Section A-Research paper

Methods For Surveillance of Pathologically Intrauterine Growth Restricted Fetuses

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Abstract

Background: To estimate the fetal weight using ultrasonic measurements of the biparietal diameter (BPD), head circumference (HC), AC, and femur length (FL), investigators developed mathematical formulas and constricted percentile nomograms of estimation of fetal weight (EFW) at different gestational ages. The most commonly used equations and nomograms are those of Shepard et al, (1982)28, and Hadlock et al. (1985), and most ultrasound machines have incorporated into their software one or both of these nomograms. The majority of the literature defines FGR as all the fetuses with sonographic estimated weight below the 10th percentile for the gestational age. In addition to the 10th percentile, investigators have used the 5th, the 3rd, and the 2.5th percentiles of the EFW at a given gestational age to define FGR. The rationale behind this variation is that the lower the percentile, the higher the probability of selecting fetuses with pathological growth restriction. Cardiotocography is the most widely used surveillance measure for monitoring PGR pregnancies. A tracing with good variability provides strong reassurance of good fetal oxygenation. It is an important tool in the follow-up of PFGR fetus. When PFGR is detected in early stages, FHR monitoring will show a sequence of changes that correlate with worsening in the fetal situation. The usual order of appearance of FHR monitoring changes is lack of accelerations, decreased variability, and onset of spontaneous decelerations. All, some, or none of these abnormalities may be present in the initial evaluation of PFGR. They not only are dependent on the severity of the fetal compromise but also on the gestational age at the time of the fetal assessment.

Keywords: Growth Retarded Fetus

Introduction

Cardiotocography is the most widely used surveillance measure for monitoring PGR pregnancies. A tracing with good variability provides strong reassurance of good fetal oxygenation. It is an important tool in the follow-up of PFGR fetus. When PFGR is detected in early stages, FHR monitoring will show a sequence of changes that correlate with worsening in the fetal situation. **(1)**

The usual order of appearance of FHR monitoring changes is lack of accelerations, decreased variability, and onset of spontaneous decelerations. All, some, or none of these abnormalities may be present in the initial evaluation of PFGR. They not only are dependent on the severity of the fetal compromise but also on the gestational age at the time of the fetal assessment. **(1)**

At less than 32 weeks' gestation, it is unusual to obtain an accelerative pattern even if the fetus is not compromised. When accelerations are present, they are usually not more than 10 bpm above the baseline. A similar situation occurs with variability, which is normally decreased in fetuses of less than 32 weeks. **(1)**

Lack of awareness of these FHR changes associated with early gestational age may lead to unnecessary preterm delivery. the usual frequency of FHR monitoring for PFGR fetuses is twice every week for 30 minutes, although daily Monitoring is sometimes performed in pregnant patients remote from term admitted to the hospital secondary to maternal conditions associated with PFGR. **(1)**

FHR monitoring is a sensitive indicator of fetal hypoxia and acidosis but lacks specificity and has a significant number of false positive results. For that reason the presence of FHR abnormalities is not by itself an indication for preterm delivery unless the pattern is ominous with repetitive spontaneous decelerations and absent variability. This pattern indicates exhaustion of the fetal compensatory mechanisms, hypoxia, and metabolic acidosis. Other abnormal FHR patterns, particularly decreased variability without associated decelerations, are not reassuring and demand confirmatory backup testing using arterial or venous Doppler, or BPP. **(2)**

A comparison between FHR monitoring and UA velocimetry demonstrated that UA velocimetry is more effective than FHR monitoring in the surveillance of the FGR fetus. FHR monitoring and evidence of its utility must be considered as level 2 to 3. Overall, nonstress testing must be considered a secondary test and should ideally not be used by itself for PGR monitoring. **(2)**

Biophysical profile

The BPP is a combination of observation of the fetal behavior with ultrasound (fetal breathing movements, fetal movements, fetal tone, and amniotic fluid volume) and FHR monitoring and is a sensitive test to determine exhaustion of the fetal reserve. The components of the BPP follow a sequential order in their disappearance that is directly related to the severity of fetal acidosis. **(3)**

The first variables in the test that are affected by fetal acidosis are the reactivity of the FHR and the fetal respiratory movements. Next affected are the fetal movements and the last variable to disappear, when acidosis is severe, is the muscle tone. This property makes the test valuable because when the NST is not reactive and the other components of the BPP are present, the fetus is not acidotic. **(3)**

When the NST is nonreactive and oligohydramnios is present (BPP score of 6) but fetal movements and muscle tone are present, the fetus may be compensating adequately or may be mildly acidotic and UA Doppler assessment is necessary to make the differential diagnosis between these situations. **(3)**

Similarly, Doppler assessment is necessary to confirm or rule out acidosis when the NST is nonreactive, oligohydramnios is present, and fetal breathing movements are not seen (BPP score of 4). BPP scores less than 4 are indicators of fetal acidosis and no backup testing is necessary. The usual frequency of BPP observations in the surveillance of the FGR fetus is weekly or twice a week. **(3)**

The modified biophysical profile (MBPP) consisting of NST plus assessment of the amniotic fluid volume and only perform the complete BPP when one or both of these variables are altered. **(3)**

UA Doppler velocimetry is better than the BPP in predicting fetal acidemia. Once the BPP score reaches 6 (nonreactive NST + decreased amniotic fluid or nonreactive NST + absent breathing movements), it should not be used further and fetal assessment will depend on other tests (UA and venous Doppler), offering earlier warning of the presence of fetal acidemia. The biophysical profile must also be considered a secondary test for PGR surveillance. **(2)**

Umbilical and middle cerebral artery Doppler

Doppler velocimetry is the best method of surveillance for fetal hypoxemia/acidemia in PFGR secondary to placental insufficiency as demonstrated by comparative trials with FHR monitoring and BPP. Furthermore, Doppler velocimetry demonstrates fetal hemodynamic alterations secondary to PFGR much before FHR monitoring and BPP exhibit abnormalities. **(2)**

Similar to FHR and BPP the UA and MCA Doppler follow sequential changes that parallel the extent of the fetal compromise. Initially the UA S/D ratio increases and the MCA S/D ratio decreases, indicating increased placental vascular resistance. Then the MCA S/D ratio becomes lower than the UA S/D, indicating centralization of flow. Next, the UA Doppler shows ADF and finally RDF is observed, indicating that fetal compensation is exhausted and hypoxia and acidosis are present. Each of these changes corresponds to more severe stages of fetal deterioration and when RDF is present fetal death is imminent. **(4)**

The presence of increased UA S/D ratio with concomitant decrease in MCA S/D ratio or the presence of centralization (UA/MCA < 1.0) are not indications for preterm delivery of the PFGR fetus. In contrast, ADF and RDF are signs of decompensation of the fetal homeostatic mechanisms and are an indication for delivery. **(4)**

In some occasions, these Doppler markers of severe fetal compromise appear at early gestational age and there is a tendency to prolong the pregnancy using daily testing rather than to deliver. This is an error because 97% of fetuses with ADF have abnormal blood gases in umbilical cord blood samples. The fetus, despite its precarious situation, will be better outside of the uterus than under continuous intrauterine conditions of hypoxia and acidosis. **(4)**

Fetuses with severe PFGR secondary to placental insufficiency usually follow a characteristic sequence of Doppler changes. In the initial stages of placental insufficiency, there is increased resistance to UA flow. **(4)**

This is followed by early Doppler changes consisting in decreased central, cerebral, and heart vascular resistance and an increased peripheral, splanchnic, and placental resistance causing redistribution of the blood flow and maximum oxygen delivery to the brain and the myocardium. As placental insufficiency increases, the fetus is no longer able to adequate oxygen supply to the myocardium signs of heart failure appear in the venous flow velocity waveforms (late Doppler changes). The period of time between early and late Doppler changes varies between 1 and 9 weeks. **(4)**

Amniotic fluid volume

Measurement of the amniotic fluid volume is important in the surveillance of PFGR. Maximum vertical pocket or AFI is used to assess amniotic fluid volume. the largest umbilical cord free pocket of fluid with diameter < 2 cm, Either an AFI <5 Cm or <10th percentile for gestational age may be used to define oligohydramnios. **(5)**

Oligohydramnios is a common finding in FGR. The incidence of FGR when the amniotic fluid volume was normal was 5% but when oligohydramnios was present it increased to approximately 40%. The cause of oligohydramnios in PFGR babies is decreased fetal urinary output secondary to redistribution of the blood flow with decreased renal perfusion and preferential shunting to the brain. **(5)**

Measurement of the amniotic fluid volume should be performed every week, and the frequency of NST should be increased if the amount of fluid decreases. The presence of oligohydramnios suggests severe fetal compromise in PFGR pregnancies but is not by itself an indication for delivery. **(2)**

This finding requires prompt evaluation with NST and with Doppler. If the Doppler shows absent or reversed diastolic blood flow, the fetal prognosis is poor and delivery is the best management. Also, if the NST shows spontaneous decelerations with absent variability the patient should be delivered. If FHR monitoring and UA Doppler do not show severe abnormalities the pregnancy can continue under close surveillance. **(2)**

The possibility of a severe congenital fetal malformation must be considered when severe oligohydramnios is found in the initial evaluation of PFGR. Severe PFGR with oligohydramnios is a common presentation of fetuses with bilateral renal agenesis or obstructive uropathy. **(2)**

Management

The prognosis and surveillance of PFGR is different depending on the gestational age at the time of diagnosis. It is possible to distinguish three groups of patients: (a) PFGR before 24 weeks (b) PFGR between 24 and 32 weeks, and (c) PFGR after 32 weeks.

Before 24 weeks of gestation

PFGR before 24 weeks is uncommon and the prognosis is extremely poor. This situation occurs in the most severe cases of abnormal placentation or is genetic in origin. Genetic FGR is usually accompanied by normal or increased amniotic fluid . volume, is asymmetric with elevated F/A and H/A ratios, and exceptionally shows ADF or RDF or centralization. **(6)**

Early severe placental insufficiency usually presents with decreased amniotic fluid and markedly abnormal uterine artery and UA velocimetry. In these cases, the placenta is small and has marked histological changes. The prognosis is poor and attempts to prolong the pregnancy usually end in fetal death. Unfortunately, early delivery usually ends in neonatal death. When early severe placental insufficiency occurs, the risk of recurrence in subsequent pregnancies is high. **(6)**

Monitoring of pregnancies less than 24 weeks with severe growth restriction consists mainly of the use of UA and DV Doppler. At this early gestational age, variability is minimal and accelerations are not present.

Therefore, two of the main variables of fetal well-being assessment with FHR monitoring cannot be reliably used. However, spontaneous decelerations of the FHR will occur when the fetus is in terminal stage. **(3)**

This leaves UA, MCA, and DV Doppler velocimetry as the most reliable tools for evaluation of the fetus at this early gestational age. Unfortunately, in the majority of these Doppler changes are already severe at the time of initial evaluation or deteriorate rapidly. If UA diastolic flow is present and the DV has uninterrupted forward flow, expectancy is clearly the best management. If UA has RDF or the DV shows interrupted forward flow, the fetus is acidotic and hypoxic and death is imminent. **(2)**

A management problem is when the UA diastolic flow is absent because the interval between this abnormality and further changes in the UA can be of several days occasionally more than 1 week. In these cases, since death is almost certain if these tiny fetuses are before 24 weeks, most likely the best option will be not to deliver although it is possible that waiting could be as harmful as delivery.**(4)**

There is no evidence that corticosteroids accelerate fetal pulmonary maturity or prevent the development of IVH in PFGR fetuses of less than 24 weeks. On the hand, there is evidence suggesting that the use of corticosteroids in severely PFGR fetuses may cause hemodynamic decompensation and worsen the outcome of the pregnancy. **(7)**

Between 24 and 32 weeks of gestation

There are changes in the etiology of FGR with in the gestational age. The majority of cases of FGR between 24 and 32 weeks are placental in origin and approximately 20% have a genetic basis. Also, approximately 20% of the cases correspond to fetuses that small but healthy. **(2)**

FHR variability is present at this gestational age although it is decreased as compared pregnancies in the third trimester. Also, discrete accelerations of no more than 10 bpm start to develop after 24 weeks and always present after 32 weeks. **(2)**

FHR monitoring becomes a useful to monitor PFGR at this gestational age. Fetal breathing movements also appear tween 24 and 30 weeks, facilitating the use of the BPP for the monitoring of these fetuses. However, the basis for the surveillance of fetal well-being at this gestational age is the UA, MCA, and DV Doppler waveforms. The frequency of fetal testing is related to the severity of the fetal compromise. **(2)**

If the UA diastolic preserved and there is no centralization of flow, UA Doppler studies are performed once every week. When centralization of flow is present, FHR monitoring twice per week is added to the weekly UA velocimetry. **(2)**

When UA shows ADF and the FHR monitoring does not show spontaneous decelerations the DV may help in the decision to deliver or to continue the pregnancy particularly if gestation is of less than 28 weeks. PGR fetuses delivered <28 weeks reportedly have a low chance of survival, suggesting that conservative management be mstituted at this stage. a **(2)**

The 'Growth Restriction Intervention Trial' (GRIT), compared the effect of early delivery against conservative management in PGR fetuses of 26-33 weeks, many with Doppler abnormalities, in which there was uncertainty regarding ideal timing of delivery. There was no significant difference in perinatal deaths and in serious long-term morbidity on 2year follow-up of survivors. There appeared to be a trend toward more favorable neurological performance for the group managed in utero. Thus, premature delivery at this GA to improve neurological outcome appears not to be justified. **(8)**

Maternal and fetal therapy

Intrauterine therapeutic options are limited in pregnancies complicated by IUGR.

Maternal rest daily in a lateral position and eliminate potential external factors, such as stress or smoking, these simple steps should maximize maternal uterine blood flow. Bed rest in the hospital may be considered to facilitates daily fetal testing. The choice of inpatient versus outpatient management is based on the severity of the maternal or fetal condition. Nutritional supplementation with high protein - caloric supplementation and multiple-micronutrients to increase energy. **(9)**

Hyperoxygenation

One study found a significant decrease in fetal mortality (85 to 20%) in cases of severe PFGR when the mother received oxygen supplementation (8 L/ min by face mask, continuously). In another similar study found a significant decrease in perinatal mortality in the group treated with hyperoxygenation (29%) as

compared with the untreated control group (68%). The number of patients in these studies is small and there is a theoretical potential for fetal and maternal oxygen toxicity that make further investigation necessary before oxygen therapy becomes an accepted therapy for PFGR. **(10)**

Aspirin

Aspirin in low doses (1-2 mg/k/day) inhibits the production of thromboxane A2 by the platelets and changes the thromboxane to prostacyclin ratio. Since low-aspirin has little or no maternal and fetal risk, administration of this medication to women at risk of PFGR is considered. **(8)**

Antithrombotic therapy appears to be a promising therapy for preventing IUGR in women considered at risk of placental dysfunction. **(8)**

Nitric oxide donor supplementary treatment with oral AGR seems to be promising in improving fetal well-being and neonatal outcome. **(8)**

Sildenafil citrate it is a specific phosphdiesterase inhibitor, is used for pulmonary hypertension in pregnancy. It is also emerging as a potential candidate for the treatment of IUGR. Sildenafil citrate vasodilate the feto-placental circulation via cGMP dependent mechanism involving increased responsiveness to nitrous oxide. **(11)**

Antenatal corticosteroids should be administered to any fetus with IUGR when delivery is anticipated before 34 weeks. **(7)**

Investigators have proposed the use of DV Doppler as an indicator of the possibility of prolongation of pregnancy in PFGR fetuses with UA ADF. If the DV waveforms show interruption or reversed forward flow or the PI is > 3.0 standard deviations from the mean, the fetal prognosis is poor and delivery is indicated. If none of these alterations exist it is permissible to continue the pregnancy with daily monitoring until further deterioration is indicated by spontáneous decelerations of the FHR, RDF in the UA, or interrupted forward flow in the DV.6 60**(11)**

Between 32 and 36 weeks, the genetic etiology drops to less 5% and the frequency of fetuses that are small but healthy increases to more than 50%. Small and normal fetuses have a normal amniotic fluid volume, symmetric anthropometric measurements, normal UA and MCA and uterine Doppler, and in follow-up ultrasounds, they grow linearly in the same percentile of the growth curve (low-growth profile). **(12)**

Small fetuses because of placental insufficiency do not grow linearly and repeated ultrasounds show that the EFW falls into lower percentiles with each subsequent measurement. **(12)**

Fetuses with placental insufficiency in the third trimester of pregnancy can be classified in three groups depending on the findings in Doppler velocimetry. **(13)**

- Women with abnormal uterine and normal umbilical Doppler
- Women with normal uterine and abnormal umbilical Doppler
- Women with abnormal uterine and umbilical Doppler

FGR with abnormal uterine and normal umbilical Doppler

Approximately 30% of PFGR fetuses with normal UA Doppler waveforms have abnormal uterine artery Doppler . Patients in this group may have unilateral or bilateral uterine artery notching but diastolic flow in the UAs is preserved. Progression of the Doppler changes is unusual in this group but their potential for adaptation is low and they frequently develop non reassuring FHR monitoring patterns and meconium-stained fluid during labor. **(14)**

These PFGR fetuses have a fourfold increase in adverse outcomes and approximately 10% of them will develop centralization of flow despite the normal umbilical S/D ratio. A decrease in MCA resistance with UA/MCA ratio < 1.0 in fetuses with normal UA and abnormal uterine Doppler is associated with an 88% incidence of FHR abnormalities and cesarean delivery. **(14)**

Antepartum surveillance will be adequate with weekly MBPP (NST + amniotic fluid volume), UA, and MCA Doppler. If the tests remain normal, delivery can wait until 38 weeks. An oxytocin challenge test before induction of labor may be useful for the early detection of those destined to develop FHR alterations during labor. **(2)**

FGR with normal uterine and abnormal umbilical Doppler

PFGR pregnancies with normal uterine and abnormal UA Doppler are rare and are at high-risk for fetal and neonatal complications. In these cases, the placental pathology is localized in the fetal side and neonatal problems may be frequent and severe. Neonatal thrombocytopenia is common. Abnormal FHR patterns develop in approximately 40% of these cases. Surveillance should include MBPP (NST +amniotic fluid volume) twice a week and UA and MCA Doppler every week. Parents should be cautioned of the possibility of abnormal outcome even if the fetus is delivered by cesarean. **(2)**

FGR with abnormal uterine and umbilical Doppler

The group with abnormal uterine artery and UA Doppler waveforms is the one at highest risk for fetal and neonatal complications. In these cases, PFGR is usually discovered early and delivery is usually required before 34 weeks. Antenatal surveillance should include the MBPP (NST + amniotic fluid volume) twice per week, UA, MCA, and venous Doppler every week, and delivery will be indicated when any of these tests indicates fetal decompensation. **(5)**

After 36 weeks of gestation

After 36 weeks of gestation, PFGR of genetic origin is uncommon and the majority of cases correspond to fetuses that are small and healthy. Constitutionally small, healthy fetuses characteristically have normal fluid volume, symmetric measurements, and normal umbilical, cerebral, and uterine Doppler. They have no placental insufficiency, can be followed like any other normal pregnancy, and delivered at term. **(2)**

At this gestational age, severe abnormalities of the UA or DV waveforms are rarely seen. However, when abnormal umbilical or uterine Doppler resistance is detected indicating placental insufficiency or the NST is nonreactive, the advantages of delivery over expectancy are clear. Generally, PGR pregnancies should be delivered at 37 weeks since the excellent neonatal outcome at this age does not justify the risk of continued intrauterine existence. **(2)**

Delivery of the Pathological Growth-Retarded Fetus

The full-term fetus has a large capacity to tolerate the hypoxic stress of labor. This capacity is reduced in PFGR due to the marked depletion of energy stores in the liver and subcutaneous tissues. With hypoxia, the energy reserves are rapidly consumed and the fetus must switch to anaerobic metabolism for the generation of energy. **(15)**

Unfortunately, anaerobic metabolism produces a large number of hydrogen ions, and metabolic acidosis appears. Thus, the intrapartum asphyxia is the major cause of perinatal morbidity and mortality in PFGR Therefore, when umbilical Doppler shows ADF or RDF, conditions strongly associated with fetal hypoxia and acidosis, or when the FHR shows ominous pattern, delivery by cesarean section is indicated. **(15)**

Vaginal delivery is not contraindicated in increased resistance in UA velocimetry but cesarean delivery should be anticipated in a large number of them. A CST at the time of admission may be useful for early identification of some of the patients that will require cesarean. **(15)**

In cases expected to have a large enough fetal reserve to tolerate the effect of uterine contractions, direct fetal monitoring using a scalp electrode and a uterine pressure catheter should be utilized as early as possible. **(15)**

Amnioinfusion should be performed early in labor if the amniotic fluid volume is decreased. The above findings emphasize the need for resorting to amnioinfusion in cases of meconium-stained liquor detected in labor to improve fetal salvage rate and minimize perinatal morbidity. **(15)**

The second stage of labor requires special attention and the obstetrician should be ready to intervene and deliver by cesarean if repetitive decelerations and decreased variability occur. In most cases, it is preferable to avoid pushing during the second stage and let the fetus descend under the exclusive effect of the uterine contractions. **(15)**

In cases of PFGR, it is not recommended to prolong the duration of the second stage for more than 1 hour in nulliparous and half an hour in multiparous patients. The best choice for pain relief during labor in PFGR is epidural anesthesia. **(15)**

Ideally, a neonatologist should be present at the time of delivery in FGR cases. The placenta in PFGR cases needs careful examination by a competent placental pathologist because in many cases this examination will provide evidence about the etiology of the problem. **(15)**

Prevention of FGR

Adolescent and pre-pregnancy nutrition, pre-pregnancy weights, poverty, and inter-pregnancy interval are the crucial determinants of fetal growth in low- and middle-income countries. Social intervention measures such as taking care of female nutrition enrichment, delaying of age at first pregnancy, preventing female gender violence (this will lead to a decrease in gender discrimination and better female nutrition), and treating chronic disease and pregnancy-induced disorders will help have a positive effect on reducing the incidence of IUGR in developing countries. **(2)**

However, some evidence-based interventions have shown to reduce the incidence of IUGR. The evidence-based proven interventions include balanced energy protein supplementation, intermittent preventive treatment of malaria in pregnancy, multiple micronutrient supplementation, insecticide-treated nets (ITN), anti-platelets for preeclampsia, and smoking cessation. **(2)**

Fetal and Neonatal Problems Associated With FGR

The importance of FGR for the obstetrician is derived from its association with problems during the newborn period and in adult life but especially during intrauterine life. Recognition of FGR, adequate surveillance of the pregnancy, and timely delivery of the compromised infant will have a significant impact in decreasing the morbidity and mortality associated with this condition. **(8)**

Antepartum Complications

Fetal hypoxia and acidosis

Prenatal and Intrapartum hypoxia and acidosis are the most important and frequent complications of FGR particularly when the growth disturbance is due to placental insufficiency. **(16)**

There is a clear relationship between FGR and stillbirths. One study found that approximately 20% of all stillborn show signs of growth restriction. **(16)**

Intrapartum Complications

The main problem during labor of fetuses with FGR is the high incidence of intrapartum hypoxia and acidosis. **(16)**

Neonatal Complications

The diagnosis of FGR is easier after the baby is born. At birth, the FGR infant shows signs of soft tissue wasting. The skin is loose and thin, and there is little subcutaneous fat. The abdomen is scaphoid, the ribs are protuberant, and the muscle mass of the arms, buttocks, and thighs are reduced. The umbilical cord is limp, thin, and frequently meconiumstained. Most of the time it is apparent that the HC is larger than the AC. The birth weight and in most cases and the placental weight are below the 10th percentile, the normal SGA baby has symmetric development of the head and abdomen and a normal amount of subcutaneous fat. **(17)**

The neonatal course of the PFGR infant is different from that of the normal SGA baby. Small and healthy newborns rarely have significant problems and in the major of cases go home after an uneventful stay in the nursery in contrast, the PFGR newborn frequently develops complications. **(17)**

The most important ones are related to perinatal asphyxia and fetal distress (persistent fetal circulation, meconium aspiration syndrome, intraventricular bleeding, hypoxic-neonatal encephalopathy); to metabolic alterations (hypoglycemia, hypocalcemia, hyperviscosity syndrome, hypothermia); and to specific cause of fetal restriction (infections, congenital malformations, chromosomal abnormalities). **(17)**

Long-Term Prognosis

Today, a large number of FGR babies survive the neg atal period; therefore, more and more attention is focused on their long-term growth and development. The main question is whether these babies will recover completely from the intrauterine malnutrition or if they will permanently suffer the consequences of the fetal insult. The most important areas with respect to long-term prognosis are the growth pattern after birth, the relation of FGR with neurological development, and the potential effects of FGR in adult disease. **(17)**

Postnatal growth

A nearly universal finding is that FGR babies as a group remain smaller than their AGA cohorts in follow-up examinations. This is found despite the occurrence, in some cases, of "catch-up growth" during the first 6 months of life. Several years after birth, 30% of FGR babies will remain below the 30th percentile for weight of children of equal age and only 10-20% will be above the 50th percentile. **(18)**

Several studies have looked for characteristics that may help to differentiate those FGR babies who will remain growth-stunted and those who will move into more normal growth patterns. It is found that if growth is to catch up, acceleration of growth has to occur during the first 6 months of life. They also found that the degree of initial growth failure does not have predictive value and that babies who are severely affected at birth have as good a chance as less affected infants of growing into normal percentiles. **(18)**

The probability of developmental problems is lower when there is catch-up growth during the first 6 months of life. The worst prognosis is for babies with FGR secondary to congenital infections or abnormalities or chromosomal defects. **(18)**

It was found that infants whose growth retardation started before 34 weeks of gestation are more likely to be below the 10th percentile at 4 years of age than are babies whose growth impairment was diagnosed after 34 weeks. **(18)**

Cerebral palsy

FGR is universally recognized as an important risk factor for abnormal neurological development and cerebral palsy. Follow-up studies between 3 and 9 years of age have clearly demonstrated that intelligence, motor skills, and speech and reading abilities are affected in PFGR. **(18)**

PFGR secondary to congenital anomalies and infections has a significant incidence of major neurological problems later in life. Minimal brain dysfunction (hyperactivity, decreased attention span, learning difficulties, poor coordination) affects approximately 25% of PFGR infants. **(18)**

Other investigators have found a mean developmental quotient depressed by nearly 10 points in infants whose growth failure had an early onset as compared to either late-onset or normal controls. The outcome of FGR and AGA fetuses affected byl asphyxia at birth is different and FGR fetuses have a higher probability than AGA fetuses of developing neurological problems in early childhood. **(19)**

Adult disease

Several epidemiologic studies have suggested an association between low birth weight and the development of chronic hypertension, abnormal lipid profile, ischemic heart disease, and type Il diabetes in adult life. 75

Commonly accepted explanation for this association that the maturation of different organs and systems is programmed to occur at critical periods during intrauterine life and that an insult or perturbation of this program by a condition that causes low birth weight will result in long-term effects on organ or system function that will be apparent during adult life. **(20)**

Gestational Programming

Barker, in his observational studies, showed that infants who were born in the 1920s and 1930s with low weight, when they grew up to adulthood had high incidence of coronary heart disease, diabetes mellitus, hyperinsulinemia, and hypercholesterolemia. **(21)**

This observation was confirmed in other studies and it was postulated that fetal life insult gave pathway to these adult diseases. This was known initially as fetal origin of adult disease (FOAD) that has been replaced now with the term “developmental origin of health and disease (DoHaD). **(22)**

Three different hypotheses have been purposed for this causal relationship, namely, fetal insulin hypothesis and mature onset diabetes of the young (MODY) genes, thrifty genotype, and thrifty phenotype (Barker hypothesis). The Barker hypothesis is the most accepted theory for DoHaD. **(22)**

Beginning in the late 1980s, however, data gleaned first from population-based epidemiologic studies, later supported by animal research, has provided strong evidence that fetal size at birth is related to a variety of health problems in later life. Furthermore, it has become clear that the risk of these conditions is not limited to those born pathologically small due to intrauterine growth restriction, but rather applies across a continuum of weights. **(20)**

Although a variety of health problems have been linked to size at birth, including stroke, breast cancer, and atopy, the most robust evidence is that correlating size at birth with adult-onset insulin resistance, hypertension, and cardiovascular disease. **(20)**
Enhanced risk is observed in those exhibiting rapid catch-up growth in subsequent life.? **(20)**
The impact of infant size at birth, and thus of the fetal in utero milieu, does not end with the first generation. Indeed, mothers themselves born small tend to have smaller than average offspring who suffer higher than average rates of infant mortality. **(20)**

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