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In utero predisposition

In utero life appears to be the most important span of life, as the developing embryo undergoes numerous adaptations and changes, which can affect its health in later life. Nowadays, the association between environmental effects on the fetal-placental unit and the risk of morbidity in childhood and adulthood has been convincingly established, although the signaling and the mechanisms that lead to these conditions, as well as the timing of the insult remain obscure, and could include the most critical periods of conception and early prenatal stage. Therefore, it is widely accepted that besides the significance of the genetic risk on morbidity predisposition, the pure risk is also mediated by the pleiotropic expression of genes inherited from both parents under a maternally-mediated modulation, guided by the uterine environment. Many stressors have been identified which through their aberrant expression, can lead to massive cellular damage, acting on proteins, lipids, and DNA, causing fetal reprogramming. Along with the epigenetic modifications, according to the hypothesis by Gluckman, the fetus will continue to face these environmental conditions it faced *in utero* even after birth, and adapt organ structural changes, e.g. liver size, blood vessels structure, skeletal muscle quality, number of functional cardiomyocytes, as well as functional changes, e.g. food uptake regulation and brain function. These changes alter hormonal and cellular processes and may predispose for disease.

Gestational diabetes is a serious stressor causing fetal reprogramming. Hyperglycemia and insulin resistance force for fetal adaptation *in utero* and play a critical role in fetal growth and adipose tissue development. Elevated maternal circulating lipids and amino acids stimulate excessive insulin secretion and insulin-like growth factors, resulting in a macrosomic infant with predisposition to insulin resistance, obesity, type 2 diabetes and later on, to metabolic syndrome. Maternal decreased concentrations of adiponectin and increased levels of TNF-α

and IL-6, constitute an inflammatory environment, while fetal leptin low levels result in macrosomia. According to the hypothesis of *Metabolic Memory,* these alterations may permanently increase the risk for high food intake, overweight or obesity, and for a diabetogenic status in later life.

Diabetes constitutes a major public health problem that grows to an epidemic state. Worldwide, the disease shows an increasing frequency at an alarming rate. About 18 million people die every year from diabetic effects on cardiovascular system and more than 1.7 billion adults worldwide are overweight, while 312 million of them are obese. In addition, at least 155 million children worldwide are overweight or obese. It is estimated that $245 billion was the economic burden for the management of diagnosed diabetes in the United States in 2012.

As the fetal programming represents a powerful process, its plasticity allows for early interventions for alternate expression patterns in the embryo and the fetus to prevent future consequences. Early specific biomarker detection with high "predictive" survival value, will allow us to promptly identify and manage gestational diabetes mellitus. As the field becomes more sophisticated, it will undoubtedly become the hot topic in the near future.

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