This is the official transcript of the lecture given by Dr. Kofinas on December 9 2009 at the obstetrical grand rounds regarding the significant effects that fetal nutrition exerts upon future adult health and disease. Read the text that corresponds to each slide and then evaluate the slide's content. The presentation can be found in the Resources/Presentations on our web site. If you have any questions about the content, email us at unborn@kofinasperinatal.org.

Slide #1:

The subject of fetal nutrition and adult health has evaded for the most part the obstetrical literature over the last 15 years. Most of the work on the subject has been done primarily by scientists other than physicians, as well as physicians other than obstetricians. Most of the physicians involved are physicians trained in pediatric specialties as well as nutritional and epidemiological scientists. It is really sad when one thinks that most of the advances in obstetrical care had come out of other specialties rather than obstetrics, such as improved blood banking techniques that saved many mothers from obstetrical hemorrhage, the use of antibiotics that saved mothers from infectious deaths, the establishment of NICU units which saved countless premature babies and even the use of steroids has been pioneered by the pediatrician Dr. Graham Liggins.

Slide #2:

Professor Liggins has done his original studies about steroid use and lung maturity prior to premature birth in sheep and subsequently did the first human studies in the late 70's early 80's. Currently, Dr. Liggins and his team at the Liggins Institute in Oakland New Zealand are quite busy studying the effects of fetal nutrition on adult health and disease.

Slide #3:

Pregnancy is a wonderful, natural phenomenon. It transforms the female body to a life generator. For this to be achieved, the maternal body must undergo certain changes in order to support the development of the fetus from a tiny, single cell to a complete human being. This includes respiratory, gastrointestinal, renal and cardiovascular changes. As you can see on this slide, a small pile of cells between 8 and 16 known as trophoblast, implants into the small at the time uterus which is smaller than a fist. Through a series of tremendous transformations, the uterus grows bigger to accommodate an ever increasing baby. If all goes well, the baby will achieve his genetic potential as dictated by his genetic code (chromosomes). Is the baby growing well? Is the baby realizing his potential in utero? That is what the question-mark on the mother's belly stands for. Unfortunately, despite all the advances in prenatal and specifically fetal imaging, accurate assessment of fetal development is not achievable in most of the cases. This is a sore subject to discuss another time. Monitoring the baby's development is crucial because we can adjust our treatment to improve any deficiencies. There are a lot of interventions that one could implement in order to improve the baby's nutrition and health for a healthier adult over the

postnatal (after birth) life span of the new human being. Poor nutrition in utero cuts short the life expectancy of the adult to be.

Slide #4:

It is indeed clear and well understood by now that the unborn is completely dependent on his mother for all necessary supplies for proper development. As you can see on the slide, every baby comes with his own genetic code. Consider this genetic code (the chromosomes of the baby) a blueprint that defines all of the characteristics and the pattern of development of the new human being in the making. Assuming that the genetic code is perfect and the expected human being out of these blueprints will be a perfect human being then it all depends on the mother and the placenta for this perfect human being to realize his potential. If a baby is genetically defective, we can do nothing to make it normal again. On the other hand, one can damage a genetically perfect baby if one does not pay enough attention to the quality of maternal nutrition and placental function. Assuming that the baby comes with a perfect genetic code, and that the maternal body is very well proportioned and ideal in terms of body weight, then the quality of food that the mother will receive during the pregnancy will define the baby's development in utero for those 9 months. So if the mother consumes unhealthy nutrients with empty calories and a lot of unhealthy refined carbohydrates, then certainly the quality of the energy and nutrients that the baby will receive, even if the placenta is perfect, will not be appropriate and will have lasting implications on to the baby's health. Assuming a normal genetic code, normal fetal maternal body composition, normal utero-placental circulation and normal maternal nutrition, then it is upon the baby with his placental vessels to pick up these nutrients and carry them through the umbilical circulation to his body. So as you can see here, the fetal-supply system can break down at multiple locations in the supply chain. For example, the mother may not eat properly and healthy foods; this can affect the baby's nutritional state.
Also, the maternal body might be deficient in nutrients prior to pregnancy; in such a case, even if the mother eats healthy and nutritious foods during the pregnancy, part of these nutritious foods are going to be consumed by the maternal body by means of redistribution and partitioning of the nutrients to improve the maternal nutritional state; this will limit the actual food the baby receives. In addition, the system can break down at the maternal circulation level in which case nutrients are not delivered to the placenta via the maternal utero-placental circulation. The baby's placental circulation must be in good order to be able to transfer the absorbed nutrients to his tissues. Finally, the quality of the placenta should be sufficient to allow these nutrients to diffuse across the placental membrane in sufficient quantities so the baby can get what it needs. So, depending on the location and magnitude of the break down in the nutrient supply-line to the fetus, the fetus may experience variable degrees of nutritional deprivation and fetal growth failure. Any imbalance at maternal-fetal placental interface and independently from the other factors, can lead to substantial deficiencies to the baby's development during the nine months of intrauterine life.

Slide #5:

This quote by Ballantyne indicates that birth marks not the beginning, but a stage in life's journey. This is a very, very powerful quote because indeed, birth is not the beginning of life a small portion of the baby's life journey. The whole journey of course for each particular baby starts at conception (union of sperm with the ovum (egg)) and continues through intrauterine life to the postnatal existence which may last as long as 100 years or more.
This quote reminds me of a poem by Kavafis titled "Ithaca" which basically describes Ulysses' problems on the way back from Troy to his homeland Ithaca. Basically, Kavafis says that what is important is not the destination; it is not important getting back to Ithaca but it is the journey towards Ithaca that counts. The poet urges Ulysses to enjoy the journey and get the most out of what life has to give him and not think of the destination. The same way, when we talk about life we have to make an effort to absolutely pay attention to the journey and not the destination; helping the baby develop normally in utero not only makes that portion of the journey very appropriate and desirable but also helps establish a certainty that the rest of the journey ex-utero and into adulthood is also going to be an enjoyable and healthy one.

Slide #6:

Life is about balance, isn't it? "Metron Ariston" is an ancient Greek quote. If we translate it literally it means moderation is perfect, which is kind of a schema oxymoron; moderation is more related to mediocrity and not to perfection. In conceptual translation, it means balance. Metron stands for balance, balance of emotion, balance of psyche and body. This is the balance that the body's homeostatic mechanisms create constantly. When there is balance in our body's systems, we can then achieve perfection and a healthy body.
When I was looking at this pile of stones for the first time, I was really fascinated, not by the actual stones, but by trying to figure out what the person who put the stones up, was thinking at the time? Was he simply bored and had nothing else to do? Or was he trying to convey a message to the people who would walk by Lake Geneva for as long as those stones would stay together? And of course, to me the sight of the stones meant balance; the kind of balance that is achieved when life is full of energy and full of happiness. If we want to keep this balance in our fetuses, it means that we have to really make an extraordinary effort to create the best possible intrauterine environment.

Slide #7:

In the last 10-15 years, maybe a little bit more, quite a significant amount of literature has been devoted to the elucidation of the relationships between fetal development and adult disease. The concept of "fetal origin of adult disease" has been very well established with not only epidemiological studies over the last 15 years but also experimental animal as well as human studies. The first time that the concept of the "fetal origin of adult disease" was suspected, was when men in Netherlands who were dying from premature cardiovascular deaths, were found to have something in common; they were in the mother's uterus at the time of the Dutch famine which was brought about by the German blockade of the Netherlands.

Slides#8 and #9

Later on, additional studies from the United Kingdom revealed that indeed, deprivation of nutrition during intrauterine life is associated with substantial morbidity from cardiovascular disease as well as mortality in both men and women. What you see in this slide basically is that a baby that weighs 4.3 kilograms at birth has the lowest possible cardiovascular mortality as an adult. In other words, a baby that is born at close to 9 lbs. and 6 oz. has the lowest chance when he gets to his middle age to suffer a fatal heart attack or a stroke. This study was done basically on men who were born in the United Kingdom between 1911 and 1930. Of significance, is the fact that for babies that are born at less than 2.5 kg which is equivalent to 5 lbs 8 oz the chance to die from cardiovascular disease is approximately twice as much as the one for the babies that are born at about 9 lbs. For women, there is a similar association but the severity of the condition is less; the reason is basically that the changes that are responsible for these deaths are less pronounced in women and they depend on the fetus' sex. Maternal weight at birth is a strong determinant of neonatal birth weight. Given that the ponderal index declines with smaller maternal birth weights and since most of the height of the neonate is defined by paternal genomic imprinting, it is no surprise that the ponderal index will be smaller which means the baby will be light for his length. What you see on this slide on the left side on the Y-axis the ponderal index. The ponderal index is something like a specific gravity of the baby, the skinnier the baby for his height, the lower the ponderal index. The normal ponderal index is approximately between 27 and 28. When mother's birth weight was at less than 5.5 lbs. or 2.5 kg, when they grew up and got into their reproductive age, their babies were much smaller, skinnier than what they otherwise would have been. This means that the babies of women born small for gestation, do not realize the nutritional advantage of their expected genetic code and of course, this leads to bad health consequences later on. In the right side of the slide we see that the father's birth weight does not really influence the birth weight and the ponderal index of the offspring.

Slide#10

Currently, all women are advised to gain weight during the pregnancy; in fact the average woman is advised to gain 12.5 kg which is equivalent of 25 lbs. This is fine for the average woman, but most women are less or more than average and certainly when a woman is underweight she needs to make up the difference from her under-weightiness in addition to the 25 lbs. Therefore, an underweight woman should gain at least 30-35 lbs. as opposed to an overweight woman who needs to barely gain a few lbs. obese women, need not gain any weight and in some instances, their babies might benefit if the mothers lose some weight.

Slide#11

What is it that affects fetal health? Genetics of course is the number one. Poor genetics mean poor health and nobody can do anything about it. Good genetics mean a healthy baby unless external factors intervene such as toxicants. Toxicants are found today every were. Every baby born in America according to a study of the environmental working group is born with 287 industrial pollutants in his cord blood. Many of those cause cancer, tissue damage, endocrine disruptions and act as obesogens (chemicals that cause obesity).

Quality of nutrition is very important and any imbalances in this matter can affect the baby permanently. Poor nutrition leads to metabolic changes that affect the metabolism permanently and irreversibly.
Stressors, can reprogram the baby's ability to respond to stress in a healthy way; this reprogramming leads to chronic stress related damage for the rest of the postnatal and adult life. Abnormal stress responses lead to hypertension, inflammation, thrombosis (clotting), heart attack, and stroke and of course, premature death.

Slide #12
Fetal programming is the process by which the baby changes the properties of his genes and thus the function of these genes. If the intrauterine environment cannot provide what the genes expect for the baby, the baby then switches off some genes and may switch on others. By doing this, the baby is able to adapt to the unexpected and for the most part hostile environment in order to survive. The sequence of events has as follows: The fetal genetic code gives the baby an expected size and growth trajectory. If the maternal nutritional supply, placental size and transfer capabilities and uteroplacental blood flow quality cannot supply the baby with what is expected of it, then fetal programming will take place for survival reasons. The baby will change his body composition to adapt to the imposed limitations, will ration growth to various organs with preferential supplies to important organs (brain, heart and the adrenals are the most important organs for the fetus) and limited supplies to the rest of the organs. Adipose tissue is the first to go, muscle is next etc. If nutritional deprivation becomes severe, the baby may even shut down blood supply to the intestines and the kidneys with irreparable damage to these organs. Such damage can then cause intestinal necrosis and kidney failure after birth. This programming as we can see later on in the lecture is irreversible.

Slide #13
The baby inherits genes from both parents that define the expected phenotype (how the baby will look like after birth). In addition, the baby may create new traits by means of epigenetic imprinting (adaptational genetic changes) due to intrauterine nutritional deficiencies.
Prenatal cues predicting a nutritionally sparse environment will cause a shift in the trajectory of structural and functional development toward a phenotype matched to that environment. In other words, the baby will be small and expect to find limited supplies of food. Such a phenotype will have a reduced capacity to cope with a nutritionally rich environment later in life, increasing the risk of metabolic disease. Postnatal cues, such as childhood overnutrition leading to compensatory growth, could further shift the positioning of the adult phenotype, exacerbating the mismatch (dashed lines) between phenotype and environment. Although there is a continuous range of possible developmental trajectories and multiple sequential cues that act during development, for simplicity only two developmental cues (before and after birth) and three trajectories are shown. If the baby's predicted postnatal environment matches the baby's phenotype, then the baby will develop normally along his expected phenotype. If however, there is a mismatch between phenotype and predicted environment, then the child and subsequent adult will have a number of metabolic problems that can cause cardiovascular disease, diabetes, hypertension etc. For example, a baby born in a small poor village in

India, with a small phenotype will develop healthier metabolism if it grows up in a nutritionally poor village in India than in New York city with plenty of easily available food.

Slide #14

The green, blue and orange lines define the range of normal growth curves in fetuses between the 10th and 90th percentiles. The three red lines define various types of growth disturbances.

When a fetus is deprived early in embryonic life it adjusts by "predictive adaptive response" and changes its growth trajectory. The baby projects limited supplies and programs its metabolic mechanisms to expect limited supplies and thus improve its survival in utero. This ability remains after birth and cannot be reversed. In an environment of abundant supply, the neonate will have difficulty adapting and will develop metabolic syndrome with all the consequences. This is the typical symmetrically growth retarded baby which has increased chances of survival in utero despite severe growth failure. The bottom red line represents such a baby.

In contrast, the baby with a normal growth trajectory that is deprived late in the pregnancy will suffer more and is at risk for death and severe brain damage. This baby projected a trajectory along the blue line (normal) and expected abundant supplies. If the supplies become sparse during the last third of the pregnancy due to maternal or fetal placental reasons, the baby will experience severe and acute deprivation that can lead to severe oxygen deficiency with brain damage and even death. The short red line in the middle of the graph represents such a baby.

Finally, the top red line represents a baby that projected an upper normal trajectory but it found himself in a much richer environment and gained more weight than the projected. Such babies do not suffer as much as the smaller babies but they are at increased risk to develop insulin resistance and diabetes later in life. The age of onset of such diabetes is becoming smaller by the day. A significant number of children are now suffering from adult onset diabetes (Type II diabetes) by the age of 10 years.

Slide #15

This chart is from the Barker's hypothesis paper. Prenatal exposure to steroids leads to down regulation of hypothalamic steroid receptors. After birth, this leads to a decreased negative feedback leading to increased steroid production (long term up-regulation of Hypothalamic Pituitary Adrenal (HPA) axis. Such increased fetal exposure to endogenous (internally secreted) steroids leads to all the metabolic abnormalities depicted in the above chart. These metabolic abnormalities then lead to the diseases described at the bottom part of the chart. Many patients are concerned that the steroids we use to treat mothers for medical problems or for the baby, may affect the baby's future health. The type of steroids we use in pregnancy for maternal indications is metabolized by the placenta and does not have any effect on the baby. However, the steroids we use for fetal reasons are only used in one or at most two doses. Single injection of steroids (Betamethasone) for lung maturity has not been associated with any long term effects up to 30 years of age with the exception of mild insulin resistance. Such steroids should not be used for more than twice if absolutely necessary.

During maternal undernutrition or placental insufficiency, the fetus reduces insulin secretion by b-cells and increases peripheral resistance to insulin. This redistributes the available glucose to the fetal brain,

heart and adrenals. If this response continues during the pregnancy, the metabolic changes will become permanent and lead to metabolic disturbances as noted in the diagram for the rest of the postnatal life.

Slide #16

Developmental plasticity is made possible by epigenetic mechanisms responsible for tissue-specific gene expression during differentiation. There are three epigenetic mechanisms:

1. Coordinated changes in the methylation of cydidine-guanosine (CpG) nucleotides in the promoter region of specific genes,
2. Changes in chromatin structure though histone acetylation and methylation and
3. Post-transcriptional control by microRNA.

The effects of maternal nutrition and behavior target the promoter regions of specific genes rather than being associated with global changes in DNA methylation. Such changes are permanent and may be transmitted intact to the next generation. Research is now in progress trying to identify ways where we can diagnose such epigenetic insults and restore to normal with specific interventions. For now, the best way to prevent such insults is to prevent placental failure with all its consequences.

Slide #17

IUGR affects many of the metabolic pathways and their intermediaries in many different ways by means of metabolic programming; such effects depend on fetal sex (men more severely affected than women), nature of insult, timing of insult and the rate of postnatal growth. Even a small insult that does not affect the fetus materially can lead to epigenetic programming with phenotypic changes that will become a benefit or a challenge in adult life depending if the adult environment matches the predicted one. Small babies with sarcopenia (decreased amount of tissue from growth failure) and increased visceral fat will survive better in an environment of limited nutritional supplies but do poorly in an environment of abundant supplies (western type of diets).

Slide #18

The diseases described in this slide have been linked with small birth weight and have been very well documented beyond any scientific doubt. Such conditions lead to premature aging, premature organ failure and of course premature death. The financial cost of these diseases is immense to our society and it challenges the survival of our health care system. What cannot be measured however is the human pain and suffering that such conditions cause to the sufferers as well to their families.

Slide #19

This slide contains diseases that have been linked to small birth weight but have not replicated as well as the ones of the previous slide. However, if history is of any value, it is a matter of time before the findings are confirmed beyond scientific doubt. The association of autism and small for gestational age infants as well as premature infants has been reported in more than one studies. Children born small for gestational age have a 3 fold risk to develop autism (300 % increased risk) than babies of normal birth

weight. The same is true for premature babies since the majority of premature babies are also growth retarded.

Slide #20

This slide demonstrates the association of large for gestational age birth weight and certain medical conditions. Large babies in this case are babies of mothers with diabetes or milder forms of insulin resistance. These babies grow in an environment of excessive carbohydrates and chronic hyperinsulinemia and they are fat with a large Ponderal Index. Such babies should not be confused with symmetrically large babies with similar birth weights but normal fat distribution. These babies are at increased risk for diabetes later in life.

Slide #21

This slide is self-explanatory. Obstetricians have the privilege to have the ability to influence the development of healthy human beings for generations to come. A healthy newborn is going to be a healthy adult and is more likely to bare healthy children.

Slide #22

Given our understanding of the impact of fetal nutrition upon the health of the future adult we must start now and be persistent in pursuing the healthiest intrauterine environment for every unborn. For this to be achieved several factors are important and appropriate actions should be taken:

1. Obstetrician/Gynecologist should counsel every woman of reproductive age during the gynecologic routine visits about the benefits of a planned pregnancy.
2. Patients should receive nutritional advice prior to contemplating a pregnancy in order to have enough time to establish healthy habits in advance and thus have a positive impact on the future pregnancy.
3. Maternal weight and body composition should be optimal prior to the initiation of pregnancy.
4. Any pre-existing conditions (diabetes, hypertension, etc.) must be well controlled prior to conception.
5. All women of reproductive age should receive vitamin and Folic acid supplements for months prior to conception in order to reduce the risk for congenital defects.
6. After conception, women should continue to practice healthy life styles and nutrition. Medications that cross the placenta and pose risks to the unborn should be avoided by all means. Any medication usage during pregnancy should be based on the fact that the benefit to the unborn exceeds the risks by far.
7. Prenatal care by a qualified obstetrical specialist is important to monitor the baby's growth and development.
8. Monitoring of placental development as well as fetal-placental circulation is of paramount importance. Placental failure has detrimental effects on fetal development. Placental problems can be detected as early as 5 weeks of gestation and with proper treatment can be corrected.

9. Finally, we should never forget that balance and common sense are the most important factors for a healthy lifestyle and a healthy pregnancy. Extremes on both sides of the spectrum are not healthy and lead to deleterious consequences.