

## Preface



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*Guest Editor*

That events in the fetal period may be critical determinants of lifelong neuropsychological function is not a new concept. However, the vast extent and diversity of fetal experiences and the broad spectrum of their postnatal impact are rapidly achieving greater recognition. Two apparently parallel avenues begin at this time to intersect in an enticing way. First, the accelerating field of neurogenetics is vitalizing our understanding of the highly programmed process of brain development and, in cases of brain dysgenesis, its derailment. Second, investigations of internal and external environmental influences are greatly expanding our understanding of their fundamental role in normal and disrupted fetal brain development. The growing body of data from both these avenues of investigation no longer labels one or the other as primary or secondary but instead highlights their complex interactions. In fact, these discoveries have led to a paradoxical decrease in the distinction between genetic and experiential influences on the developing fetal brain. Increasingly we recognize that the expression of genetic programming may be influenced by environmental factors, even in a trans-generational epigenetic manner. Conversely, genetic predisposition may render some fetuses more vulnerable than others to acquired insults and disrupted brain development. Advanced fetal neuroimaging suggests that several fetal brain anomalies previously believed to have an as-yet-undiscovered genetic basis may instead result from acquired insults that disrupt the primary developmental program.

With these new intersections in mind, this issue of *Clinics in Perinatology* includes selected topics that highlight areas of major progress in fetal neurology. Inevitably, other very exciting developments could not be included because of limited space. We begin by reviewing recent advances in our understanding of the genetic and environmental factors involved in normal and abnormal brain development. Areas of focus include fascinating new insights into the development of the cerebral cortex and of the cerebellum. Drs. Diaz and Gleeson offer insights into the role of specific gene products in neuronal migration and organization and the important role of transient structures, such as the subplate zone, during neocortical development. Equally exciting are the significant advances in our understanding of cerebellar development with its complex

patterns of cellular migration, as presented by Drs. ten Donkelaar and Lammens. Few areas of human dysmorphology have been as difficult to categorize in a clinically meaningful manner as anomalies of the posterior fossa. The growing body of genetic and histogenetic information about cerebellar development discussed in their review will hopefully lead to a more rational and prognostically useful template for posterior fossa dysgeneses.

As the discipline of fetal neurology grows and the notion of informed brain-oriented management develops, it will be of critical importance that the normal mechanisms of oxygen/substrate supply to the developing brain be understood and become measurable. In the human fetus, both these challenges remain daunting. My article discusses current concepts of fetal oxygen/substrate supply, largely extrapolated from animal experiments, followed by Dr. Redline's review of placental mechanisms of impaired cerebral oxygen/substrate supply. Dr. Limperopoulos then reviews brain growth impairment in the fetus with congenital heart disease and discusses potential mechanisms by which cardiovascular malformations may disrupt the normal delivery of oxygen/substrate to the fetal brain, impair normal compensatory responses in the fetal circulation, or both. Drs. Gunn and Bennet follow with a discussion of experimental studies into the mechanisms and manifestations of different "doses" of oxygen/substrate deprivation. Their work emphasizes the importance of being able to detect and measure brain insults in the fetus and highlights our current inability to do so reliably.

A multitude of toxic substances and infectious agents are capable of injuring the immature brain and disrupting its developmental program. Here we review two important forms of toxic disruption of normal brain development. Dr. Lester and colleagues first discuss exogenous maternally transmitted substances, prescribed or illicit, capable of disrupting fetal neurotransmitter systems and thereby mediating later neurodevelopmental disturbances, a phenomenon termed "behavioral teratology." Dr. Lerman-Sagie and colleagues review the increasing recognition of an endogenous form of developmental neurotoxicity in fetuses with inherited errors of metabolism; in these cases, the deprivation or excessive accumulation of metabolic substances may disrupt normal structural brain development. The importance of this phenomenon is that clinicians diagnosing a structural brain malformation in infants with neurodevelopmental impairment may assign culpability to a primary (and assumed static) genetic mechanism, whereas progressive neurologic failure may result from ongoing brain toxicity due to the underlying metabolic defect. The role of infection in mediating injury to the immature brain has received widespread attention in recent years; much of it focused on the cytotoxic effects of inflammatory cytokines on the immature oligodendrocyte. However, other infectious agents, particularly viral agents, are capable of disrupting normal brain development and causing encephaloclastic parenchymal injury. Dr. Bale addresses the complex interplay between fetal infection, inflammation, and brain development, wherein the manifestations of fetal infections are determined by the concurrent developmental events in the fetal brain.

The final series of reviews focuses on recent advances in diagnostic techniques for the assessment of fetal well-being. Drs. Bennett and Gunn offer a detailed review of the fetal heart rate response to hypoxia, based on an elegant series of experimental studies in fetal sheep. Drs. Wolfberg and Norwitz discuss a number of innovative patterns not only to extract meaningful quantitative information from the variability patterns in the fetal heart rate (FHR) recording but also to interrogate the fetal electrocardiogram waveform. These techniques are early in development, and extensive validation studies will be necessary before they enter clinical practice. Although the value of FHR monitoring techniques as currently applied has been questioned extensively,

ongoing exploration of fetal heart signals remains a very important avenue of research for several reasons. First, the FHR signal is easily accessible, and its measurement widely available. In addition, with the paucity of other promising techniques on the immediate horizon, the FHR signal is likely to remain, at least for the foreseeable future, the only continuous physiologic fetal signal readily available during the intrapartum period.

The successful application of magnetic resonance imaging (MRI) with its vastly superior soft tissue resolution has revolutionized studies of the human fetus, and especially of the fetal brain. Dr. Prayer and colleagues discuss the rapid advances in fetal MRI to date and the anticipated future developments, which promise to open other avenues for fetal brain study. Finally, the lack of established techniques for assessing fetal electrocortical function has confined our assessment of fetal brain function to analysis of fetal movements and behavioral state change. The technique of magnetoencephalography is now firmly established in epilepsy. As presented by Dr. Lowery and colleagues, the successful application of this technique to the noninvasive assessment of fetal electrocortical activity presents a hugely exciting opportunity for more informed fetal neurologic evaluation in future.

In the preface to their book *Fetal Neurology* some 20 years ago, Joseph Volpe and Alan Hill introduced clinicians to the notion of a distinct new discipline focused on “the time of life...that is often the most critical and invariably the most mysterious.” Well, certainly the mystery continues! Although their anticipation of a distinct new discipline within a decade of that publication was perhaps optimistic, there can be no denying that a remarkable set of diagnostic instruments has continued to accrue over the intervening period. Given our burgeoning understanding of the immature brain and the hazards confronting it and given the comprehensive battery of diagnostic tools now at our disposal, we have little excuse to further delay in rallying expertise around the critical challenges of ensuring fetal brain well-being.

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