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Review Article

Intrauterine Growth Restriction and Associated Factors: A Narrative Review

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Abstract

Background

Intrauterine growth restriction (IUGR) is associated with perinatal morbidity and mortality. It is a common problem and early diagnosis is essential. Around 75% of the IUGR babies are born in South Asia. Fetuses born with this condition not only encounter health problems in the immediate neonatal period but also are at high risk of non-communicable diseases in the adulthood. A variety of factors are associated with development of IUGR. A comprehensive approach to examine all of these factors as a cause of IUGR has not been reported. The objective of this review was to search and review the overall findings regarding the factors associated with IUGR.

Methods

Published literature in English was retrieved through searches of PubMed or MEDLINE, CINAHL, and the Cochrane Library in 2010 using appropriate controlled vocabulary via MeSH terms (fetal growth restriction and small for gestational age) and key words (fetal growth, restriction, growth retardation, IUGR, low birth weight, small for gestational age). Results were reviewed from both observational and interventional studies including randomized control trials/controlled clinical trials, and observational studies.

Findings

Diagnosis of IUGR is based upon clinical examination and ultrasound. Majority of the etiological factors include restricted gas exchange and nutrient delivery to the fetus. This can occur due to fetal factors, placental factors, uterine factors or nutritional deficiencies.

Conclusion

Intrauterine growth restriction (IUGR) is the leading cause of fetal mortality and morbidity. As an etiology, each of placental findings, maternal factors and fetal factors have been reported to be associated with IUGR. Women should be screened for clinical risk factors and for infectious diseases for intrauterine growth restriction by means of a complete history, clinical examination and ultrasonography. Moreover, women need to be counseled on the good nutrition during pre-conception and conception period. These strategies might reduce the chances of IUGR and associated complications.

Keywords: *Intrauterine growth restriction; Placental Factors; Fetal Factors; Nutritional Factors*

Introduction

Fetal or intrauterine growth restriction (IUGR) is a commonly encountered condition in obstetrics [1]. Not only, it is associated with perinatal morbidity and mortality but is also difficult to diagnose and manage. It is the second leading cause of perinatal mortality after prematurity. "Therefore, it is essential to identify and diagnose it early and take an immediate action. Small for gestational age fetuses is defined as" birth weight below 10th percentile of growth curve of gestational age or "birth weight below the 10th percentile of the recommended gender-specific birth weight for gestational age reference curves" [2]. Another satisfactory definition of IUGR has been suggested by the American College of Obstetricians and Gynecologists (ACOG) as describing "A fetus that fails to reach his potential growth" [3].

Fetal growth restriction is one of the commonest problems faced by both obstetricians and neonatologists [4]. It frequently presents dilemma for the obstetricians with regards to management of the pregnancy and delivery. Fetuses with growth restriction encounter problems such as still births, birth hypoxia, hypothermia, hypoglycemia, pulmonary hemorrhages, necrotizing enterocolitis, impaired neurodevelopment and inadequate cerebral function in childhood [4]. As adults they are at increased risk of heart diseases, hypertension and type II diabetes [5].

Every year out of 30 million newborns with fetal growth restriction 75% are born in Asia, mainly in South Central Asia [6,7]. Where 30% of African children are under weight, corresponding figure for south Asia is over 50%. According to a community based study in Karachi, the incidence of term fetal growth restriction was 24.4% among 738 singleton births. The prevalence of IUGR in Pakistan is 25% [8].

Clinically high risk factors for fetal growth restriction includes maternal weight < 10 percentile for height, history of previous infants with fetal growth restriction, maternal vascular diseases like essential hypertension, pregnancy induced hypertension, diabetes mellitus or collagen disorders, maternal cardiac disease severe enough to cause maternal polycythemia, alcohol or drug addiction and sickle cell anemia [9]. Intrauterine growth restriction is an important public health problem. A variety of factors have been reported to be associated with this clinical condition and it is important to analyze the data on causes and factors associated with the disease in order to plan for appropriate public health interventions. The purpose of conducting this review was to synthesize the findings from published studies regarding factors associated with development of intrauterine growth restriction.

Methods

Published literature in English was retrieved through searches of PubMed or MEDLINE, CINAHL, and the Cochrane Library in 2010 using appropriate controlled vocabulary via MeSH terms (fetal growth restriction and small for gestational age) and key words (fetal growth, restriction, growth retardation, IUGR, low birth weight, small for gestational age). Results were reviewed from both observational and interventional studies including randomized control trials/controlled clinical trials, and observational studies.

Findings of the review

Brief overview of Fetal Embryology

Human development begins with fertilization; a process by which spermatozoa from male and oocyte from female unite to form a zygote [10]. It is at this stage that genetically programmed fetal growth trajectory is decided for an individual.

Following fertilization within fallopian tube the embryo travels the remainder of tube and reaches uterine cavity in about three days [11,12]. By this time cell replication has reached to morula stage, shortly after, embryo progresses to become a blastocyst, the last stage before implantation. The blastocyst contains inner cell mass which is the forerunner of fetus and trophoblast which develops into placenta [11,12]. Implantation occurs approximately seven days after fertilization. Fusion of embryo to endometrium is accomplished by formation of trophoblast syncytium on the fetal side. Space between trophoblast cells become filled with blood from ruptured capillaries and eroded glands [12]. The fluid acts as a nutrient bath called embryotroph [13].

Organogenesis occurs during 4th - 8th week of intrauterine development. The period called "Embryonic period" [12]. Organogenesis of main systems completes by the end of this period. 9th - 38th week of gestation is called "Fetal period". The transition from an embryo to a fetus is neither abrupt nor spectacular, but the name change signifies embryo has acquired unmistakably human characteristics [12,13].

Development during the fetal period is primarily concerned with growth of the body, growth and differentiation of tissues and organs that are already formed during the embryonic period. Initial development of placenta and fetal membranes occur for more rapidly than development of the fetus itself. In fact, during the first 2-3 weeks after implantation of blastocyst the fetus remains almost microscopic in size, but there after the length of the fetus increases almost in proportion of age [14]. During the fourth and fifth months the length increases rapidly at the rate of 5 cm/ month. At 12 weeks, the length is about 10 cm, at 20 weeks 25 cm and at term, (40 weeks), 53 cm about 2 inches. Because the weight of the fetus is proportional to the cube of length, the weight increases approximately in proportion to cube of the age of the fetus [15]. Weight remains minuscule during the first 12 weeks and reaches 0.454 kg only at 23 weeks (5 and ½ months) of gestation. Then during the last trimester of the pregnancy fetus gain tremendously, so that 2 months before birth, the weight averages 1.362 kg, 1 month before 2.043 kg and at birth 3.18 kg. The birth weight varies from as low as 2.043 kg to 4.994 kg in normal fetus with normal gestation period [14]. A very important change that takes place during fetal life is the relative slowdown in the growth of head as compared to the rest of the body [16]. Period from 26 - 29th week is important as lungs, pulmonary circulation and nervous system has just matured to sustain life [17].

Diagnosis of IUGR

Clinical examination of women suspected of fetal growth restriction includes assessment of maternal weight gain, blood pressure, abdominal palpation of fetal size, amniotic fluid volume and measurement of symphysis fundal height [4]. Recognition of IUGR begins with an accurate gestational age (GA) assessment. This is determined by measuring the crown lump length (CRL) by ultrasound in early pregnancy. The most reliable method in antenatal diagnosis of fetal growth restriction is ultrasonography. Serial ultrasound biometries may then be able to identify the fetus that does not reach its potential growth. Commonly used methods for estimating fetal size are clinical palpation, fundal height (FH) measurement and ultrasonic fetal biometry. Ultrasound must be considered the method of choice as it is highly reliable and reproducible. The commonly used ultrasound biometric parameters in the late 2nd and during the 3rd trimester are the bi parietal diameter (BPD), head circumference (HC), abdominal circumference (AC) and femur length (FL) and trans-cerebral diameter. From these measurements the estimated fetal weight can be calculated. The Latest in this series is trans-cerebellar diameter. Fetuses that do not reach their growth potential will still have cerebellar growth until late in the process of IUGR. When there is doubt in calculating exact gestational age, the trans-cerebellar (TCD) diameter can be used as gestational age independent sonological predictor for the diagnosis of fetal growth restriction [6]. Ultrasound has proved to be one of the most valuable tools in the antenatal diagnosis and follow up of fetal growth restriction [18]. It has been found that as the percentage of pregnancies undergoing ultrasound examination increases fetal growth restriction decreases [19].

Antenatal diagnosis of fetal growth restriction can therefore help obstetricians in early and comprehensive management of conditions, thus decreasing the perinatal mortality and long term complications associated with the condition.

Brief overview of Fetal Sonographic Anatomy

Fetal Cranium

Ultrasound introduced an entirely new dimension in studying the fetal anatomy in uterus. Advent of latest, artifact free digital sonography and three-dimensional sonography are a further leap forward in better understanding the detailed fetal anatomy. The fetal skull is best examined in axial plane [20]. In early pregnancy the intracranial structures can be well studied, however as pregnancy advances the thickness of bone of skull increases, causing increased acoustic shadowing. The lateral ventricles are prominent features of brain in early second trimester; however, as pregnancy advances they shrink in size. Choroid plexus is prominent until 20th post menstrual week

but is barely visible at term [21]. Until the 20th week the brain has smooth surface with few sulci and gyri, progressively the gyri and sulci become more prominent.

The medial and lateral ventricles are made by cavum septum pellucidum, it extends one third of the distance from the frontal to the occipital calvarium. The cerebellar hemispheres are seen as low echogenic circular structures, however as pregnancy advances they become more echogenic. The normal fetal cerebellar growth exhibited a more than two-fold increase in size during the second half of the pregnancy [22].

Thoracic Contents

The major thoracic contents are heart, lungs and great vessels. The heart occupies 1/3rd of chest and breathing movements can be identified by early second trimester [23]. Fetal breathing is a useful indicator of fetal wellbeing; prior to 28 weeks breathing is shallow, rapid and occurs in short episodes. The transition from thorax to abdomen is smooth; diaphragm appears as an echogenic line separating lungs and heart from stomach [23].

The abdomen

It consists of liver, intestine, spleen, renal tract and great vessels. It contains two cystic structures, stomach and urinary bladder. Normogram of normal fetal liver length are available for evaluation of suspected abnormalities of liver size [24]. Fetal hepatic volume measurement in conjunction with other biometric measurements is under evaluation as one of the sonological predictors in diagnosing fetal growth restriction [25]. The umbilical vein enters the liver anteriorly and gall bladder appears as an echoic structure lateral to the umbilical vein. Stomach is usually identified from 6th week of pregnancy onwards and from 18 - 20 week it is visualized easily. Both kidneys are identified from 14th week onwards; the renal size is 1/3rd of the abdomen circumference at all gestational ages [26]. The bladder should be routinely seen as an ovoid echo free cystic structure arising from pelvis by 14th week of gestation; it should normally have no internal echoes [26].

Musculoskeletal System

It is important to measure femur length and to study limb morphology in every 18th – 20th weeks scan. O' Brein and colleagues in 1981 introduced fetal femoral length measurement as another method of assessing gestational age in the early pregnancy [27-29]. The femur length has been shown to be as an accurate indicator of gestational age as bi parietal diameter [28]. Fetal bone growth is very rapid in second trimester and early third trimester of pregnancy after that it progressively slows down. By the end of the second trimester the long bones are seen as linear echo dense structures with posterior shadowing.

Amniotic Fluid

The amniotic fluid forms a cushion around the fetus and is responsible for the exchange of nutrients. The amniotic fluid is formed until 14th week as transudate across the fetal skin and membranes. After the 14th week the fetal urine becomes the major contributor to the amniotic fluid volume. In term pregnancies amniotic fluid index (AFI) ranges from 68-169 mm and in postdate pregnancies it is 67-174 mm. However, the values for each week of gestation are statistically distinct [30].

Fetal Growth Physiology

Growth involves an increase in the size of organism by either an increase in the number of cells or their size [31]. In human embryo there is high degree of organization and the blood supply is well maintained to all areas of developing embryo [32]. The intrauterine growth is affected both by genetic features and by inadequate supply of essential nutrients to the fetus.

Genetic Control

Growth involves an increase in the size of organism by either an increase in the number of cells or their size [31]. In human embryo there is high degree of organization and the blood supply is well maintained to all areas of developing embryo.

There are three phases of fetal growth and development [33]. 'Phase of hyperplasia'; this phase comprises of replication or proliferation followed by 'phase of migration' where cells move and aggregate to form tissues and organ rudiments. It is finally followed by 'phase of hypertrophy' when the cells increase in size and become a part of definitive functional structures [33].

The cascade of genetic activity which controls differentiation and growth is influenced by molecular and growth factors, they also control expression of other genes. The genome is also responsible for the production of the system, which controls growth and differentiation both from early embryonic existence and throughout life.

Nutrient Supply

Fetus can concentrate various nutritional elements required for fetal growth and development in the presence of normal functioning placental unit even in the face of the maternal deficiency of some of the nutrients. Placenta provides an important path way for transfer of nutritional substances from mother to fetus by simple diffusion, facilitate and other transport mechanisms [34]. The fetus relies for its nutritional supply on the vascular supply of uterus and the function of the placenta. In a pregnancy the uterine arteries which are called spiral arteries, become flask shaped vessels by the removal of their muscular and elastic layers by invading trophoblast [35].

This causes them to widen and they allow an unimpeded flow of the maternal blood to the placental bed, thus maximizing the exchange potentials of the placenta [36]. The vascularity of the placenta is also very important and pathology of placental vascularity severely affects the growth of the fetus, placenta may also modulate the growth in the fetus not only by changes in nutrient supply but also through the secretion of growth controlling substances [28,36].

One of the controlling and modulating factor is placental growth hormone, this is product of GH –V gene specifically expressed in syncytiotrophoblastic layer of human placenta [37]. Placental growth hormone differs from pituitary growth hormone by 13 amino acids, it has somatogenic and a low electro genic effect and is secreted by placenta in continuous non pulsatile manner. This gradually replaces the pituitary growth hormone which becomes undetectable. Placental growth hormone is significantly decreased in pregnancies which show intrauterine growth restriction [37].

Fetal CNS Growth

Fetal brain grows rapidly during the 2nd and the 3rd trimester; there are three main growth spurts before birth [38]. First one occurs by 12th to 18th week where neuroblast proliferation occurs. Second growth spurt occurs at approximately 25th week where glial cells proliferate and finally third one occurs around 30th week and comprises of cerebellar growth spurt [39,40].

Fetal Growth Factors

The family of fetal growth factors is increasing rapidly for various developmental processes in utero, these phenomena involve induction, proliferation, migration, aggregation, programmed cell death and maintenance of cell lines. Most of growth factors are primarily through autocrine or paracrine mechanism [38]. Although some, such as angiotensin II, have other classic endocrine actions as well. Most of these factors act via cell membrane receptors and have a variety of 2nd messenger systems. While most stimulate growth, however, transforming growth factor inhibit the fetal growth [41]. Others are epidermal growth factors, nerve growth factors, vascular endothelial

growth factors, müllerian inhibitory substances, inhibin etc. IGF-1 mRNA has been identified from 12 weeks in all fetal connective tissues and mesenchyme, it has two receptors, IG-1 receptor is structurally similar to the insulin receptors and there is much cross reactivity. IGF-1 binding proteins are also present in utero. Birth weight is inversely proportional to concentration of IGF-1 binding protein and directly proportional to the concentration of IGF-1 [38].

Pathophysiology of Growth

Intrauterine growth restriction

The intrauterine growth restriction is diagnosed when the fetal growth rate deviate significantly from established norm. It was about 30 years ago that physicians first recognized fetal growth restriction. Warkany and coworkers in 1961, reported normal value of infant weights, length and head circumferences and defined fetal growth retardation [42]. Grnenwald pioneered the concept of small size fetus due to chronic placental insufficiency in 1968 [36]. Most commonly used method of assessing fetal growth is based upon serial clinical examination during pregnancy by abdominal palpation [43]. The growth restriction fetuses show poor or static incremental growth and diminution in quantity of the liquor amino [18,44].

Traditionally small for gestational age fetuses have been cataloged as either symmetric or asymmetric in utero to attempt and to identify both etiology and prognosis. Symmetrical fetal growth restriction affects the head as well as the body [45]. This group includes group of individuals whose growth restriction has either occurred early in gestation or therefore affected the growth of the head or a situation so severe that all growth has been affected. Insults during organogenesis early in pregnancy such as chromosomal abnormalities, drugs and infections cause symmetrically small fetuses [46].

Asymmetrical fetal growth restriction usually refers to fetuses affected either later in gestation or in which pathological process has permitted redistribution of blood supply preferentially to brain allowing continued oxygen and nutrient delivery and therefore near normal head growth (brain sparing effect). At the same time this redistribution has reduced blood flow to the body and produced a lag in somatic growth. This pattern of growth is typical of utero placental insufficiency, placental dysfunction [47].

Pathophysiology

Normally a fetus requires an adequate supply of nutrients and oxygen across the placenta via uteroplacental and fetoplacental circulation [48]. Abnormalities on either side of the placental circulation can cause insufficiency of supply and lead to fetal growth restriction [49].

The majority of the etiological causes of fetal growth restriction prevent adequate gas exchange and nutrients delivery to the fetus to allow it to thrive in the utero. This process can occur primarily because of maternal diseases causing decreased oxygen carrying capacity (e.g Cynotic heart diseases, haemoglobinopathy, and decrease oxygen delivery secondary to maternal vascular disease (e.g diabetes with vascular disease, hypertension, autoimmune disease affects the vessels leading to the placenta) or placental damage resulting from maternal disease (e.g: smoking, thrombophilia, some auto immune diseases) [50].

Maternal side of placental circulation is formed by the action of endovascular trophoblast on spiral arteries and converts them into uteroplacental channels in two stages. The first wave acts on decidual segments of spiral arteries while the second wave converts the myometrial segment of spiral arteries into funnel shaped channels. These changes continue well into second trimester and blood flow becomes pressure dependent and there is loss of auto regulation. Uteroplacental insufficiency has its origin in the failure of these appropriate physiological adaptations of spiral arteries [47]. Oxygen reaches the intervillous spaces via uteroplacental circulation in early pregnancy, when increasing fetal requirements surpass the capability of uteroplacental circulation to maintain the normal growths then fetal adaptations begin. This eventually become recognized as fetal growth restriction and is characterized by progressive malnutrition

and increasing hypoxia which leads to asphyxia [51]. However, if the fetus has already reached a good size, before placental perfusion becomes inadequate the fetal growth restriction cannot be recognized [47].

Etiological Factors

Multiple etiological factors can reduce fetal cell number or reduce fetal oxygen availability and eventually produce growth restriction. These are broadly divided into categories of fetal factors, placental factors, uterine factors and nutritional deficiencies [52].

Fetal factors (53)

Maternal gene

There is familiar predisposition to growth restriction which is transmitted through maternal line with sisters having higher risk of growth restriction than sister in law.

Karyotype anomalies

Chromosomal anomalies account for 5 to 8% of cases of growth restriction especially the more severe cases. An abdominal circumference below 10th percentile is associated to 10% risk of chromosomal anomalies while a circumference below 5th percentile is associated to 19% incidence, although traditionally the fetus with chromosomal anomalies is thought to be symmetrical, most cases are in fact symmetrical. Placental abnormalities and therefore placental insufficiency is common with abnormal karyotypes.

Skeletal Dysplasia

Abnormal bone growth is an obvious but relatively infrequent cause of growth restriction (incidence 1 in 10,000 among live births).

Most major congenital anomalies are associated with a greater risk of growth restriction.

Multiple gestations

Fetal size is reduced with each additional fetus in part to decreased placental oxygen availability. In some cases differences in growth are associated to unequal distribution of placental circulation.

Uniparental dysomy

A relative recent concept in which both chromosomes from homologous pair are derived from the same parent (1 in 6000 concepts) in these cases due to imprinting, one gene may be suppressed in a male or female and therefore manifest as a single gene deficiency.

Fetal endocrine factors

Central endocrines like growth hormone, thyroid hormone, glucocorticoids do not have major role in controlling fetal growth. There are studies that reveal children with congenital deficiency of growth hormone have only slight reduction in birth length but normal birth weights [54]. Insulin promotes growth by increasing the rate of glucose uptake, utilization and increase amino acid tissue accumulation. It has been found to cause fetal cell proliferation anabolism [54].

Placental Factors (56)

Single umbilical artery

A classical defect associated with growth restriction which may be associated with inadequate drainage of all cotyledons towards the fetus. However due to greater association with congenital anomalies such as renal agenesis, other factors may be involved.

Velamentous insertion

Usually associated with other placental abnormalities but also umbilical cord flow may be compromised.

Bilobed Circumvalate Battledore placentas

Almost any type of placental abnormalities may be associated to abnormal fetal growth.

Placental hemmorrhage

By sequestering a large amount of fetal blood and reducing the area for adequate gas and metabolic exchange.

Placenta Previa

Implantation of placenta in an area of decreased perfusion such as the lower uterine segment may produce growth impairment.

Placental abruption and infarction

In many cases may produce significant placental insufficiency.

Abnormal decidualization

Such as occurs in cases of pre-eclampsia may be implicated in both etiologies.

Uterine factors

Mullerian anomalies

May compromise placental circulation and produce growth restriction.

Uterine myomas

May reduce the area of placental perfusion However the incidence of abruption is greater and probably more significant.

Nutritional deficiencies (57)

Maternal starvation

Various studies have shown that maternal starvation is rarely a cause of growth restriction except in the most severe cases. However, there is an association of zinc deficiency with growth restriction.

Infectious factors

Certain infectious diseases can also cause growth restriction in fetus. Infections such as rubella may produce decreased number of cells. Cytomegalovirus causes cytolysis and localized tissue necrosis. Other such factors include herpes simplex, varicella zoster, syphillus and trpanosomiasis. Infections such as chlamydia and mycoplasma may cause growth restriction but yet have unproven etiologies.

Maternal factors

Any medical condition that produces chronic maternal hypoxemia decreases oxygen carrying capacity or vascular insufficiency can produce growth restriction. Conditions such as chronic pulmonary disease and cynotic heart diseases can also cause growth restriction. Chronic or sickle cell anemia can also lead to IUGR. The birth weight and head circumferences were significantly low in infants born to women with moderate to severe anemia [58].

Hypertension is associated with two to three-time greater risk of growth restriction which is not improved by antihypertensive treatment. Placenta from pregnancies complicated with growth restriction shows vascular damage which may be caused by pregnancy induced hypertension [59].

Another factor is pre gestational diabetes, which is associated to vascular compromise and increased risk of anomalies. Diabetic mothers are at considerable risk to have babies who suffer from IUGR. In a study carried out on 165 women who suffered from diabetes. It was shown that there was a significant although small reduction in fetal BPD in the presence of poor glycemic control during first half of pregnancy [60].

Maternal height and weight is also one of the important factors. It has been shown that mothers with small height and weight tend to have smaller babies, growth restricted babies had mothers who were significantly younger, with longer parity and lower weight [61].

Maternal ethnicity is also associated with growth restriction. Considerable racial and ethnic differences persist as regard birth outcome after different other parameters have been adjusted. However, these racial differences are not in early pregnancy and most of the factors appear to act in second half of the pregnancy [62].

Drugs

Tobacco is single most common and most preventable cause of growth restriction. It exhibits a dose dependent relationship with heavy smokers having children with average birth weights of 458 gms less than nonsmokers and passive smokers having children with an average 192 gms less [63]. This risk is increased three times among smokers of 20 cigarettes per day and increases 1-5 times for each 10 cigarettes smoked.

It is difficult to analyze use of alcohol and drugs individually as the tendency to use alcohol and drugs together is higher. There exists both a dose dependent relationship and increased risk based on greater risk of fetal anomalies [64].

Therapeutic drugs such as warfarin, phenytoin, folic acid antagonists and antineoplastic agents have also been implicated as risk factors. Recently, use of beta blockers has been identified as a risk independent of the presence of chronic hypertension. Toxins have an important effect on fetal growth especially smoking [65]. One of the important causes of fetal growth restriction is increased apoptosis. Apoptosis is a normal phenomenon; however, it increases in fetal growth restriction. The incidence of apoptosis was significantly higher in placentae from pregnancies with intrauterine growth restriction, compared with normal placentae [66]. Risk factors for fetal growth restriction:

The risk factors have been classified into five broad categories [67].

1. Low maternal pre pregnancy weight, height and low weight gain during pregnancy.

2. Poor prior obstetric history. High parity, previous low birth weight, still birth and neonatal death.

3. Pregnancy complications: hypertension and bleeding etc.

4. Maternal medical diseases, vascular and renal diseases etc.

5. Environmental factors: Malnutrition, low socioeconomic status and high altitude.

Implication of Fetal Growth Restriction

Fetal growth restriction causes a spectrum of perinatal complications, including fetal deaths, prematurity, neonatal death, fetal compromise in labor, neonatal morbidity, induction of labor and cesarean delivery.

A fetus which suffers from growth restriction has 6-8 times high mortality rate as compare to counterpart [68]. Fetal growth restriction has both short and long term implications. The immediate outcomes of these infants are poor; they are prone to meconium aspiration and may suffer from birth asphyxia. These neonates are at risk of hypoglycemia because of inadequate glycogen reserves secondary to fetal malnutrition, moreover their gluconeogenic pathways are not responsive to hypoglycemia [69].

In response to hypoxia during intrauterine life the fetus increases red blood cell production; there is transfer of blood volume from the placental circulation to fetal circulation [69]. The result is polycythemia which in turn leads to hyper viscosity and hyperbilirubinemia when the red blood cells break down.

These neonates are also more prone to hypothermia because of inadequate fat reserves [69]. There is also a link between fetal growth restriction and sudden infant death syndrome.

The impact of fetal growth restriction does not simply end with the neonatal time period, studies have now shown that effects continue into adulthood life [70]. The overall concept is that fetal gene expression is under the influence of nutrition. If nutrition is inadequate, there are certain developmental adaptations which take place. These adaptations may be a decrease in the cell number or preferably shunting of blood to brain. It is the persistence of these adaptations which is thought to be link between intra uterine growth restriction and adult onset diseases [71]. The link between poor school performance and fetal growth restriction has also been studied [72]. These children were also shown to have more behavioral and emotional problems [72].

The neurological outcome of these children is dependent on the degree of growth restriction (mild, moderate, severe), time of onset of maturity at birth. Those fetuses affected by early onset fetal growth restriction between 10-17 weeks have serious neurological sequelae. It is during this time that neuronal cellular multiplication take place and because of malnutrition, multiplication is limited, leading to profound neurological damage. In adulthood these babies appear to be at increased risk of high level of cholesterol, cardiovascular diseases, diabetes, renal damage, cerebral palsy and epilepsy. Impaired glucose tolerance and NIDDM have also been associated with impaired fetal development [71,73]. During fetal life, insulin stimulates cell division in areas such as skeletal muscles. Insulin resistance arises in skeletal muscles when the fetus needs to conserve glucose. In short term the fetus would be thin because of decrease muscle mass and glucose would preferentially be shunted to the brain. In long term persistence of insulin resistance at the peripheral skeletal muscles would lead to impaired glucose tolerance or NIDDM [74]. Preliminary evidence also suggests that impaired fetal nutritional supply may lead to alteration in fetal neuroendocrine development, leading to increased cortisol level during childhood [75].

Coronary heart disease is one of the long term complications of fetal growth restriction [76]. However, the majority of small fetuses have no underlying pathology and their catch up growth and neurological development have been found to be not different from those of the well grown fetus [72].

Conclusion

Intrauterine growth restriction (IUGR) is the leading cause of fetal mortality and morbidity. As an etiology, each of placental findings, maternal factors and fetal factors has been reported to be associated with IUGR. Women should be screened for clinical risk factors and for infectious diseases for intrauterine growth restriction by means of a complete history, clinical examination and ultrasonography. Pregnant women should be screened during first and second trimester of the pregnancies to identify the high risk women. If intrauterine growth restriction is suspected, further assessment can assist in making the diagnosis. Moreover, women need to be counseled on the good nutrition during pre-conception and conception period. These strategies might reduce the chances of IUGR and associated complications.

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