian in July 2016. Databases included Scopus, PubMed, Cochrane Library, Web of Science, Embase, and Google Scholar. Keywords and MeSH terms used included: "sildenafil citrate", "Viagra®", "phosphodiesterase-5 inhibitor", "pregnancy", "labor", "preeclampsia", "hypertension", "fetal growth restriction", "pulmonary hypertension", "mode of delivery", "hypotension", "haemorrhage", "visual disturbances", "fetus", "newborn", "neonate", "Apgar", "perinatal death". All publications reporting the use of Sildenafil citrate and L-Arginine in human pregnancy with full text or abstract written in English and available electronically were collated for review.

RESULTS

15 articles were reviewed for this publication. All abstracts were screened and full text of articles were reviewed. Outcomes examined included maternal (hypotension, visual disturbances, headache, dyspepsia/epigastric pain), obstetric (mode of delivery, postpartum haemorrhage), and perinatal (gestational age at delivery, birth weight, Apgar score, acidosis at birth (cord artery pH).We concluded from this there is an increase in NO levels which subsequently resulted in increased birth weight of IUGR fetuses and prolonged gestational age and there is a decrease in neonatal morbidity. From few publications we concluded that L-Arginine and Sildenafil citrate has no effect.

Hypotension

9 studies (79 pregnancies) reported information on maternal BP. It reported significant reduction in maternal BP.

Visual disturbance

Of the 4studies (81 pregnancies) that reported on visual disturbance .Detailed 14 women affected by visual disturbance.

Headache

it is the most commonly reported maternal symptoms.

Dyspepsia and epigastric pain

There is no difference in rate of dyspepsia and eigastric pain.

Congenital abnormalities

7 publications that included 35 babies reported no congenital abnormalities.

DISCUSSION

This review summarizes the available information on IUGR in which the fetus growth is restricted in utero which remains a serious health problem; it affects not only neonatal but also adult phenotype and quality of life. It is related to increased risk of perinatal complications such as hypoxemia, low apgar score with possible negative effects on neonatal outcomes.

By supplementation of L-Arginine and sildenafil citrate to pregnant women diagnosed with IUGR there was an increase in birth weight of the baby, improved apgar score of neonates and with good perinatal outcomes. There was a reduction in NICU admission. Routine fetal surveillance in IUGR umbilical artery S/D ratio done by Doppler ultra sonography hence it determining increased resistance and monitoring of fetus. L-Arginine also improves fetal weight more in case of idiopathic IUGR or where mother is nutritionally deficient whereas sildenafil citrate is increasingly used for pulmonary hypertension in pregnancy and also improves endothelial function of women whose pregnancies are complicated by IUGR.

Hence during antenatal care all pregnant women and high risk cases should be screened to detect IUGR in earlier stages will decrease perinatal mortality and morbidity.

CONCLUSION

We concluded that sildenafil citrate improves endothelial function of myometrial vessel from women whose pregnancies are complicated by IUGR. Sildenafil citrate may offer a potential therapeutic strategy to improve uteroplacental blood flow and also increases birth weight of babies in IUGR pregnancies and we also concluded L-arginine supplementation is superior in increasing birth weight and prolonging gestational age at labor of IUGR fetus.

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