

## The Great Obstetrical Syndromes: a paradigm shift

The perinatal period is crucial in determining the future health of an individual. Several studies have indicated that abnormalities during fetal and neonatal life can lead to chronic disease in adult life. For example, chronic hypertension, diabetes, stroke, and death from coronary artery disease in adults has been linked to intrauterine malnutrition. Under-nutrition during the fetal and postnatal periods has been shown to cause permanent changes in lipid metabolism and hemostatic factors, which greatly increase the risk of cardiovascular disease. Men with a history of being born with short stature and small abdominal circumference have been shown to have low lipoprotein cholesterol, elevated concentrations of fibrinogen and factor VII, all risk factors for cardiovascular disease. Some cases of male infertility have also been linked to intrauterine exposure to environmental estrogens.

The notion that intrauterine conditions play a role in determining adult health has been long held for over 150 years. The association between cerebral palsy and intrapartum hypoxia is an early example, which inspired the introduction of electronic fetal heart rate monitoring during labor to reduce the incidence of cerebral palsy. However, its failure to predict disease, as dashed by randomized clinical trials and epidemiological studies, became a milestone event that taught a valuable lesson about the obstetrical diagnoses as doctors are beginning to understand today: perinatal conditions, or what they call the “great obstetrical syndromes” are characterized by multiple etiologies.

Perinatal medicine is currently at a stage when only clinical syndromes can be identified, and not yet specific pathways to disease. The complexities that underlie obstetrical syndromes is reflected in the five common conditions responsible for perinatal mortality and morbidity: premature labor/delivery, premature rupture of membranes, small for gestational age, congenital anomalies and pregnancy induced-hypertension. For example, it is unclear whether premature labor is due to infection, vascular insult, uterine over distension, or some other pathological process. Likewise, small for gestational age does not indicate whether it is caused by viral infection, cytogenetic disorder or retarded intrauterine growth.

Many obstetrical syndromes also result from adaptive responses of the maternal-fetal unit to pathological insults. More specifically, pre-eclampsia is a response to early alterations in uteroplacental vascular resistance where raised blood pressure is a symptom of disease rather than the cause. Premature labor is a response to intrauterine infection that allows the fetus to exit a hostile environment. Fetal growth retardation is likewise, an adaptation to intrauterine under-nutrition. With this in mind, it is understandable why antihypertensive therapy to treat pre-eclampsia and tocolysis to treat preterm labor does not work. These therapies treat the maternal-fetal responses to disease rather than target the disease process directly.

Furthermore, most obstetrical syndromes have a long subclinical phase and are the late clinical manifestations of chronic pathophysiological processes. For example, abnormal Doppler waveforms in uterine arteries or abnormal blood pressure responses to angiotensin II can be detected weeks before the onset of pre-eclampsia. Ascending uterine infections can also be detected days or weeks before preterm labor or preterm premature rupture of membranes.

While the long subclinical phase offers an opportunistic chance for early disease detection, it must be considered that the diversity of etiologies and low prevalence of obstetrical syndromes will make it unlikely for any one test to identify all cases. A large number of women would have to be unnecessarily screened and the test would have to be highly sensitive in order to eliminate excessive false-positives.

Despite the hurdles, obstetricians and neonatologists have high hopes for the early detection, treatment, and prevention of perinatal conditions. In order to be successful and effective, the foundations of perinatology must be merged with the techniques of developmental biology. While screenings to predict the five most common perinatal conditions are already in use, the pathophysiological mechanisms that drive the great obstetric syndromes must be defined on the molecular and cellular scale in order to detect them earlier and prevent the permanent impact of clinical onset.

At Kofinas Perinatal we have been focusing on early detection of placental pathology that is responsible for the obstetrical syndromes. Early detection allows us to intervene with the appropriate treatments and change the outcomes for the better. Such treatments according to our protocols reduce preeclampsia, preterm birth and preterm rupture of membranes by as much as 90%. Severe early intrauterine growth retardation, which affects 2-3 % of all pregnancies, is a rare event in our patients because of such early detection and proper treatment.