Neurodevelopment after Fetal Growth Restriction

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Introduction

Fetal growth restriction (FGR) secondary to placental dysfunction is associated with a range of adverse long-term outcomes. Among these, neurodevelopment has received considerable attention because it can have a profound impact on the quality of life and potential of the individual [1, 2]. Because the developing brain exhibits plasticity as well as a limited potential for regeneration following injury, it is important to understand the antecedents of abnormal neurodevelopment in order to determine the potential for prevention [3]. One of the challenges in understanding these antecedents is the variation of the risk profile that is determined by the clinical phenotype of FGR. The aim of this overview is to provide an estimate of the neurodevelopmental impact of various aspects of the disease.

Phenotype and Risk Profile of Early- and Late-Onset Fetal Growth Delay

Early- and late-onset FGR represents two distinct clinical phenotypes of placental dysfunction [4]. Early-onset FGR is associated with reduced placental perfusion due to a decrease in villous cross-sectional vascular area, which
leads to elevated umbilical artery (UA) blood flow resistance once villous damage exceeds 30% [4]. Typically, FGR is established by the second trimester, and the diagnostic hallmark is the combination of fetal measurements below the 10th percentile in association with abnormal UA Doppler [5]. Late-onset FGR is established in the third trimester. It is more common than early-onset disease, and is associated with a range of placental abnormalities including villous immaturity that interfere with gas and nutrient exchange but have less pronounced effects on villous vascular resistance [6]. Therefore, UA Doppler may be normal, but the fetus may react with decreased middle cerebral artery (MCA) impedance in response to hypoxemia [7]. Because of the variations in underlying placental disease, the diagnostic hallmark of late-onset FGR is a small fetal size <10th percentile associated with any of the following: (1) elevated UA Doppler index, (2) decreased cerebroplacental Doppler ratio (UA/MCA index), (3) decrease in the MCA Doppler index even if the UA is normal [4].

Following the time of diagnosis, early- and late-onset FGR differ significantly in clinical progression. In early-onset disease, elevated UA Doppler resistance is followed by MCA brain sparing, escalating blood flow resistance in the UA with progressive reverse shunting in the aortic isthmus followed by deterioration of venous Doppler parameters and finally the biophysical profile score. Progression to the point of delivery, typically taking 4–6 weeks, is determined by the timing of UA end-diastolic velocity reversal. In contrast, in late-onset FGR progression may take up to 9 weeks and is subtle; UA Doppler may be normal, a decrease in the CPR may occur or isolated MCA brain sparing may be observed [8]. Biophysical abnormalities may not extend beyond loss of heart rate reactivity or decrease in the amniotic fluid index [4]. Due to these differences in clinical behavior nutritional deprivation, fetal deterioration and delivery considerations also differ in their timing in relationship to fetal neurodevelopmental milestones.

FGR and Delay in Fetal Neurodevelopment

Fetal developmental milestones correlate with the transition of neurogenesis to accelerating synaptogenesis reflecting the increasing sophistication of central regulation of physiological and behavioral variables [9–11]. In the first trimester, individual activities such as tone and breathing occur randomly. By 20 weeks, diurnal variation of fetal movement and heart rate patterns, with increased activity in the second half of the day, emerges [12]. Coupling of physiological inputs (e.g. linking of fetal breathing frequency to maternal glucose levels) and rest-activity cycles become established from 26 to 28 weeks [13, 14]. Fetal heart rate reactivity in response to movement, fully established by 32 weeks’ gestation, allows correlation of heart rate patterns to behavioral states. Fetal behavioral states 1F–4F, which correspond to their neonatal counterparts, are established between 32 and 36 weeks’ gestation [15, 16]. At this time, there is also integration of behavioral and cardiovascular control that allows modulation of individual vascular beds during different behavioral states [17–21]. The factors that regulate this neuronal maturation include sufficient nutrient delivery as well as immune and endocrine placental-fetal interactions [3].

Early-onset FGR is associated with delay of fetal neurodevelopmental milestones [22–24]. Behavioral state establishment and heart rate reactivity may be delayed by up to 4 weeks. In contrast, late FGR occurs after establishment of behavioral states, and therefore is more likely to result in abnormal movement quality and state transitions [25–30]. Despite this delay in intrauterine behavioral development, the FGR fetus retains the sequential loss of dynamic variables in response to worsening metabolic status [14].

Although the relationship between placental dysfunction and fetal neurodevelopmental delay is recognized, there is limited information about the long-term developmental impact of this prenatal delay [1]. A decrease in the amount of movements is more likely a response to deepening hypoxemia and is less predictive of 2-year motor delay [31, 32]. In contrast, abnormal fetal movement quality, particularly if persistent beyond delivery, has a stronger relationship with motor delay at age 2 [33–37].

Parameters of Fetal Growth and Neurodevelopment

In the fetus, nutrient delivery and cardiovascular dynamics are linked, and nutrient streams are partitioned at three important sites: the ductus venosus (DV), foramen ovale and aortic isthmus [38]. Decrease in transplacental nutrient delivery triggers DV redistribution of venous return at the expense of the liver. When placental blood flow resistance is elevated or when MCA brain sparing is triggered, there is redistribution of cardiac output toward the myocardium and brain [38]. However, the relative increase in blood flow resistance in the descending aorta also promotes retrograde shunting of nutrient-poor
In late-onset FGR, slowing subsequently poorer school achievement ability and defects in short-term memory, with eventually head growth may no longer be maintained and the fetus becomes symmetrically small (abdomen and head are equally affected) [1, 4, 38–40].

Widely utilized prenatal measures of fetal size include the estimated fetal weight, the head circumference (HC), AC and HC/AC ratio expressed as percentiles. Small fetal head size is one of the most powerful prenatal predictors of adverse neurodevelopment, independent of gestational age or the degree of fetal compromise of Doppler or biophysical parameters. In early-onset FGR, a disproportional reduction in head growth and overall reduction of fetal size predict cerebral palsy, psychomotor and cognitive development [41, 42]. In late-onset FGR, slowing head growth is associated with a decrease in perceptual performance, motor ability, cognition, concentration ability and defects in short-term memory, with subsequently poorer school achievement [43]. The relationship between head growth and neurodevelopment appears to be a continuum as each standard deviation in size decrease increases the rate of suboptimal outcome by 10% in one study [44].

The powerful impact of decreased head size on neurodevelopment suggests that cerebral nutritional deprivation during the evolution of placental dysfunction is a central mechanism mediating developmental impacts [1].

Impact of Cardiovascular Compromise on Neurodevelopment

Most Doppler studies do not control for the clinical phenotype of FGR or the degree of cardiovascular information that is required to accurately reflect the degree of compromise [1, 2]. The majority of studies evaluate single, mostly arterial vascular beds, which is a confounder in early-onset FGR where widespread cardiovascular responses are characteristic. This is less of an issue for late-onset FGR where Doppler abnormalities typically do not extend beyond the cerebral circulation.

In early-onset FGR, loss of UA and descending aortic end-diastolic velocity are associated with abnormal acid base balance, decrease in the CPR or MCA PI correlated with deepening hypoxemia, and abnormal venous Doppler parameters provide the closest stratification for acedia and stillbirth risk [4]. Absent or reversed UA end-diastolic velocity (UA AREDV) has an independent impact on neurodevelopment from the late second trimester onward. This is reflected in lower motor developmental index at age 2 and lower cognitive performance thereafter [45, 46]. In childhood, UA AREDV survivors have more than twice the rate of major neurologic sequelae and a 10% higher rate of minor neurologic sequelae, while the intelligence quotient is similar [47]. At age 6 years, fine motor and gross motor scores are over 20% lower than in AGA controls, and Kaufman ABC scores are lower for all domains [48, 49]. In particular reversed end-diastolic velocity is an independent risk factor for adverse motor and cognitive development all the way to adolescence [50].

In early-onset FGR requiring delivery prior to 30 weeks, neonates with prenatal evidence of cardiac compromise are likely to have the worst motor development [51–55]. In fetuses with milder placental disease delivered between 30 and 31 weeks delivered prior to DV deterioration, MCA brain sparing is associated with lower scores in areas of habituation, social-interactive, motor performance and attention [56]. However, neither venous, cerebral or central Doppler studies, nor the biophysical profile score add risk stratification that is independent of the UA Doppler status, gestational age at delivery and the degree of growth restriction and confounders such as steroid use and neonatal complications, especially intracranial hemorrhage [57–60].

Late-onset FGR babies are at increased risk for lower cognitive developmental scores irrespective of prenatal Doppler status. When the UA Doppler is abnormal, the rate of suboptimal neurodevelopment at age 2 may be as high as 15% [61]. The impact on behavioral domains such as attention, habituation, motor, social-interactive and state regulation seems to predominate in small for gestational age neonates [62] and translates to significantly lower scores in the problem solving and social domains compared to AGA controls [63]. These domains are related to frontal lobe function, and several observations support the concept that this area of the brain is especially vulnerable to fetal nutrient deficiency in the third trimester [64]. When cerebral artery Doppler findings are considered, it becomes apparent that regional specialization of the fetal brain and regional changes in cerebral blood flow resistance interact to produce specific developmental abnormalities. MCA brain sparing is associated with lower ASQ scores in communication, problem solving and personal-social areas [65]. A larger study that
evaluated impedance changes in anterior and middle cerebral vascular territories showed that the former were related to emotional-reactive, attention and somatic scores, while the latter related only to somatic complaint scores [66]. Power Doppler studies utilizing more sensitive techniques provide evidence of regional shifts in cerebral perfusion that occur even earlier before measurable differences in individual cerebral vascular beds can be measured with conventional Doppler [67, 68].

**Fetal Deterioration before Delivery**

The basic concept that fetal deterioration prior to delivery has a long-term impact is based on cordocentesis data indicating a closer relationship between neurodevelopment with acidemia rather than hypoxemia [69]. It is difficult to translate these findings in clinical studies that evaluate birth pH since the latter may be related to perinatal deterioration as well as intrapartum events. Several studies have considered the birth pH in addition to other parameters defining the severity of FGR. Only one study indicated that a pH <7.00 may be a cofactor for a low Bayley or Griffiths score <85 [55].

An abnormal biophysical profile score can be considered as strong evidence for a prelabor pH <7.20 and has been shown to be associated with an increased risk for cerebral palsy in unselected populations [14, 70]. However, early-onset FGR does not have an independent impact on 2-year neurodevelopment [53]. In less severe forms of early-onset FGR, incremental vascular deterioration beyond the UA Doppler affects several behavioral domains [56]. Similarly, in late-onset FGR, patients that are delivered for maternal rather than fetal indications tend to have better neurodevelopmental outcomes [61, 71]. One can hypothesize that in these studies improved neurodevelopment occurred because delivery occurred before fetal deterioration. To this date, it remains to be determined which prenatal testing parameters stratify the type of fetal deterioration that is most predictive of neurodevelopment.

Several studies indicate that current surveillance parameters do not achieve this. Recent observational studies indicate that neither UA status nor cerebral Doppler studies stratified the risk for cognitive development in term FGA pregnancies [72, 73]. In the DIGITAT trial, randomization of delivery timing with safety criteria to intervene for fetal indications did not produce any significant differences in early infant development either [74]. It therefore appears that in early-onset IUGR there are a multitude of additional factors dictated by disease severity that have a far greater impact on neurodevelopment than fetal deterioration prior to delivery. In term FGA, however, deterioration seems to have a contributing effect, and it remains to be determined which prenatal measures provide the best definition of the associated neurodevelopmental impact.

**Impact of Delivery Timing**

The timing of delivery determines the gestational age when transition to extrauterine life occurs. The majority of studies in FGR pregnancies are observational, where gestational age at delivery is determined by several factors including the speed and degree of fetal deterioration, physician preference and local practices. In the randomized GRIT and DIGITAT trials, delayed delivery was essentially timed by the physician perception that ongoing expectant management is no longer safe [75, 76]. Accordingly, evaluating the precise relationship between fetal surveillance parameters that defined the delivery indication and neurodevelopment is only possible through secondary analyses. In contrast, the TRUFFLE study specified delivery criteria for the randomization arms, and therefore will allow examination of the developmental impact of these decision indicators [77]. Despite these limitations, important information on the impact of delivery timing on neurodevelopment has emerged.

In early-onset FGR, gestational age at delivery shows a consistent independent relationship with parameters of motor development with a maximum impact for infants delivered before 28 weeks [53, 54, 78–80]. This impact is independent of other variables of fetal disease such as the severity of growth delay and the degree of cardiovascular and biophysical deterioration. In the GRIT study, 98% of patients completed 2-year follow-up. The rate of cerebral palsy was greater for patients randomized to immediate delivery prior to 31 weeks’ gestation, and prematurity-related complications were important contributors to this risk [81]. Based on several studies, the rate of cerebral palsy for early-onset FGR ranges between 8 and 12% for women delivered before 32 weeks [53, 55, 81, 82]. The predominance of motor impact and the contributory role of neonatal complications suggest that intraventricular hemorrhage is an important mediating factor for poor neurodevelopment [57–60]. A smaller proportion of GRIT participants completed standardized assessment of cognition, language, behavior and motor ability at 6–13 years. There were no differences in the rates of severe dis-
ability and individual domain scores between the two delivery arms, and results were comparable to other preterm cohorts without FGR [83].

The findings of the DIGITAT trial in term small for gestational age children confirm observational data indicating that gestational age difference at delivery does not contribute to 2-year neurodevelopment for patients delivered beyond 38 weeks gestation [72, 74]. For patients delivered before that, several observational studies indicate that gestational age is related to motor, social-interactive, habituation and cognitive subscales [62, 71, 84].

These studies suggest that in early-onset FGR, gestational age itself and the prematurity-associated liabilities determine childhood motor development. In late-onset FGR, gestational age becomes a smaller contributor, and further studies are necessary to determine which fetal variables at the time of delivery are the main determinants of neurodevelopment [85].

Conclusions

There is great heterogeneity in the studies evaluating neurodevelopment in patients with FGR. This is due to the fact that our understanding of the clinical phenotype of early and late FGR is actively evolving. As a consequence, the classification of fetal disease has to be inferred from studies’ findings rather than a uniform application of prospective classification. Despite these differences, the following principal concepts are emerging.

In early onset FGR, the nutritional and vascular restriction in placental function limits the neurodevelopment potential. Prematally, this is evident through the late achievement of fetal milestones. The magnitude of impairment relates to the degree of restriction of head and body growth. Placental Doppler is the most powerful predictor of the clinical deterioration and the circumstances surrounding delivery. With gestational age as the major determinant, fetal status at delivery and prematurity-related complications interact as determinants of neurodevelopment. It remains to be determined if interventions other than modulating disease course have any hope at improving neurodevelopment.

In late FGR, the significant nutritional impact occurs when fetal behavioral states have emerged. Nutritional deprivation impacts on behavioral domains rather than motor functions. As the impact of prematurity is no longer an issue, identifying prenatal markers for adverse neurodevelopment holds greater promise than in early-onset FGR. To this date, these markers have not been sufficiently delineated to guide clinical management.

References

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