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Postnatal Complications of Intrauterine Growth Restriction

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Abstract

Intrauterine growth restriction (IUGR) is defined as a velocity of fetal growth less than the normal fetus growth potential because of maternal, placental, fetal or genetic cause. This is an important cause of fetal and neonatal morbidity and mortality. Small for gestational age (SGA) is defined when birth weight is less than two standard deviations below the mean or less than 10th percentile for a specific population and gestational age. Usually IUGR and SGA are used interchangeably, but there exists subtle difference between the two terms. IUGR infants have both acute and long term complications and need regular follow up. This review will cover various postnatal aspects of IUGR.

Keywords: Intrauterine growth restriction; Small for gestational age; Placental genes; Maternal genes; Fetal genes; Developmental origin of health and disease; Barker hypothesis

Introduction

Intrauterine growth restriction (IUGR) is defined as a velocity of fetal growth less than the normal fetus growth potential for a specific neonate as per the race and gender. IUGR is deviation from the normal or expected fetal growth pattern and the term is applied for neonates having features of malnutrition and in-utero growth retardation at birth. Small for gestational age (SGA) is defined as birth weight being less than two standard deviations (2SD) below the mean or less than 10th percentile as per specific population and gestational age norms. Small for gestational age has been further classified into moderate SGA (defined as SGA with birth weight from 3rd percentile to less than 10th percentile) and severe SGA (defined as birth weight less than 3rd percentile) [1]. The "normal" neonate has been defined as new-born with birth weight from 10th percentile to 90th percentile as per the gestational age, gender and race with no clinical features of malnutrition and IUGR. The IUGR and SGA have been used in-place of each other but there exists subtle difference between the two and in this review article IUGR and SGA have been used interchangeably. The infants who are appropriate for gestational age (AGA) as per birth weight can be IUGR, provided they have clinical features of in-utero growth retardation and malnutrition at birth [2]. In this review article we have covered postnatal aspects of IUGR in brief and details on IUGR can be read from other excellent review articles of the author [3–5].

There is high incidence of IUGR in developing countries when compared to developed countries and the main burden of these infants in decreasing order is seen in Asia, Africa and Latin America continent [6].

Types of IUGR

There are three types of IUGR: Asymmetrical IUGR (Malnourished babies), Symmetrical IUGR (Hypoplastic small for date) and Mixed IUGR (Table 1). Mixed IUGR are seen usually in developing countries and they have both decrease in cell number and cell size. This category of IUGR have clinical features of both symmetrical and asymmetrical IUGR and this type results when symmetrical IUGR is affected in third trimester due to placental causes [7].

Causes of IUGR

The intrauterine growth restriction can be result of maternal, placental, fetal, or genetic causes and can also result due to combination of any of these factors (Figure 1 and Tables 2-5) [3,8-12].

Postnatal Diagnosis of IUGR

The diagnosis of IUGR infant postnatally can be done by clinical examination (Figure 2), anthropometry [13-15], Ponderal Index (PI=[weight (in gram) × 100] ÷ [length (in cm) 3]) [2,16], Clinical assessment of nutrition (CAN) score [17], Cephalization index [18], mid-arm circumference and mid-arm/head circumference ratios (Kanawati and McLaren's Index) [19]. The gestational age assessment of

Characteristics	Symmetrical IUGR	Asymmetrical IUGR
Period of insult	Earlier gestation	Later gestation
Incidence of total IUGR cases	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

Table 1: Features of symmetrical and asymmetrical IUGR.

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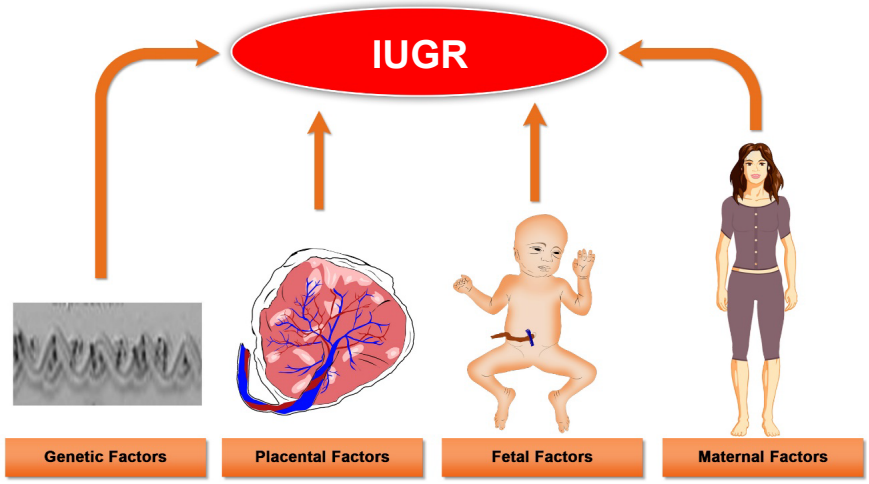

Figure 1: IUGR can be the result of maternal, fetal, placental, genetic cause or can be combination of either of the combination.

- Maternal age (less than 16 years and more than 35 years)
- High altitude and maternal hypoxia
- Low socioeconomic status and developing country
- Ethnicity or race
- Maternal substance abuse (smoking both active and passive, alcohol, illicit drugs like marijuana or cocaine)
- Maternal medication (warfarin, steroids, anticonvulsants, antineoplastic agents, anti-metabolite, and folic acid antagonists)
- Moderate to heavy physical work
- Maternal pre-pregnancy height and weight (BMI less than 20, weight less than 45 kg or more than 75 kg)
- Parity (none or more than 5 birth)
- Inter pregnancy interval (less than 6 months or 120 months or more)
- Previous delivery of a SGA newborn
- Assisted reproductive technologies (ART)
- Pregnancy poor medical care
- Pregnancy severe maternal starvation.
- Pregnancy poor weight gain
- Maternal Bronchial asthma, cyanotic congenital heart diseases
- Hematologic and immunologic disorders (Acquired thrombophilias, such as anti-cardiolipin antibodies and lupus anticoagulant)
- Maternal medical disorders (hypertensive disorders (gestational and non-gestational), diabetes associated with vasculopathy, chronic renal disease, systemic lupus erythematosus, antiphospholipid syndrome, sickle cell disease
- Pathological conditions in pregnancy like preeclampsia and diabetes associated with vasculopathy
- Maternal infection and parasite infestations (TORCH, malaria, tuberculosis, urinary tract infections and bacterial vaginosis)

Table 2: Maternal causes for intrauterine growth restriction.

- Placental weight (weight less than 350 g)
- Abnormal uteroplacental vasculature
- Placental dysfunction (PIH, pre-eclampsia)
- Thrombophilia-related uteroplacental pathology
- Confined placental mosaicism (CPM)
- Avascular villi
- Decidual or spiral artery arteritis
- Multiple infarctions
- Partial molar pregnancy
- Syncytial knots
- Chronic inflammatory lesions
- Single umbilical artery
- Abruptio placenta
- Velamentous cord
- Placental hemangioma
- Placental infections (Placental malaria)
- Infectious villitis
- Multiple gestation
- Chronic villitis of unknown etiology (CVUE)
- Reduced expression of enzymes for redox regulation (thioredoxin, glutaredoxin)

Table 3: Placental causes for intrauterine growth restriction.

IUGR neonates is not accurate as physical component are underscored/over scored and neurological component are unaffected [20,21].

Short and Long Term Complications

These IUGR neonates face numerous short term complications after birth and includes perinatal asphyxia, meconium aspiration syndrome (MAS), persistent pulmonary hypertension (PPHN), hypothermia, hypoglycemia, hyperglycaemia, hypocalcaemia, polycythaemia, jaundice, feeding difficulties, feed intolerance, necrotizing enterocolitis (NEC), late onset sepsis (LOS), and pulmonary haemorrhage (Figure 3 and Table 6) [4,21]. These IUGR infants need long term follow up as they are prone to develop many complications when they become adult like poor physical growth and small height in adulthood. The IUGR infants because of in-utero epigenetic modifications are more likely to develop "Developmental origin of health and diseases (DoHaD)" in their adolescence and adulthood (Figure 4). These infants can also develop subtle to major cognitive and neurodevelopmental abnormalities. The common neurological problems encountered in these children includes [22–25]:

- Lower scores on cognitive testing
- School difficulties or requirement of special education
- Gross motor and minor neurologic dysfunction
- Behavioural problems (attention deficit hyperactivity syndrome)
- Growth failure

Fetal factors for intrauterine growth restriction
• Constitutional small (50–70% of SGA fetuses, with fetal growth appropriate for maternal size and ethnicity) • Chromosomal abnormalities [(trisomies 13, 18, 21), autosomal deletions, ring chromosomes and uniparental disomy] • Genetic syndromes (Bloom syndrome, Russell-Silver syndrome, Cornelia de Lange syndrome, Brachmann–de Lange syndrome, Mulibrey Nanism syndrome, Rubenstein–Taybi syndrome, Dubowitz syndrome, Seckel syndrome, Johanson–Blizzard syndrome, Fanconi syndrome, Roberts syndrome, and De Sanctis–Cacchione syndrome) • Major congenital anomalies (Tracheo-esophageal fistula, congenital heart disease, congenital diaphragmatic hernia, abdominal wall defects such as omphalocele and gastrochisis, neural tube defect like anencephaly and anorectal malformation) • Multiple gestation • Congenital infections (TORCH, Malaria, congenital HIV infection, syphilis) • Metabolic disorders (agenesis of pancreas, congenital absence of islets of Langerhans, congenital lipodystrophy, galactosemia, generalized gangliosidosis type I, hypophosphatasia, I-cell disease, Leprechaunism, fetal phenylketonuria, transient neonatal diabetes mellitus)

Table 4: Fetal factors for intrauterine growth restriction.

Genetic factors for intrauterine growth restriction
• **Placental Genes:** Placental 11B-Hydroxysteroid Dehydrogenase Type 2 mRNA reduced activity, Placental growth factor (PlGF) under-expression, SERPINA3 upregulation, Homeobox (DLX3, DLX4, MSX2 and GAX, ESX1L, HLX1) under-expression, Cullin (CUL4B and CUL7), STOX1, NEAT1 (Nuclear Paraspeckle Assembly Transcript 1) over-expression, Trophoblastic miRNAs (micro RNA) (miRNA-424 and miRNA- 141) over-expression, Anti-apoptosis Bcl-2 under-expression, Placental Insulin-like growth factor 1 (IGF1) under-expression, Placental Insulin-like growth factor 2 (IGF2) over-expression, Insulin like growth factor binding protein (IGFBP)-3 over-expression, Epidermal growth factor (EGF) under-expression • **Maternal Genes:** Endothelin-1 (ET-1) over-expression, Leptin under-expression, Visfatin over-expression, Thrombophilia genes (factor V G1691A or factor II A (20210)) mutation, higher level Soluble vascular cellular adhesion molecule-1 (sVCAM-1), higher level Soluble E-selectin (sE-selectin), higher maternal serum and neonatal umbilical cord Asymmetric dimethylarginine (ADMA) levels • **Fetal Genes:** High urinary Protein S100B, Genetic deletion of IGF1 (Insulin Like growth factor 1) and SHOX, Insulin-like growth factors 1 receptor (IGF-1R) mutation leading to decreased IGF-I-receptor function, N-terminal parathyroid hormone-related protein under-expression, Low Nitric Oxide

Table 5: Genetic factors for intrauterine growth restriction.

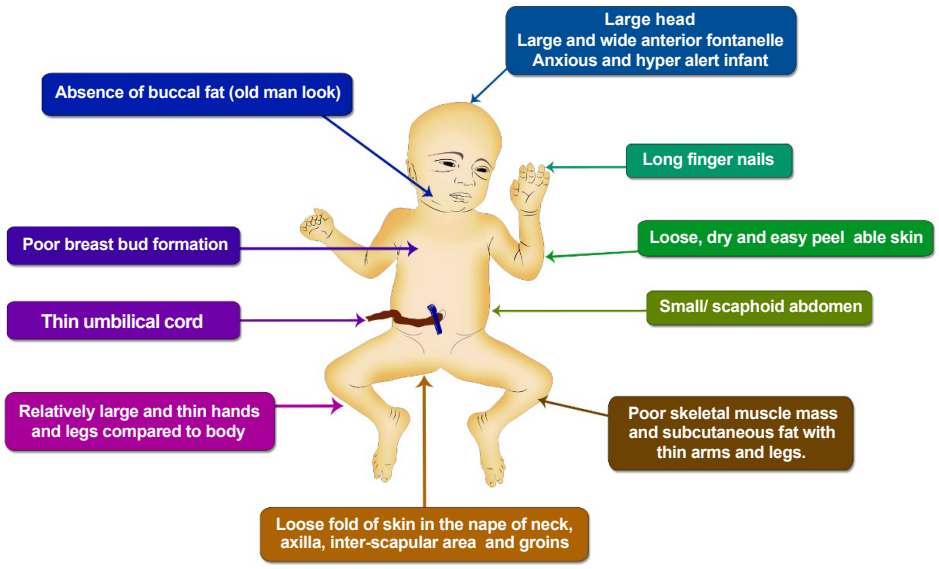

Figure 2: Clinical features of infants at birth that are having intrauterine growth restriction.

- Lower strength and work capacity
- Cerebral Palsy
- Low social competence
- Poor academic performance
- Lower Intelligence
- Hyperactive behaviour
- Poor perceptual performance
- Poor visuo-motor perception, motor incompetence, reading and mathematics learning

Developmental Origin of Health and Disease (Dohad)

Barker showed that infants born in the 1920s and 1930s with low weight, when became adult had high prevalence of syndrome X, coronary heart disease, diabetes mellitus, hyperinsulinemia and hypercholesterolemia [26–28]. This was known as Fetal Origin of Adult Disease (FOAD), and recently this term FOAD has been replaced with "Developmental origin of health and disease (DoHaD)" [29]. The three different hypothesis purposed for this causal relationship are Fetal Insulin Hypothesis and MODY Genes [30], thrifty genotype [31,32] and thrifty phenotype (Barker Hypothesis). The Barker Hypothesis is the most accepted theory for DoHaD [33]. These IUGR infants are more develop number of adult disease in their lifetime [34] (Table 7 and Figure 5).

Thrifty Phenotype (Barker Hypothesis)

Barker hypothesis states that fetal life environment has long term effect on the postnatal life [35]. According to this theory when fetus

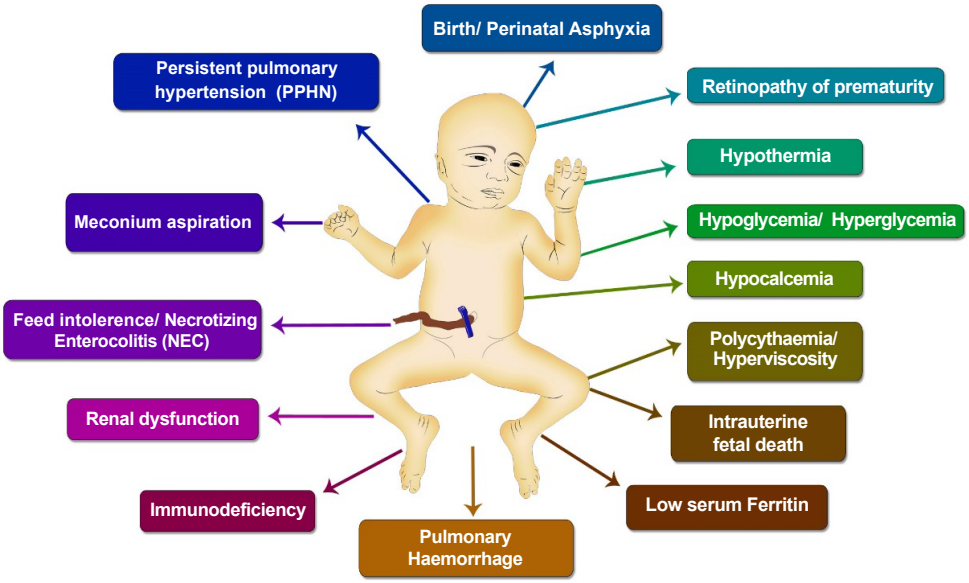

Figure 3: Short term neonatal complications seen in intrauterine growth restricted neonates.

	Immediate Complications of Intrauterine Growth Restricted Newborn	
Morbidity	**Pathogenesis/Pathophysiology**	**Prevention/Treatment**
Intrauterine fetal death	Usually result of Placental insufficiency causing chronic hypoxia Fetal congenital malformation Maternal and fetal infection Sentinel events like Abruptio placentae, cord rupture or prolapse Placental infarcts and preeclampsia	Needs regular antepartum and intrapartum monitoring with planned delivery Plan delivery in case of severe/worsening fetal distress in tertiary care level center
Neonatal Mortality	Antepartum, intrapartum and postpartum neonatal insults Contributed by other neonatal morbidities	Tertiary level neonatal care
Perinatal/Neonatal Asphyxia	Chronic fetal hypoxia superadded with acute fetal hypoxia Acute sentinel event like Abruptio placentae, cord rupture or prolapse Placental abnormalities leading to insufficiency Pre-eclampsia/eclampsia	Needs regular Antepartum and Intrapartum surveillance Regular fetal growth monitoring by USG and plotting on customized growth chart Early detection of IUGR/SGA Regular Biophysical profile (BPP) Delivery at appropriate time and place having appropriate neonatal facilities Delivery attended by person skilled in neonatal resuscitation
Hypothermia	Poor thermoregulation mechanism Increased surface area with large head Poor subcutaneous and body fat leading to less thermogenesis and lower insulation Less brown fat Deficiency of catecholamine in body Increased insensible water loss through skin Other associated neonatal morbidities like Hypoglycemia and Hypoxia	Warm delivery room with temperature around 26 to 28°C Using cling wrap, heated mattress and warm humidified gases in delivery room Protect heat loss by radiation, conduction, convection and evaporation. Maintain thermo-neutral temperature in nursery Early breastfeeding Rooming in with mother/ Warm Transport Early skin to skin contact in delivery room
Hypoglycemia	Poor glycogen stores of liver and muscles Poor other alternative energy source like ketones Decreased fat (adipose tissue) Decreased ability to oxidize free fatty acids and triglycerides for gluconeogenesis Poor gluconeogenesis and glycogenesis Decreased production of glucose Low level counter-regulatory hormones like epinephrine and glucagon Secondary to other associated comorbidities including polycythaemia, hypoxia, hypothermia Heightened insulin receptors sensitivity	Monitoring Blood sugar for initial 48-72 h of post-natal life as per the protocol Early breast feeding within one hour of birth and if required formula supplementation Intravenous glucose when sugar is less than 25 mg/dl or symptomatic neonate
Hyperglycaemia	Low insulin production secondary to immature pancreas Insulin resistance Too much exogenous glucose infusion Increased epinephrine and glucagon level	Sugar monitoring as per protocol Avoid high glucose concentration administration Treatment of symptomatic hyperglycaemia with infusion titration and insulin
Hypocalcemia	Decreased transfer of calcium in-utero Secondary to hypophosphatemia induced by chronic hypoxia. Immaturity of parathyroid glands	Calcium supplementation Monitoring of calcium levels

Polycythaemia/ Hyperviscosity/ Leukoneutropenia	Placental insufficiency causes chronic intra-uterine hypoxia that leads to high fetal erythropoietin Transfusion of blood from mother to foetus	Monitor haematocrit at 2, 12 and 24 h after birth Regular feeding Prevent excessive postnatal weight loss Fluid supplementation and partial exchange transfusion if symptomatic
Persistent pulmonary hypertension (PPHN)	Abnormal of pulmonary vasculature with thickened tunica media up-to intra-acinar arteries as result of chronic in-utero hypoxia Other associated morbidities like birth asphyxia, hypoglycemia, hypothermia, hypocalcemia, polycythaemia, hypoglycemia and sepsis	Avoid hypoxia and hyperoxia Normalization of metabolic milieu Cardiovascular support Selective and non-selective pulmonary vasodilator Mechanical ventilation if required
Pulmonary Haemorrhage	Abnormal pulmonary vasculature Other associated co-morbidities like hypothermia, polycythaemia, asphyxia and neonatal sepsis	Gentle ventilation Management of co-morbidities Supportive care for pulmonary hemorrhage
Meconium aspiration	Chronic in-utero hypoxia Intrapartum hypoxia secondary to any sentinel event	Regular monitoring during intrapartum for meconium passage No role of amnio-infusion for prevention of meconium aspiration syndrome (MAS) Resuscitation as per the NRP 2015 guidelines Establish regular respiration. No need role of tracheal suctioning for both vigorous/ depressed newborns born with meconium stained liquor
Bronchopulmonary dysplasia (BPD)	Antenatal hits to fetal lung like chorioamnionitis, fetal infection and preeclampsia Abnormal pulmonary vasculature Post-natal insults to neonatal lungs like ventilation, hypoxia, hyperoxia, neonatal sepsis and Patent ductus arteriosus	Antibiotics to mother in case of chorioamnionitis Gentle ventilation Preventing hypoxia, hyperoxia, and neonatal sepsis
Feed intolerance/ Necrotizing enterocolitis (NEC)	Decreased intestinal perfusion secondary to redistribution of blood to vital organ in response to chronic hypoxia Focal intestinal ischemia Poor motility	Minimal enteral nutrition to be given Protocolised increase in daily feeds Cautious start of enteral feeding Use of probiotics and lactoferrin Use only breast milk (either owns mothers milk or donor milk) Supportive treatment in case of development of NEC
Renal Problems	Chronic in-utero hypoxia and perinatal asphyxia leads to renal tubular injury	Cardiovascular support Maintain adequate renal perfusion
Immunodeficiency	Chronic in-utero and post-natal malnutrition Congenital infection Reduced number of T and B lymphocytes Poor immunological maturity	Early, aggressive and optimal nutrition Promoting breast feeding Prevention of neonatal sepsis
Retinopathy of prematurity (ROP)	Intrauterine hypoxia Altered levels of growth factors Diminished antioxidant capacity Post-natal insults like hyperoxia, hypoxia, and sepsis	Targeted saturation (90-95%) ROP screening of susceptible Treatment if required
Ferritin	Low levels Defective transport through placenta Increased premature delivery	

Table 6: Immediate complications of intrauterine growth restricted new-born.

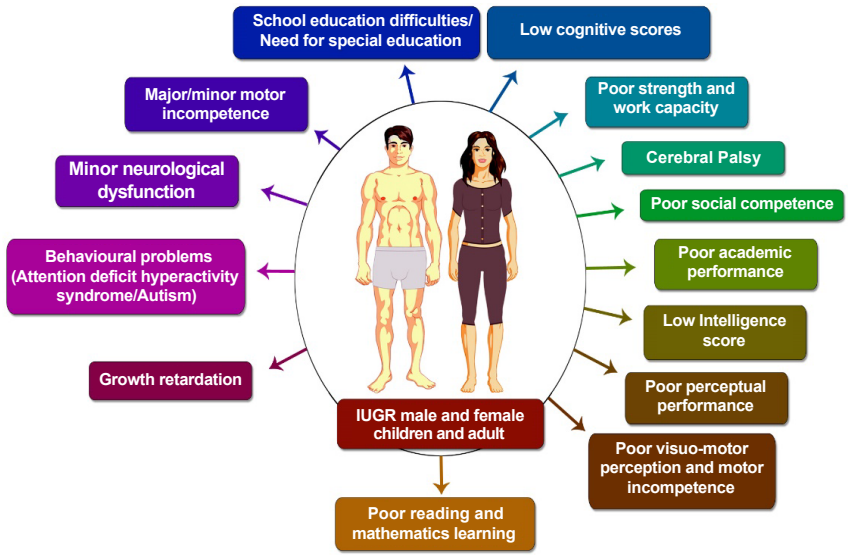

Figure 4: Increased risk for various physical and neurodevelopmental problems in intrauterine growth restricted neonates when they reach their childhood and adulthood.

	Various "developmental origin of health and diseases (DoHaD)" seen in IUGR neonates in adulthood.
• Hypertension • Ischemic Heart disease/Stroke • Type 2 diabetes • Kidney disease • Liver disease • Hypercholesterolemia • Metabolic syndrome X • Obesity • Lung abnormalities- reactive airways disease • Cancer- breast, ovarian, colon, lung, blood • Schizophrenia/Parkinsonism • Alzheimer disease • Polycystic ovarian syndrome, premature pubarche • Shortened life span • Depression, anxiety, bipolar disorder • Immune dysfunction • Osteoporosis • Social problems • Poor cognitive performance	

Table 7: Immediate complications of intrauterine growth restricted new-born.

is faced with adverse conditions in-utero, the reason being maternal, placental or fetal, than the fetus undergoes various adaptations to survive in these adverse conditions. The various adaptations are cephalization (brain sparing effect on the cost of growth of other system of the body), decreased synthesis and increased resistance to the fetal insulin and insulin like growth factor-1 (IGF-1) and up-regulation of the hypothalamo-pitutary adrenal (HPA) axis. These changes are called as "epigenetic modification" and these modification take place during the critical time period of fetal growth, making them permanent or 'programmed' in the genes of the foetus [36]. These epigenetic modifications with postnatal mismatch of nutrition, suboptimal daily habits and infant's genetics and epigenetics, make these IUGR neonates to develop DoHaD in adulthood (Figure 6) [37].

Prevention of IUGR

The intervention those are effective in reducing the birth of IUGR includes balanced energy protein supplementation [38], intermittent preventive treatment of malaria in pregnancy [39], multiple micronutrient supplementation [40], insecticide-treated nets (ITN) [39], anti-platelets for preeclampsia [41,42] and smoking cessation [43].

Conclusion

Intrauterine growth restriction is an important cause of neonatal mortality and morbidity. These neonates face many acute problems during peri-partum and after birth. They are more likely to develop "Developmental origin of health and disease (DoHaD)" in adulthood that makes the regular follow up a necessity and needs a protocol for it so that any deviation of these IUGR neonates's growth from normal can be picked up early (Figure 7).

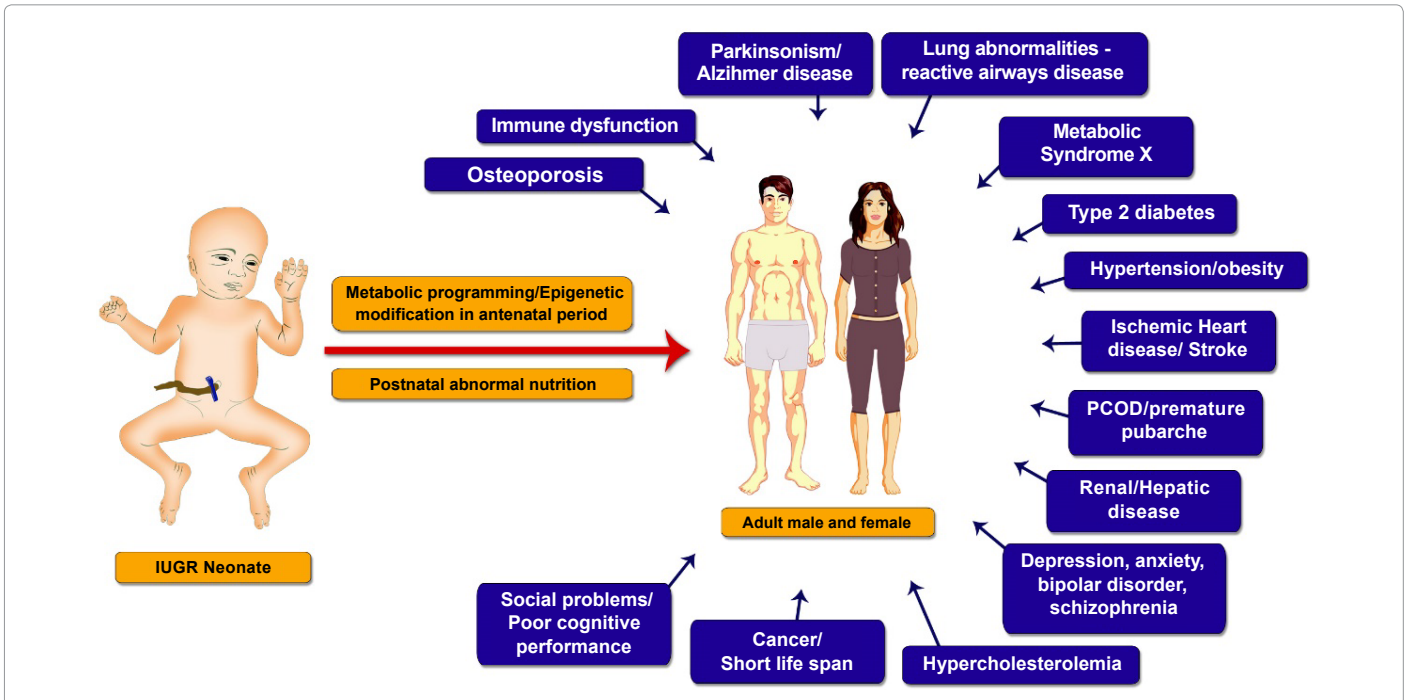

Figure 5: Figure showing various adult diseases the IUGR infant is prone to develop in his adulthood as per "Developmental origin of health and diseases (DoHaD)". IUGR infants undergo epigenetic modification in-utero and postnatally have abnormal nutrition and growth leading to various disease of adulthood in these infants.

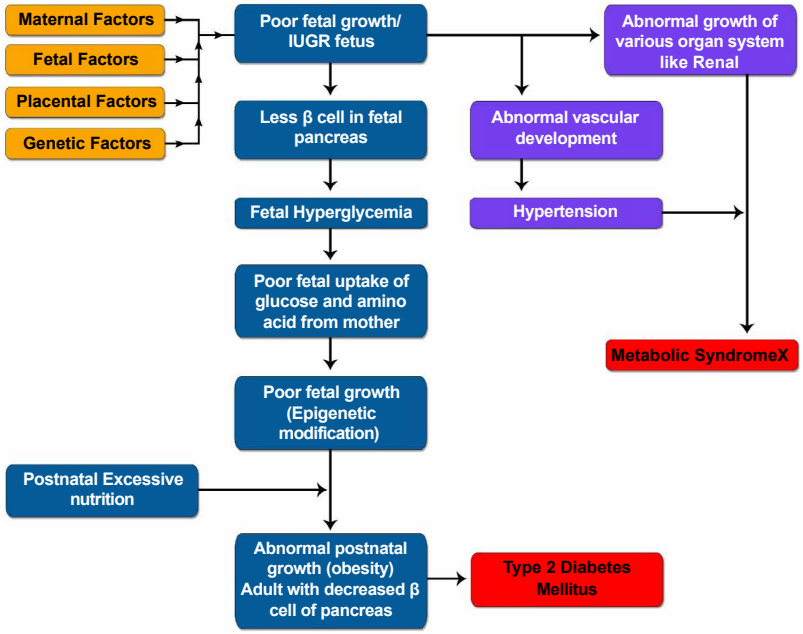

Figure 6: Barker hypothesis (Thrifty phenotype) explaining the fetal origin of adult disease (FOAD) or "Developmental origin of health and diseases (DoHaD)" in IUGR infants.

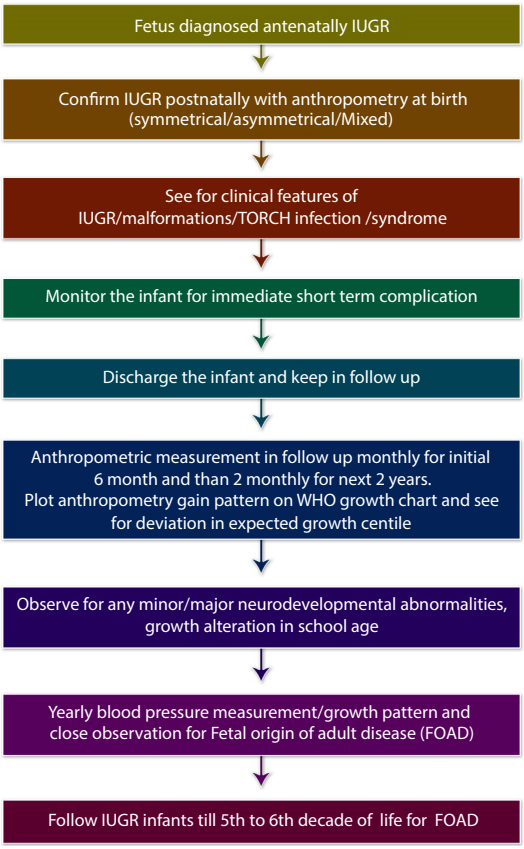

Figure 7: Follow up programme of infants who are born with intrauterine growth restriction.

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