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# ORATIONS

## Prevention of Cerebral Palsy: The Role of the Fetal Biophysical Profile

**Frank A. Manning**
Professor, New York University School of Medicine

In postnatal life it is a widely accepted and generally proven clinical fact that a sustained interruption in the delivery of oxygen in the brain, either as a result of diminished blood oxygen content (hypoxemia), diminished oxygen delivery (ischemia) or both (asphyxia), can cause necrosis of neurons with resultant permanent motor and cognitive deficiencies. Experimental observations in mammalian fetuses and serendipitous human clinical observations suggest that the fetus in utero is also as risk for permanent cerebral injury when confronted with a sufficiently severe and sustained hypoximic/ischemic insult. There is no doubt that fetal asphyxial insults can and do occur in the intrapartum and antepartum periods. The mammalian fetus has evolved compensatory mechanisms to prevent or ameliorate the effect of asphyxia. The acute compensatory responses involve selective sequenced shutting down of non-essential biophysical activities and can net the fetus an immediate 20% or more reduction on oxygen consumption. The reflex chemoreceptor response results in redistribution of cardiac output away from non-essential organs towards essential organs (brain, heart, thymus, placenta). The fetal biophysical profile is based on a dynamic ultrasound survey of these acute responses (heart rate accelerations, fetal breathing, movement and tone) and the reflex response (amniotic fluid volume). There is a highly significant inverse exponential relation between the fetal biophysical profile score and the presence and degree of asphyxia. Thus the fetal biophysical profile score can be used as a *reliable accurate proxy* for asphyxia. In a study of in excess of 66,000 pregnancies whose offspring were followed for up to 18 years of age we have observed a highly significant inverse exponential relation between last fetal biophysical profile and the incidence of cerebral palsy, mental retardation, delayed development and attention deficit disorder. In a prospective clinical trial we compared the incidence of cerebral palsy and other adverse neurological sequelae in offspring of 26,000 high risk pregnancies managed by serial fetal biophysical profile similar endpoints in 75,000 predominantly low risk pregnancies managed without serial fetal biophysical profile testing. The incidence of cerebral palsy in the tested population was 1.3 per 1000 as compared to 4.74 per 1000. This difference was highly significant ($p < 0.0001$). In the tested population there were significant reductions on the incidence of language delay, developmental delay, mental retardation, cortical blindness, cortical deafness and attention deficit disorders. We conclude that antenatal recognition of evolving hypoxemia.\/ischemia and timely intervention can prevent some infants from sustained neurological injury.

## Foetal Medicine: Multi-specialty Approach

**Sharad Gogate**
Director, FMCS & Surlata Hospital. Former Chief, Foetal Medicine Clinic, LTM Medical College, Mumbai.

**Foetal Medicine Consultancy Service** (FMCS) ***A Multi-specialty Team Approach***
Foetal Medicine Programs have been functioning in centres across the world for many years, though in India this concept is quite new. We started the first multi-specialty Foetal Medicine program in 1990-91 in Sir HN Hospital Mumbai. It was a learning experience for all of us. After that I was instrumental in setting up department of Foetal Medicine at LTM Medical College in Mumbai in 1992, since 2003 I have been running FMCS at my private Surlata Hospital.
The reasons why we require multi-specialty approach are,

- The information in the field of Foetal Medicine & Clinical Genetics is expanding at such exponential rate that no single specialty or individual can provide comprehensive management of Foetal 7disorders.
- Hence a multi-specialty approach is needed to tackle these complex problems.
- This approach allows the utilization of the combined expertise and scientific resources of the entire faculty for evaluation, counseling and management of rare, complicated diseases in a seamless fashion. This also saves lot of time and avoids confusion due to separate consultations with individual specialists.

**Partners in the program**

- Obstetrician/Perinatologist, he should act as the team co-ordinator. As he enjoys maximum confidence of the pregnant woman and her family,
- Genetic counselor, acts as valuable inter-phase between the medical team and the patient and family members,
- Neonatologist, preferably with experience in clinical genetics,
- Paediatric surgeon,

These four forms the core group and bring other specialists depending upon the individual case requirements. They require many more experts like,

- Imaging specialist viz. Ultrasonography, MRI etc.
- Cyto-geneticist & molecular geneticist ,
- Biochemist for IEM ,
- Microbiologist & Immunologist

**Problems in Obstetric program requiring Foetal Medicine services**

Foetal Medicine program can provide most valuable help and guidance in following situations,

- Genetic problems in Male & Female Infertility,
- Advanced parental age,
- Unexplained IVF failures in ART program,
- Repeated pregnancy losses,
- Family history of genetic disorders,
- Genetic screening and diagnosis for chromosomal, single gene and multi-factorial disorders,
- Structural anomalies on USG scan,
- Unexplained still births/neonatal losses,
- Peri & Pre-conception counseling for high risk cases.

**How are the services provided in FMCS?-1**

- FMCS works in close co-operation with patient, family and referring physician in an advisory role.
- Each referred patient will be examined thoroughly; history in exhaustive details is elicited by the core group. Previous investigations are reviewed. After consulting the relevant specialty colleagues additional invasive/non-invasive tests are done.
- Complicated cases are reviewed by the entire faculty of FMCS to arrive at final diagnosis (where ever possible).

Once the final diagnosis is arrived at (at least in most of the cases)

- Natural history of the disease/disorder, risk of recurrence and management options are evaluated in detail by the group.
- Patient, family members are extensively counseled about the problem under consideration and all the fears and queries are answered and management options are explained.
- Patient is sent back to the referring physician for further management with summary of case, management options, recommendations and follow-up instructions. Full cooperation from FMCS is assured.
- Close follow-up is requested from the referring doctor and the patient, as it is valuable for improving our performance as well as to build a sound data base for each anomaly/problem.

***What are the services offered in FMCS?-1***

- Evaluation, counseling, risk assessment of families at high risk for genetic disorders,
- Pre-marital, pre-conception, prenatal counseling and therapy,

- Genetic screening tests and counseling for various disorders like,
  a) Maternal serum screening for NTD, Aneuploidy, Thalassemia and other haemoglobinopathies, Inborn Errors of Metabolism (IEM), familial cancers etc.
  b) Anomaly scans in first, second trimesters and third trimester scans for foetal maturity and viability. 3-D, Doppler and MRI studies.
- Genetic screening and counseling in ART programs
- Interventional studies like foetal tissue sampling (Chorion Villous Sampling, Amniocentesis, Foetal blood sampling), foetal therapy etc.
- Cytogenetic, molecular genetic studies for diagnosis and management of various genetic anomalies

Work audit of several Foetal Medicine programs in Mumbai city will be presented in the talk.

**Conclusions:**

- Genetic factors are responsible for more than one third disorders/diseases seen in clinical practice hence it is vital to give due importance to them in evaluation and management.
- Genetic factor combines with environmental factors for manifestation of genetic disorder
- Meaningful impact on the incidence and severity of genetic disorders can be made by a national network of comprehensive, multi-specialty foetal medicine programs. The emphasis on preventive aspects and integrating them in the Maternal & Child Health services at all levels. It is definitely cost effective

## Post Genomic Era-Revolution in Prenatal Diagnosis

**Amit Chakravarty**
Genetic Center, Kolkata, Institute of Genetic Engineering , Kolkata

Rapid progress in genome science and a glimpse into its potential applications have spurred observers to predict that biology will be the foremost science of the 21st century. Technology and resources generated by the Human Genome Project and other genomic research already are having major impacts on research across the life sciences. Doubling in size between 1993 and 1999, the biotechnology industry generated 151,000 direct jobs and 287,000 indirect jobs. Revenues totaled $20 billion directly and $27 billion indirectly.

DNA underlies every aspect of human health, both in function and dysfunction. Obtaining a detailed picture of how genes and other DNA sequences function together and interact with environmental factors ultimately will lead to the discovery of pathways involved in normal processes and in disease pathogenesis. Such knowledge will have a profound impact on the way disorders are diagnosed, treated, and prevented and will bring about revolutionary changes in clinical and public health practice.

DNA-based tests are among the first commercial medical applications of the new genetic discoveries. Gene tests can be used to diagnose disease, confirm a diagnosis, provide prognostic information about the course of disease, confirm the existence of a disease in asymptomatic individuals, and, with varying degrees of accuracy, predict the risk of future disease in healthy individuals or their progeny. Currently, several hundred genetic tests are in clinical use, with many more under development, and their numbers and varieties are expected to increase rapidly over the next decade. Most current tests detect mutations associated with rare genetic disorders that follow Mendelian inheritance patterns. These include myotonic and Duchenne muscular dystrophies, cystic fibrosis, neurofibromatosis type 1, sickle cell anemia, and Huntington's disease.

Recently, tests have been developed to detect mutations for a handful of more complex conditions such as breast, ovarian, and colon cancers. Although they have limitations, these tests sometimes are used to make risk estimates in presymptomatic individuals with a family history of the disorder. One potential benefit to using these gene tests is that they could provide information that helps physicians and patients manage the disease or condition more effectively. Regular colonoscopies for those having mutations associated with colon cancer, for instance, could prevent thousands of deaths each year

The potential for using genes themselves to treat disease or enhance particular traits has captured the

imagination of the public and the biomedical community. This largely experimental field—gene transfer or gene therapy—holds potential for treating or even curing such genetic and acquired diseases as cancers and AIDS by using normal genes to supplement or replace defective genes or bolster a normal function such as immunity.

More than 500 clinical gene-therapy trials involving about 3500 patients have been identified worldwide (June 2001). The vast majority (78%) take place in the United States, followed by Europe (18%). Although most trials focus on various types of cancer, studies also involve other multigenic and monogenic, infectious, and vascular diseases. Protocols generally are aimed at establishing the safety of gene-delivery procedures rather than effectiveness, and no cures as yet can be attributed to these trials.

**Some Current and Potential Applications of Genome Research**

**Molecular Medicine**

- Improve diagnosis of disease
- Detect genetic predispositions to disease
- Create drugs based on molecular information
- Use gene therapy and control systems as drugs
- Design "custom drugs" based on individual genetic profiles

**Microbial Genomics**

- Rapidly detect and treat pathogens (disease-causing microbes) in clinical practice
- Develop new energy sources (biofuels)
- Monitor environments to detect pollutants
- Protect citizenry from biological and chemical warfare
- Clean up toxic waste safely and efficiently

**Risk Assessment**

- Evaluate the health risks faced by individuals who may be exposed to radiation (including low levels in industrial areas) and to cancer-causing chemicals and toxins

**Bioarchaeology, Anthropology, Evolution, and Human Migration**

- Study evolution through germline mutations in lineages
- Study migration of different population groups based on maternal genetic inheritance
- Study mutations on the Y chromosome to trace lineage and migration of males
- Compare breakpoints in the evolution of mutations with ages of populations and historical events

**DNA Identification**

- Identify potential suspects whose DNA may match evidence left at crime scenes
- Exonerate persons wrongly accused of crimes
- Identify crime, catastrophe, and other victims
- Establish paternity and other family relationships
- Identify endangered and protected species as an aid to wildlife officials (could be used for prosecuting poachers)
- Detect bacteria and other organisms that may pollute air, water, soil, and food
- Match organ donors with recipients in transplant programs
- Determine pedigree for seed or livestock breeds
- Authenticate consumables such as caviar and wine

**Agriculture, Livestock Breeding, and Bioprocessing**

- Grow disease-, insect-, and drought-resistant crops
- Breed healthier, more productive, disease-resistant farm animals
- Grow more nutritious produce
- Develop biopesticides
- Incorporate edible vaccines into food products
- Develop new environmental cleanup uses for plants like tobacco

Deriving meaningful knowledge from the DNA sequence will define research through the coming decades to inform our understanding of biological systems. This enormous task will require the expertise and creativity of tens of thousands of scientists from varied disciplines in both the public and private sectors worldwide.

The draft sequence already is having an impact on finding genes associated with disease. Genes have been pinpointed and associated with numerous diseases and disorders including breast cancer, muscle disease, deafness, and blindness. Additionally, finding the DNA sequences underlying such common diseases as cardiovascular disease, diabetes, arthritis, and cancers is being aided by the human SNP maps generated in the HGP in cooperation with the private sector. These genes and SNPs provide focused targets for the development of effective new therapies.

Contrary to the scepticism that characterised the planning stages of the human genome project, the technology and sequence data resulting from the project are set to revolutionise medical practice for good. The expected benefits include: enhanced discovery of disease genes, which will lead to improved knowledge on the genetic basis of diseases; availability of DNA-based diagnostic methods, which will find widespread application in prenatal and preimplantation diagnosis, carrier screening, presymptomatic testing and population screening; the availability of more effective and more tolerant drugs, which will result in more effective therapies characterised by higher potency and reduced incidence of adverse reactions.

However, there are still a number of technological, ethical, legal and social obstacles that must be addressed before these medical advances are incorporated into routine clinical practice.

## Role of Color Doppler In Fetal Well-Being

**Adi Dastur, Geeta Shah***
Consultant Obstetrician and Gynaecologist, Consultant Radiologist*, Wadia Maternity Hospital, Mumbai

Doppler ultrasound has become a part of routine antenatal fetal surveillance during the past 1 decade. It provides insight into the intro-placental and fetal arterial, venous circulation non-invasively. Doppler examination has a key role in the detection of hypoxic risk since abnormal blood flow patterns can be demonstrated before the clinical manifestation of fetal disorder. Doppler velocimetry facilitates judgment in the diagnosis, monitoring of fetal well-being during pregnancy and labor, scheduling antenatal tests and timing of the delivery. The contributions of obstetric US to improving maternal well-being and fetal health have been recognized as a key component in all countries around the world. Fetal Doppler indices provide information that is not readily obtained from more conventional tests of fetal-being. Fetal and placental flow dynamics study examined by color Doppler ultrasound is an effective method in the assessment of fetal well being. The examination protocols and the techniques will be discussed in detail.