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Editorial

Fetal growth restriction – A caregiver's nightmare!

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Fetal growth restriction (FGR) also known as intrauterine growth restriction (IUGR) earlier, increases the risk of stillbirth as well as neonatal morbidity and mortality. It is a condition commonly associated with multiple etiologies, mainly placental malfunction, which prevents the fetus from reaching its genetic growth potential. Fetal size has been used to define FGR, usually using abdominal circumference or estimated fetal weight that is lower than the tenth percentile when compared to reference standards for gestational age. Some smaller fetuses are small by constitution based on their genetic growth potential and are not growth restricted.[1]

All small for gestational age (SGA) infants may not be associated with an underlying pathological cause.[2] FGR and SGA are not interchangeable terms. But a large number of SGA neonates also have FGR and a large number of FGR neonates are SGA. Hence, it's necessary to differentiate between SGA and FGR using fetal growth curves depending on constitutional features. This will allow to identify typical SGA neonates from those with FGR.[3] FGR and SGA are frequently used synonymously but identification of FGR is crucial.[4]

The fetal growth is a complex process and is regulated by several factors originating from fetus, placenta and mother. The etiology of FGR is diverse, involving a variety of environmental and genetic variables. The fetal DNA contributes to the growth of the fetus in its earliest phases, but in the later phases of pregnancy, environmental, nutrition and hormonal factors play a significant role.[4] A negative intrauterine environment affects fetal programming, which in turn affects long-term metabolic effects and postnatal catch-up growth.[5] Phillips et al observed association between being thin at birth and the chance of developing diabetes as an adult.[6,7] They found that FGR neonates exhibit elevated insulin sensitivity, impaired pancreatic beta-cell activity, hypoglycemia and hypoinsulinemia even after birth.[6,8] The risk of insulin resistance, metabolic syndrome and cardiovascular disease is increased by excessive postnatal feeding and the sedentary lifestyle.[9] Increased insulin sensitivity at birth in FGR may be significantly influenced by thyroid hormones.[10] Overweight and a BMI >17 kg/m2 are strongly associated with insulin resistance in SGA

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children, which can appear as early as one year of age. Their decreased ability to absorb glucose through the action of insulin lead these newborns at higher risk of developing metabolic syndrome.[9] Increased weight in the initial three months of life is related to central adiposity, decreased insulin sensitivity and increased insulin resistance in early adulthood of these neonates. In the FGR state low levels of adiponectin, leptin and high levels of visfatin, ghrelin leads to obesity. Increased risk of cardiovascular diseases is linked with IUGR by stimulating the renin-angiotensin system (RAS), disrupting the placental mTORC and TGF signaling pathways, causing high blood pressure and impairing endothelial function. Adverse intrauterine environments impair the development of the fetal lungs, resulting in structural alteration of lungs and impaired respiratory function in later life. Uteroplacental insufficiency (UPI), effecting 10% of pregnancies, is the most common cause FGR. The fetus receives little oxygen and nourishment and placental function is also impaired. In human pregnancy, kidney development starts in the 3^{rd} week and ends in the 36^{th}. Based on Brenner's theory, adult onset of kidney diseases and hypertension is directly related to the number of nephrons present at birth in FGR mouse model. Aberrant oxidative stress, lipid metabolism and inflammation have a major impact on the FGR associated fatty liver.[11] FGR also increases the risk of decreased glomerular filtration rate (GFR), elevated albumin creatinine ratio leads to renal abnormalities.[9] FGR-affected neonates may be more vulnerable to adverse developmental outcomes later in life. Cerebral palsy, motor abnormalities, neuromotor diseases and visuomotor disorders are examples of neurological disorders. A recent study revealed that FGR neonates have delayed motor and mental development than those with appropriate gestational age (AGA).[12] Development in utero has a major effect on the risk of disease later in life, even though the causes are unknown. DNA methylation has a role in the intrauterine programming of disease and may be indicators of diseases in later life.In comparison to AGA neonates, FGR have hypo DNA methylation. The difference in DNA methylation between neonates with FGR and AGA suggests that certain genes are differentially methylated and may be associated with FGR-related abnormalities through differential gene expression.[13] Based on recent methylation EPIC array, hypomethylation of PTPRN2 and HLADQB1 may cause Type 1 diabetes. This hypomethylation is mediated by ROS and inflammatory mediators and lead to pancreatic beta cell apoptosis.[14]In addition, FGR raises the risk of hip fractures, osteoporosis, sensorineural hearing loss, retinal degeneration etc.[9]

Considering their increased risk of intrauterine death and neonatal morbidity, antenatal examination should identify fetuses which fetuses would be most benefit from early delivery intervention. FGR can be monitored with ultrasound and the umbilical artery/ middle cerebral artery Doppler. If a Doppler scan shows absence or reverse end-diastolic flow (AREDF), make plan for an early delivery. Middle cerebral artery doppler was shown to be a better predictor of fetal outcome in FGR than umbilical artery in terms of sensitivity, specificity and predictive value. Amniocentesis and TORCH (Toxoplasma, rubella, cytomegalovirus, herpes and others) screening should be performed while taking consideration of symmetric FGR.For fetal acid base status, ductus venosus was thought to be a surrogate marker. Fetal heart rate does not appear to be beneficial in predicting perinatal mortality among IUGR. Another important aspect of prenatal care is the inclusion of corticosteroids as supplements. If the fetal age is between 24 and 35 weeks, it may be appropriate to administer single dose of corticosteroids to promote lung maturation.[9,15,16]

Conclusion, Glucose homeostasis plays a significant role in management FGR neonates. The plasma glucose levels should be maintained above 50 mg/dL prior to 48 hours of age and above 60 mg/dL beyond 48 hours of age. For IUGR neonates, breast milk is the best; however, some neonates may also benefit from lactoferrin and probiotics. Hypothermia is common in FGR neonates. It is essential to provide a thermoneutral environment (wrapped in plastic, warming mattress, radiant warmer and early skin-to-skin contact) after delivery.[9,16]FGR neonates have a higher risk of infection because of their immature immune system. All infants born with FGR should have close monitoring and regular follow up for better outcome. There is currently no effective treatment available for FGR, except from providing supportive care and treating infection when diagnosed.

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