Cerebral Blood Flow and Metabolism in the Developing Fetus

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• Fetal brain • Fetal circulation • Brain development
• Fetal hypoxia • Fetal energy metabolism

Acute and long-term oxygen substrate deprivation is a major cause of disrupted fetal brain development and long-term neurologic morbidity. Before truly informed and meaningful brain-oriented fetal care can become a clinical reality, major advances will be required in the understanding of fetal brain hazards and the mechanisms by which normal brain development is derailed. Although a myriad of potential insults may disturb brain development, this article focuses primarily on those intrinsic systems that reduce the risk of fetal cerebral energy deprivation by maintaining a positive balance in cerebral oxygen–energy substrate demand and supply. Because of the inability of the human fetal brain to direct measurements of hemodynamics and metabolism, current understanding is based in large part on data from experimental animal models and from studies of the premature infant, or ex utero fetus. Although both models have provided important insights, neither is ideal, and the understanding of the primary and compensatory support systems for in vivo brain metabolism in the human fetus remains poor. This article reviews the current status of this understanding.

ENERGY SUBSTRATE DEMANDS FOR NORMAL FETAL BRAIN DEVELOPMENT

The energy demands of the developing brain can be classified broadly as those required for its structural growth (accretion) and maintenance and those required for the functional activation of neuro-axonal and glial populations of the brain. These two sources of energy demand are of course wholly interdependent, and particularly

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during the later stages of development, the microstructural development of the immature brain depends heavily on activation-related trophic stimulation.[1–3] Given the rapid increase in brain mass, which is caused by explosive development of synaptic, dendritic, and axonal elements in the cortical and subcortical gray matter, the cerebral oxygen substrate demands increase exponentially during the later stages of pregnancy.

Structural Brain Development

Anatomic events in early brain development provide the structural substrate upon which later functionally driven changes in microstructural development are imposed. The critical events in brain development of the human fetus are reviewed in more detail in other articles in this issue; however, the broad stages of brain development may be summarized as follows. Primary neurulation leading to formation of the neural tube occurs before 4 weeks of gestation, and by 5 weeks, the neural tube has a well-defined rostral–caudal and dorsoventral organization. Development of the prosencephalon commences between 8 and 12 weeks of gestation, with neuronal proliferation and migration occurring between 8 and 20 weeks of gestation. These phases are followed by major events in cortical organization starting around 20 weeks of gestation and persisting well into postnatal development. Although myelination of the posterior fossa structures occurs during the fetal period, that of the supratentorial tissues occurs primarily after term gestational age.

Around the 11th week of gestation, formation begins of the transient subplate layer, which serves as a relay holding area for thalamocortical projections; this is the site of the first synapses, the activity of which is critical for developing cortical and thalamic projections.[4] Between 24 and 28 weeks of gestation, there is a period of major refinement of cortical connections with an explosive increase in cortical synapse formation and remodeling, and the development of functionally coordinated outputs from the cerebral cortex.[5–7] In fact, the developing cortex has about 40% more synapses than the mature brain, with the excess synapses being trimmed back by active remodeling. These cortical activities coincide with a phase of major disassembly of subplate synapses and the energy-dependent programmed death of subplate neurons.

Between 28 weeks of gestation and term, these cortical events are largely responsible for an almost threefold increase in brain weight.[8] The features of this period of accelerated brain growth have been described by quantitative in vivo magnetic resonance imaging (MRI) studies in premature infants[9] and more recently in the fetus (see the article by Limperopoulos elsewhere in this issue). Such studies have shown that over the course of the third trimester, the cerebral cortex volume increases fourfold,[9,10] as does the volume of the cerebellar hemispheres.[10] This phase of rapid cortical development demands a major increase in energy supply, because cerebral microstructural development depends on functional activation of neuroaxonal units, which in turn depends upon repeated restoration of transmembrane ionic gradients by energy-dependent enzymes (such as Na-K/adenosine triphosphatase [ATPase]).

Functional Brain Development

The functional development of the fetal brain can be viewed from both electrochemical and behavioral perspectives. The accelerated electrochemical maturation of the brain during the latter half of gestation is associated with an increasingly complex repertoire of fetal movement patterns and the emergence of behavioral states. The onset of spontaneous electrocortical activity in the developing human brain remains unclear. Scalp electroencephalography (EEG) recordings in premature infants, however, show bursts of activity alternating with periods of quiescence as early as 24 weeks