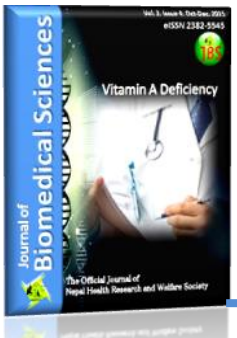

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REVIEW ARTICLE

Understanding intrauterine growth restriction (IUGR): a review

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ABSTRACT

Intrauterine Growth Restriction (IUGR) is defined as the inability of a fetus to gain the normal growth potential due to maternal-placental-fetal factors. These factors mainly involve metabolic disorders, infections, substance abuse and exposure to harmful substances. Incidence of IUGR is higher in developing countries. Proper diagnosis at suitable time is necessary for proper treatment and management. Although, the mechanism is not clear but oxidative stress, immunological factors, aryl hydrocarbon receptor and adduct formation are some pathways which are involved in IUGR. The aftermaths of IUGR involves post-birth complications, perinatal mortality and morbidity. Therefore, management and treatment involves use of both pharmacological (Tocolytics, Corticosteroids, antibiotics) and non-pharmacological methods (bed rest, cerclage). This review highlights the possible risk factors, mechanisms, other biochemical pathways involved, as well as pharmacological and non-pharmacological management of IUGR.

Keywords:
Intrauterine growth restriction, low birth weight, oxidative stress, pharmacological treatment, risk factors

Introduction:

IUGR may be termed as the inability of foetus to gain its intrinsic growth potential due to various anatomical or functional disorders and disease in maternal-placental-fetal unit. IUGR can be defined as a condition in which foetus weight is found to be below 10^{th} percentile for its gestational age and below 2.5^{th} percentile for abdominal circumference [1]. The term IUGR and short for gestation age (SGA) are often used as synonyms to each other with a subtle difference between them. In developing nations, like India, IUGR babies having low birth weight are born pre-term (>37 week of gestation) with only 6.7% born prematurely. IUGR has been categorized into two types, depending on pattern of growth restricted. IUGR or SGA has been classified as - symmetric and asymmetric.

In symmetric IUGR, foetus develops very slowly throughout the entire period of pregnancy and affected from a very early stage. In symmetric IUGR, length, head circumference and weight is low, which usually results from process originating early in pregnancies [2-3].

In asymmetric IUGR**,** foetus grows normally in the first-two semesters but encounters difficulties in the third trimester. Nutritional deficiency and altered utero-placental functions are usually related with asymmetric IUGR [4]. Muscle growth, glycogen levels and body fat also gets limited with a slight decrease in energy substrate levels [5]. Growth of bones and therefore fetal length are less affected whereas cardiac output redistribution results in preferential substrate delivery to the brain [6-7].

Epidemiology

In United States, IUGR occurs in about 5-8% of live births and about 2% of term births. Gestation period can be measured as a continuous variable, and pregnancies generally considered as full term at 40 weeks after the last menstrual period (LMP). About 30% of babies born in India have low birth weight [8-9]. The prevalence and incidence of IUGR is inversely related with gestational age and variation occurs between different populations, countries, races. Incidences rates of IUGR is higher in developing countries which may be due to deliveries occurring at homes are mostly low birth weight (LBW).

Diagnosis of IUGR

It can be done by proper ultrasound as well as by calculating first day of the last menstrual period (LMP). Gestation age plays a crucial role while diagnosing IUGR. After calculating gestation period, appropriate methods for diagnosing IUGR involve Doppler Ultrasonography. Correlation between USG measurements and gestational age; Fundal height that donot coincide with gestational age. Ultrasound biometry has been used as the standard method for assessing fetal growth. Amniotic fluid index, altered biparietal diameter, head circumference, abdominal circumference and femur length are some parameters used for proper diagnosing IUGR.

Risk Factors

IUGR is a manifestation of fetal, maternal and placental disorders that affect fetal growth. Perinatal morbidity and mortality depend on the degree or severity of IUGR *i.e.* small foetus is more vulnerable than larger (Table 1).

Table 1 - Risk factors affecting IUGR

Maternal Factors	Diabetes, hypertension, chronic renal disease,
	urinary tract infections, malaria, tuberculosis,
	Poor maternal nutrition, starvation during pregnancy, maternal calorie deficiency, Phenylketonuria, unexplained elevated maternal alpha-fetoprotein level,
	Alcohol, tobacco, cigarette, drugs *etc.*
	Polycyclic Aromatic Hydrocarbons (PAHs), Pesticides, Phthalates,
	Multiple pregnancies, improper care, pregnancies at earlier age
	Low Socioeconomic Status
	People residing at high Altitudes
Foetal Factors	Russell-silver syndrome and Bloom Syndrome, Multiple Gestation
	Karyotopic disorders such as trisomy 13 and 18, Uniparenteraldisomy, Ring chromosomes, Triploidy, Turner's syndrome
	Cytomegalovirus, Toxoplasmosis, Rubella, Herpes, Systematous Lupus Erythematous
Placental Factors	altered nutritional and respiratory supply, Altered Uteroplacental Vasculature, Preeclampsia, Placentae Accretia,
	Abruptio Placentae, Placenta previa, infarctions, Circumvallate placenta, Syncytial knots, Placental Hemangioma, multiple gestation

Maternal factors associated with IUGR involves chronic diseases such as cardiovascular disease, diabetes, hypertension, chronic renal diseases [10-14]. About 3-fold perinatal mortality was seen for hypertensive mothers as compared to normotensive IUGR mothers. Metabolic syndromes such as poor maternal nutrition, starvation during pregnancy, phenylketonuria also contributes towards occurrence of IUGR. Maternal calorie deficiencies, low protein diet, diabetes, hypertension are also associated with IUGR [15]. Multiple pregnancies, improper care, pregnancies at earlier age contribute towards IUGR. Substance abuse such as alcohol, cigarette, tobacco *etc.* increases the risk of IUGR deliveries. Various drugs such as warfarin, antineoplastic agents, steroids, antimetabolites, anticonvulsants and folic acid antagonists are also responsible. Low socio-economic status,

exposure to numerous chemicals and pollutants such as pesticides, polycyclic aromatic hydrocarbons, particulate matter, phthalates are also various factors associated with incidence of IUGR. Pregnancy in high altitude is also prone towards IUGR due to lack of oxygen supply to the developing foetus [16-18].

IUGR results in altered infant growth with higher risks of mortality, morbidity, impaired mental development and the risk of chronic adult disease [19-21]. Various infections during pre-natal such as cytomegalovirus, rubella, herpes, toxoplasmosis, system lupus erythematous, anti-phospholipid syndrome, urinary tract infections, malaria, tuberculosis also contribute heavily towards IUGR etiology. Such infection carries about 5-15% of the total burden of IUGR.

Placental factors- imbalanced/altered nutritional and respiratory supply to the placenta results in reduced growth of developing fetus and hence results in IUGR complications. Placental factors responsible for IUGR are altered utero-placental vasculature, preeclampsia, abruptio placentae, infarctions, circumvallate placenta, placenta previa, syncytial knots, placental hemangioma, infections as well as multiple gestation [22-23]. Fetal factors involve infections such as cytomegalovirus, toxoplasmosis, Rubella, Herpes and Bloom syndrome, multiple gestation, karyotopic disorders, ring chromosomes [24-25].

Development of central nervous system during pregnancy is mediated by levels of thyroid hormone present [26]. Placental growth and functioning is regulated by thyroid hormone in synergism with epidermal growth factor (EGF) [27-28]. Earlier studies reported stimulation of trophoblastic endocrine function along with enhanced production of human chorionic gonadotropin and human placental lactogen. In IUGR, altered thyroid hormone action results in reduced placental weight and altered placental morphology. Moreover, enhanced binding of T3 to thyroid receptor in trophoblastic cells results in decrease in amount of T3 for efflux to fetal circulation and thus, further contribute to decreased thyroid hormone levels in IUGR fetuses [29]. Estradiol is one of the main estrogen produced by female ovary and placenta, and in adrenal glands and male testes in smaller amount [30]. Placenta is one of the major source of circulating estradiol [31]. Estradiol concentration during follicular phase is less than 0.1 ng/ml which reach about 0.4 ng/ml during luteal phase and about 6-30ng/ml during conception [32]. About 98% of the estradiol bounds to sex hormone binding globulin (SHBG) and the remaining binds to serum protein, albumin. Estriol (E3) is another estrogen which acts as an index used to associate with occurrence of IUGR. Moreover, it has been suggested that decreased estriol levels are associated with placental or fetal pathological condition [33]. Women with complication of IUGR contain less than half the normal levels of estriol. Another study concluded altered adrenocortical function and reduced estriol levels in IUGR infants [34]. It has been suggested that E2 and E3 levels are normally restored in normal pregnancies but in IUGR, E2 levels get decreased which indicate decreased placental functioning [35].

Progesterone is a potent vasodilator as well as muscle relaxant and its concentration increases with pregnancy. It is secreted by corpus luteum in ovary and is produced via steroid precursors in testes, adrenal cortex, placenta as well as ovary. Although, IUGR is a multi-factorial complication, some studies favours the evidence about occurrence of IUGR with decreased progesterone levels as well as reduced placental lactogen [36].

Altered maternal endocrine status including reduced levels of progesterone is associated with IUGR [37]. However, there is lack of knowledge regarding impact of progesterone on pregnancy outcomes. More information is required regarding formulation, dosage forms, routes of administration (oral vs IM vs vaginal).

Pathophysiology

Oxidative stress: Oxygen and carbondioxide are exchanged through feto-maternal barrier, placental epithelial layer via diffusion. Transfer of gases depends on rate of uterine and umbilical blood flow, haemoglobin-oxygen binding capacity, placental surface as well as permeability. However, excessive reactive oxygen species (ROS) can cause cellular damage and impact tissue function as a result of lipid peroxidation, protein and amino acid modifications and DNA oxidation which corresponds to extravillous trophoblast invasion and reduce the development of placental vasculature. It leads to placental insufficiency, which results in decreased exchange of nutrients and wastes between maternal and fetal circulations. Vessel instability, angiogenesis and vessel remodelling results due to shift towards angiopoietin-2 in angiopoietin-1:angiopoietin-2 ratio due to hypoxia [38]. Due to inadequate trophoblast invasion, remodelling of uterine vasculature into spiral arteries is deficient in IUGR pregnancies [39-40]. This results in altered flow rate of maternal blood which further causes damage to the placental villi and harming transport as well as endocrine function of placenta.

Immunologic Factors: Maternal immunological factors such as cytokines, macrophages, lymphocytes and natural killer cells (NK cells) have been showed to be associated with IUGR. Cytokines plays a vital role in the maintenance of normal pregnancy through placental growth as well as modulation of maternal immunological response to prevent conceptus rejection [41]. T helper-1 (Th-1) and T helper-2 (Th-2) cytokine cells are the two of the major subsets of CD4+ T-helper cells.

Th-1 cells secretes various proinflammatory cytokines IL-2, IFN-y, TNF-à and TNF-ß; which further activates macrophages and various cell- mediated reactions and delayed hypersensitivity [42]. However, Th-2 cells predominantly appears to cause IUGR. Higher levels of TNF-à causes IUGR by decreasing amino acid uptake by fetus as well as enhanced vasoconstriction of placental vascular beds, inhibits growth of trophoblast [43-44]. However most likely pathophysiological mechanism of TNF-à

involves apoptosis of trophoblast layer which leads to abnormal placentation, inadequate spiral artery remodelling as well as uteroplacental insufficiency [45].

Aryl Hydrocarbon Receptor pathway: The AhR-ARNT complex binds AhR/dioxin/xenobiotic response elements (AREs/DREs/XREs), activates the transcription of cellular detoxification machinery. This AhR is localized to fetal endothelium, allantoic as well as viteline vessel. AhR also interacts with hypoxia-induced factors HIF-1à. This result in restricted oxygen supply to the fetus. Activated AhR elevates CYP1A1 activity which has been correlated with LBW, premature birth, morbidity and mortality.

Adduct formation: PAH-DNA adducts were found in cytotrophoblasts as well as syncytiotrophoblasts of the placenta lining the chorionic villi, which reach into the maternal blood [18]. Studies have revealed alterations in maternal intervillous spaces and fetal capillary volume and surface area in IUGR placenta which results in altered blood flow in both the uterine and umbilical placental circulations, based on Doppler studies [46-51]. Maternal exposure has been associated with reduced syncytiotrophoblast apoptosis and trophoblast hyperplasia within trophoblast compartment [51-52].

Treatment: Pharmacological management

Although use of medicine does not show any therapeutic improvement in IUGR but still their use is rate limiting. Some of the pharmacological medications used in IUGR are:

Antenatal corticosteroids: They speed up the development of fetal organs within the mother. They help in enhancing the growth of lungs. Dexamethasone and betamethasone are the main corticosteroids used to treat IUGR. Administration of corticosteroids produces a considerable reduction in respiratory distress, cerebroventricular haemorrhage, necrotizing enterocolitis. Repeated doses of corticosteroids are administered for preventing neonatal respiratory disorder. However, main issues regarding administration of corticosteroidal therapy is the difficulties in identifying women at risk of preterm deliveries in time to administer corticosteroids [32, 53].

Antibiotics: IUGR is often manifested by presence of various bacterial infections such as cytomegalovirus. Proposed pathophysiological mechanism of these infections involves transplacental blood-borne infection, activation of cytokines and infection to placenta. Antibiotics like broad spectrum (ampicillin-sulbactam), narrow spectrum (ampicillin), macrolide antibiotics (erythromycin, azithromycin), ceftriaxone, clindamycin and erythromycin are some of the useful antibiotics used for the management. Administration of ampicillin and erythromycin following use of amoxicillin showed term to prolonged pregnancy and helpful in reducing infections and morbidities [54]. Tocolytics are the medicines which acts by slowing down as well as stopping the labour contractions; helps in prolonging pregnancy allowing other interventions such as administration of corticosteroids to further reduce risk of preterm delivery as well as IUGR. Drugs involved in this class are-

Betamimetics: Terbutaline is the main β2-adrenergic agonists. Other agents involve albuterol, fenoterol, nylidrin, metaproterenol and orciprenaline [55]. Betamimetics decreases intracellular calcium levels which reduces myometrial contractility. However, decreased level of β2 receptors result in desensitization (tachyphylaxis), which favours short duration of action of these agents [56].

Calcium Channel Blockers: Nifedipine and Nicardipine are the two main calcium channel blockers used during pregnancy. They acts by inhibiting calcium influx into myometrial cells. Lower calcium concentration results in activation of myosin light chain kinase and thereby myometrium contraction [57].

Magnesium sulphate: Magnesium sulphate has been used as main tocolytic agent since long times. Possible mechanism of action involves competition with calcium ions at plasma membrane voltage-gated channels and /or at motor end plates. Inhibition of calcium at motor end plate prevents release of acetylcholine into synaptic cleft as well as transmission of excitation. Calcium inhibition at plasma membrane voltage-gated channels inhibits influx of calcium intracellularly, further activation of myosin light chain kinase and therefore, myometrial contractility [58].

Oxytocin receptor blockers: Atosiban is used as drug of choice in this category. Possible mechanism of action of this class is same as that of β2-agonist. This is done by blockage of oxytocin receptors, inhibiting oxytocin-induced conversion of phosphatidylinositol to inositol triphosphate and release of calcium into the cytoplasm [59].

Prostaglandin Inhibitors: Indomethacin is used as PGs analogue achieving its effects by reversibly binding to COX. Prostaglandins are formed from sequential oxidation of arachiodonic acid via COX or PG synthase. These enhance formation of myometrial gap junctions by affecting uterine muscle contractions which results in increased calcium levels and thus amplifying activation of myosin light chain kinase [32].

Non- Pharmacological methods:

Proper Diet: Proper food habits have a direct effect on development of foetus as well as mother. Improper food habits results in malnutrition which further leads to poor development of foetus into the womb. This may result into preterm deliveries, IUGR, neonatal mortality and morbidity. Therefore it is necessary to provide proper diet as well as proper nutrition to the developing foetus.

Cerclage: It refers to the stitch in cervix which may help in keeping cervix closed and preventing early birth of fetus. This stitch gets removed by end of 37th weeks of gestation. Cerclage is used by keeping safety parameters in mind regarding the susceptibility, adverse effects or any other reactions. Although, it is the least effective method used.

Bed rest: Although Bed rest does not seem any huge impact on IUGR, but it helps in keeping patient calm and preventing high muscle contractions during pregnancy which may help in prolonging pregnancy.

Conclusion

As the understanding of etiology of IUGR is still an enigma, successful approach towards proper diagnosis, awareness, treatment and management can acts as main stay for reducing prevalence of IUGR all over the globe. More emphasis should be laid on risk factors associated with IUGR. The main aim of drugs should be to reduce perinatal mortality as well as morbidity. Substance abuse should be avoided for proper health care. Various Biomonitoring studies using placenta, cord blood, maternal blood should be done in order to examine the toxicity and role of various toxicants in IUGR. There is a need for clear vision about the numerous factors and mechanisms resulting in IUGR. Moreover, new methods, drugs and techniques should be explored for better management of IUGR patients. Summarizing, the common liaison between patient, caretakers and doctors helps a lot in fighting against IUGR.

Study limitations & future scope

This review article has limited information regarding the possible etiology, probable mechanisms as well as treatment of this disease. Vast understanding of the topic is required involving the animal models, mechanism, cellular and molecular levels, enzymes involved and more possible drugs for the management of IUGR. Newer methods need to be explored for diagnosing and managing IUGR. Since more emphasis has been laid on pharmacological management of IUGR, less has been evidenced about Non-Pharmacological therapy. However, increased incidences of side-effects or adverse effects were seen due to Pharmacological therapy. Therefore, newer non-pharmacological methods should be explored and used.

Competing interests

None declared.

Authors' contribution

Verma P and Chaudhary H searched the literature, drafted the manuscript, revised and corrected. Final manuscript was approved by both authors for publication.

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