Imprinting in Early Life Predisposes to Diseases in Adulthood

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Introduction

Prenatal development and early childhood are influenced by endogenous and environmental factors that act in concert by causing structural and functional changes that may persist for the life span. This phenomenon is termed "early-life programming."[1] The concept of early-life physiological "programming" or "imprinting" tries to explain the associations among prenatal environmental events, altered fetal growth and development, and the occurrence of diseases in later life (as previously reviewed).[1] Such programming factors include nutrients and endogenous hormones; they may also involve environmental exposure to biological materials, chemicals, drugs, medical devices, and physical factors.[2]

Early-life programming reflects the action of certain factors on a specific tissue during a sensitive developmental period or "window," thereby affecting its development, organization, and function. Different cells and tissues are sensitive at different times; therefore, the effects of environmental challenges will have distinct consequences, depending not only on the challenge involved but also on its timing.

Developmental immunotoxicity and health risks for adulthood

Developmental immunotoxicity (DIT) is an increasing health concern because DIT outcomes predispose children to certain diseases; the diseases with increasing incidences in recent decades include childhood asthma, allergic diseases, autoimmune conditions, and childhood infections.[3] The enhanced vulnerability of the developing immune system for environmental influences is based on unique immune maturation events that occur during critical windows in early life (e.g., negative selection against autoreactive T cells in the developing thymus).

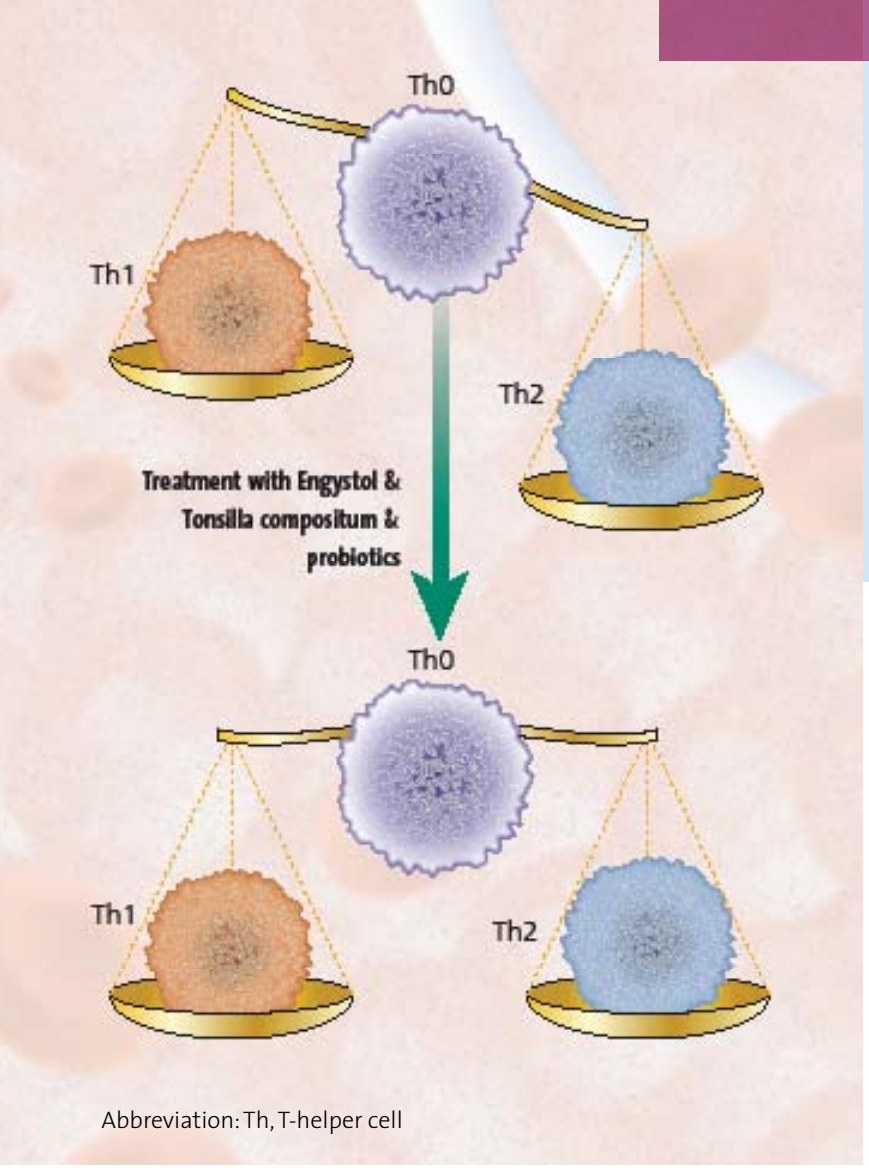
Environmental influences on prenatal development and immunologic responses

The in utero environment is thought to play a major role in the risk of later life disease. The semiallogeneic pregnancy state is characterized by a suppression of graft rejection because during the course of maturation, the potential for maternal-fetal allogeneic reactions must be minimized. This situation is associated with an impairment of the fetal and neonatal immune system, which may influence the specific nature of DIT outcomes.[4] The last-trimester fetus and the neonate normally have decreased T-helper cell (Th) 1–dependent functions, and postnatal acquisition of necessary Th1 capacity is a major concern with DIT.[4] Evidence for the reduced Th1 capacity of newborns is reflected by the fact that the production of interferon γ (the hallmark Th1 cytokine) is severely reduced in the neonate.

In utero exposure to pesticides, such as polychlorinated biphenyls, or tobacco smoke is known to produce a range of immunotoxic outcomes (e.g., immunosuppression, autoimmunity, or misregulated tissue inflammation). Beyond T cells, dendritic cells and macrophages are sensitive targets to chemicals, resulting in macrophage dysregulation, changes in innate immunity, and inflammatory damage.

Immune response during early life

A cesarean delivery can affect neonatal immune responses and can increase the risk of atopy. Children born by cesarean section have a 2-fold higher odds of atopy than those born by vaginal delivery (odds ratio, 2.1; 95% confidence interval, 1.1-3.9). In multivariate analyses, birth by cesarean section was significantly associated with increased odds of allergic rhinitis (odds ratio, 1.8; 95% confidence interval, 1.0-3.1), but not of asthma.[5] This study demonstrated that cesarean delivery may be associated with allergic rhinitis and atopy, particularly among children with a parental history of allergies. This could be explained by lack of contact with the



Abbreviation: Th, T-helper cell

Figure 1. Immune Dysregulation in the Young: T-helper (Th) Cell 2 Predominance
A Th2 profile is associated with atopy.

maternal vaginal/fecal flora during cesarean delivery.

During the neonatal period, the mammalian host is exposed through mucosal surfaces to a broad spectrum of environmental macromolecules and microbial agents. The neonatal mucosa has all major elements of innate and adaptive immunologic repertoire. The early neonatal period is also characterized by a relative deficiency in antigen-presenting cell functions, altered cell-mediated immune responses, and a relative increase in apoptosis and eosinophilic responses.[6] Recent investigations have shown that the nature of mucosal microflora acquired in early infancy determines the outcome of mucosal inflammation and the subsequent development of mucosal disease, autoimmunity, and allergic disorders later in life. It seems that altered mucosal microflora in early childhood affect signaling reactions that determine T-cell differentiation and/or the induction of tolerance. Reduced Th1 and increased Th2 cytokine expression in the respiratory tract, associated with increased allergic disease, has been correlated with reduced exposure to microbial agents associated with Th1 responses. These observations suggest that the interaction between the external environment and the mucosal tissues in the early neonatal period and infancy may be critical in directing and controlling the expression of disease-specific responses in later life.

Thus, early-life toxicologic exposure to xenobiotic infectious agents or stress may be pivotal in producing the later-life onset of increased childhood infections; neurologic disorders; fatigue-related illnesses; autoimmune diseases; allergic diseases, including asthma; food allergies; and even cancers (e.g., childhood leukemia).[7]

Childhood allergic diseases

The incidence of asthma in industrialized countries has increased dramatically in recent decades, with the consequences of significant public health cost. In 2002, there were already approximately 16 million adolescents with asthma.[4] For childhood allergic asthma and rhinitis in particular, various toxins, infectious agents, airborne pollutants, and maternal smoking were identified as significant risk factors.[2] In addition, the likelihood is discussed that fetal-expressed genes promoting Th2 may continue to be inappropriately expressed in some neonates, thereby increasing the risk of asthma.

In an 8-year prospective study of 308 children, younger than 7 years, who had recurrent wheezing, a personal history of allergic disease, parental asthma, atopy, and late-onset symptoms were identified as prognostic risk factors for asthma symptoms. The origin of this disease may be traced to early childhood (i.e., the years before exposure to allergen).[8]

In summary, it was proposed that managing the fetal and neonatal immune system to reduce the persistence of the fetal immune phenotype and to promote rapid and effective Th1 maturation has the potential to significantly reduce the risk of asthma in childhood[4] (Figure 1). Fur-

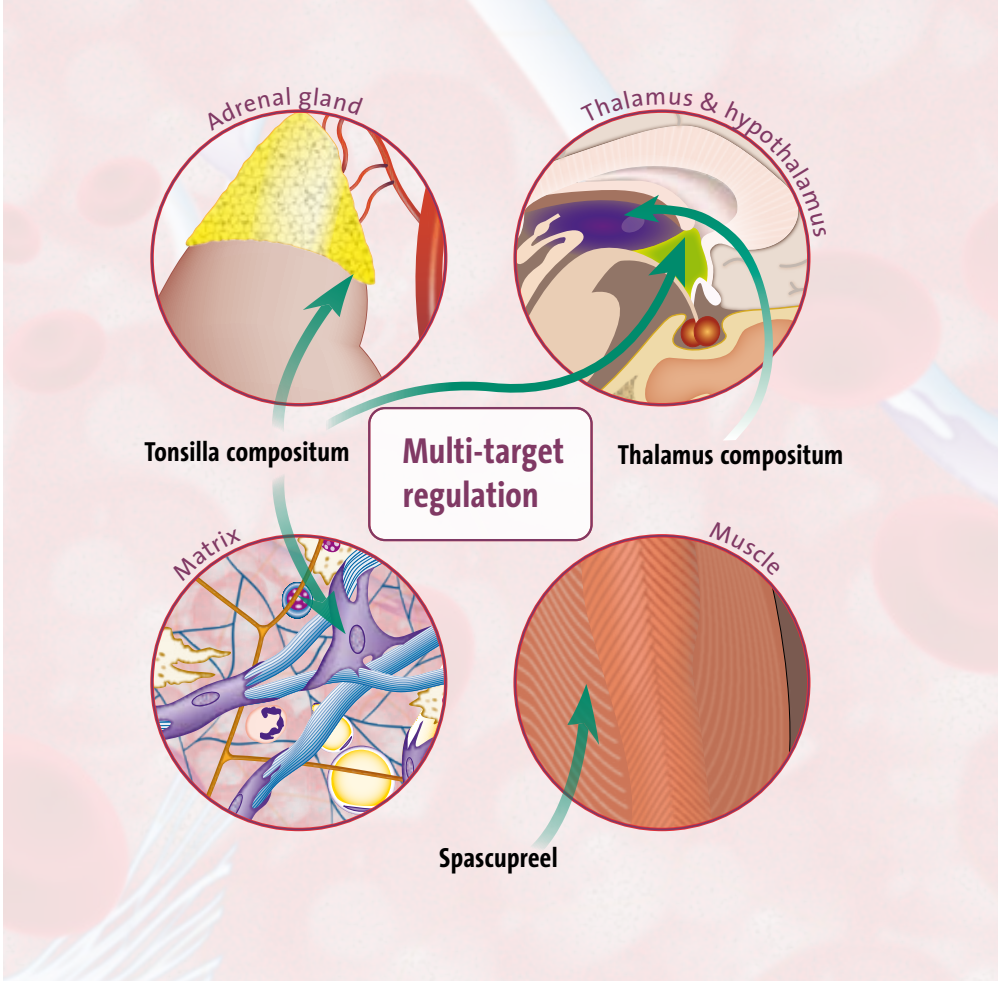


Figure 2. Treatment of Hypothalamic-Pituitary-Adrenal Axis Dysfunction in Stressed Individuals and Patients With Chronic Pain Syndromes: Tonsilla compositum, Thalamus compositum, and Spascupreel

thermore, an increased risk for several childhood allergic diseases was identified after maternal use of antibiotics during pregnancy.[2]

Childhood neurologic disorders

Another example is chronic fatigue syndrome (CFS) in children, for which the causes are certainly early-life events.[9] Immune dysfunction is recognized as part of the CFS phenotype but has received comparatively less attention than aberrant neurologic or endocrine function. However, recent research results suggest that early-life immune insults, including DIT, which is induced by xenobiotics, may offer an important clue to the origin of CFS. Pediatric fibromyalgia seems to be a variant of CFS, with a predominance of hypothalamic-pituitary-adrenal (HPA) dysfunction[10] (Figure 2). Fibromyalgia is most common in midlife, but may be seen at any age. It is characterized by chronic widespread pain.[11] The syndrome is associated with a constellation of symptoms, including fatigue, nonrefreshing sleep, and irritable bowel. Central nervous system sensitization is a major pathophysiologic aspect of fibromyalgia; in addition, various external stimuli, such as trauma and stress, may contribute to the development of the syndrome.

Many early postnatal neurologic lesions associated with postnatal neurobehavioral diseases are recognized as being linked to a prenatal immune insult and inflammatory dysregulation (e.g., autism, autism spectrum disorders, and increased risk of schizophrenia). Also, neurologic diseases of later life may be connected to DIT because the gestational environment is thought to be important in both Parkinson and Alzheimer diseases.[2,12]

Cancer

Dysfunctional immune responses may even lead to cancer, and childhood leukemia is thought to be directly linked with DIT.[2,7] A key risk factor seems to be an early-life dysfunctional immune response to common childhood infections.

Prenatal imprinting of the metabolic syndrome

Prenatal glucocorticoid stress

Glucocorticoids are powerful mediators of early-life developmental processes. Their potent effects on tissue development (i.e., the accelerated maturation of organs, notably the lung) underline their widespread therapeutic use in obstetric and neonatal practice in threatened or actual preterm delivery. In contrast, glucocorticoids are rarely used in the antenatal treatment of fetuses at risk of congenital adrenal hyperplasia.[1,13-14] However, glucocorticoid administration during pregnancy reduces offspring birth weight. It was hypothesized that prenatal stress derived from DIT, as previously described, or exposure to excess glucocorticoids might represent a mechanism linking fetal growth with adult pathophysiology.[15] Epidemiological evidence suggests that particularly low birth weight is associated with an increased risk of cardiovascular, metabolic, and neuroendocrine disorders in adult life.

Experimental studies in rats have shown that the birth weight is reduced after prenatal exposure to the synthetic steroid dexamethasone, which readily crosses the placenta; or to carbenoxolone, which inhibits 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD2), the physiological fetal-placental "barrier" to mater-

nal glucocorticoids. As adults, the offspring exhibit permanent hypertension, hyperglycemia, increased HPA axis activity, and behavior reminiscent of anxiety. Physiological variations in placental 11β-HSD2 activity correlate directly with fetal weight.

In humans, 11β-HSD2 gene mutations cause low birth weight. Moreover, low-birth-weight newborns have higher plasma levels of cortisol as a potential stress hormone throughout adult life.[1,13]

In human pregnancy, severe maternal stress affects the offspring's HPA axis and is associated with neuropsychiatric disorders; moreover, maternal glucocorticoid therapy may alter offspring brain function.[13]

Low birth weight and metabolic complications

Numerous studies have revealed an association between lower birth weight and the subsequent development of the common cardiovascular and metabolic disorders of adult life (i.e., hypertension, insulin resistance, type 2 diabetes mellitus, and cardiovascular disease–related deaths).[1] The early-life events described above that alter birth weight are important predictors of adult morbidity.

In a study[16] of 22,000 US men, those who weighed less than 2.2 kg at birth had relative risks of adult hypertension of 1.26 and of type 2 diabetes of 1.75 compared with those with an average birth weight. Similar observations were made in women.[17] Moreover, the association between birth weight and later cardiometabolic disease seems largely independent of classic lifestyle risk factors (e.g., smoking, adult weight, social class, excess alcohol intake, and sedentariness) that are additive to the effect of birth weight.[18]

Prenatal origin of obesity, cardiovascular disease, and insulin resistance

The fetal origins of obesity, cardiovascular disease, and insulin resistance have been investigated in a wide range of epidemiological and animal studies, which revealed an adaptation of the nutritionally manipulated fetus to maintain energy homeostasis for ensuring survival.[19] One consequence of such developmental plasticity may be a long-term resetting of cellular energy homeostasis, most probably via epigenetic modification of genes involved in a number of key regulatory pathways.[20] For example, reduced maternal-fetal nutrition during early to mid gestation affects adipose tissue development and adiposity of the fetus by setting an increased number of adipocyte precursor cells.[21] More important, clinically relevant adaptations to nutritional challenges in utero may only manifest as primary components of the metabolic syndrome if followed by a period of accelerated growth early in the postnatal period and/or if offspring become obese. This suggests that obesity is not simply the result of lifestyle but has developmental determinants that are not of genetic origin. Thus, an understanding of the mechanisms that mediate the epigenetic changes is crucial to determine dietary and pharmaceutical approaches that can be applied in the postnatal period.

Fetal undernutrition and hypoxia are associated with an increased susceptibility to a number of adult-onset metabolic disorders. In addition to obesity, these include cardiovascular disease and insulin resistance.

Interestingly, premature neonates also have an increased cardiovascular risk in adult life.[18] It was observed that different feeding regimens, particularly in human premature neonates, have long-term metabolic consequences.[19] Some developmental responses may persist through several generations. For example, the female reproductive tract develops in the first half of human fetal life. Girls who were growth retarded in utero have a reduced uterine size, and this reduction may lead to impaired uterine-placental function when these women become pregnant.

On the other hand, there is increasing evidence that maternal obesity is linked to numerous metabolic complications, including subfertility, gestational diabetes, hypertensive disorders of pregnancy, and throm-

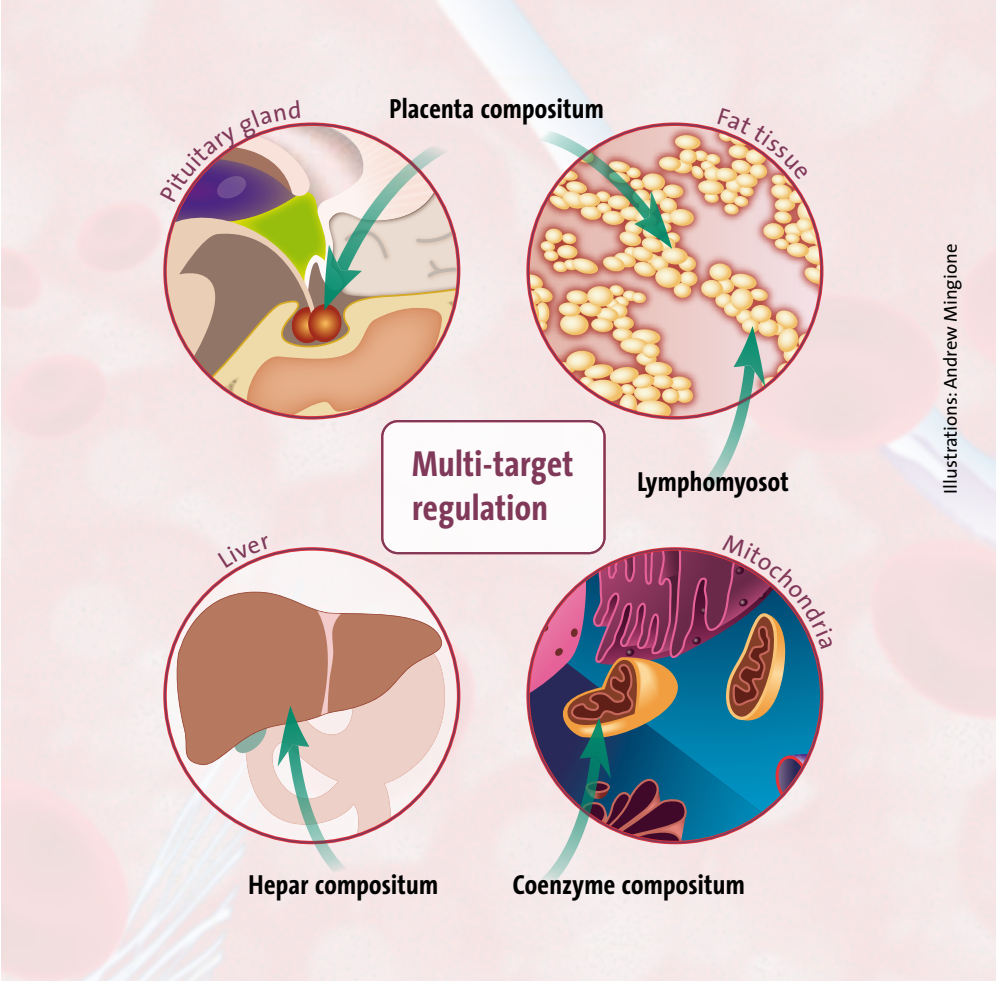


Figure 3. Treatment of Metabolic Syndrome and the Hypothalamic-Pituitary-Adrenal Axis in Children: Placenta compositum, Lymphomyosot, Hepar compositum, and Coenzyme compositum

boembolism, with potential long-term health consequences for both mother and child. Obesity and diabetes in women before pregnancy, gestational diabetes, and glycosuria (both diagnosed and ascertained during pregnancy) result in a higher mean birth weight and an increased offspring obesity risk.[22] Thus, maternal lifestyle should be altered as possible to improve maternal and fetal outcomes.

Metabolic syndrome in childhood

Mechanisms for the development of metabolic syndrome in early life

The risks for obesity and insulin resistance may be programmed in utero as a result of decreased or increased birth weight because of the reasons previously described.

The development of metabolic syndrome, however, is the result of a complex interaction of specific genes and environmental influences.[23] A primary mechanism accounting for perinatal adaptation is the epigenetic modification, via DNA methylation, that affects gene expression permanently, with consequent endocrine and behavioral changes persisting into adulthood. In addition, genetic polymorphisms in a regulatory pathway may accompany environmental factors acting on fetal development and, thus, the origins of many human diseases. Polymorphisms in the insulin promoter gene and a parental background of metabolic syndrome predispose children to be overweight and to have insulin resistance (Figure 3).

In addition, an enhanced release of inflammatory cytokines (tumor necrosis factor α and interleukins 1 and 6) is correlated with the extent of adiposity in adolescents. These cytokines decrease insulin receptor signaling, thereby contributing to the insulin resistance state.

Childhood weight gain and obesity have been shown to be linked to the overall mortality risk in adulthood, including the risk from cardiovascular disease. A recent update[24] of the worldwide prevalence of metabolic syndrome in overweight children and adolescents between the ages of 2 and 19 years indicated a rate of up to 60%.

Nonalcoholic fatty liver disease in children

Further metabolic consequences of obesity include nonalcoholic fatty liver infiltration, which is rapidly emerging in the pediatric population.

Nonalcoholic fatty liver disease is increasingly prevalent in pediatric individuals, in parallel with increasing obesity, and can lead to liver inflammation, fibrosis, and even cirrhosis.[25] Nonalcoholic fatty liver disease is thought to occur as a consequence of an increase in free fatty acid release into the portal circulation by abundant visceral adipocytes. This results in higher triglyceride levels and subsequent excessive intrahepatic lipid storage. The prevalence of fatty infiltration of the liver was recently estimated at 9.6% of the US pediatric population. Fatty liver prevalence differs significantly by race and ethnicity (Asians, 10.2%; blacks, 1.5%; Hispanics, 11.8%; and whites, 8.6%). The highest rate of fatty liver was seen in obese children (38%).

Pediatric nonalcoholic fatty liver disease may improve with lifestyle therapy (maintaining weight and

regular exercise) and agents that improve insulin sensitivity. Thus, identifying effective strategies for treating these obesity-related comorbidities in children and adolescents is crucial to the prevention of future cardiovascular disease and poor health outcomes.

Metabolic risk factors for sexual development of female adolescents

A risk factor for female sexual development of adolescents, connected with type 2 diabetes mellitus and cardiovascular disease, is polycystic ovary syndrome (PCOS). Polycystic ovary syndrome refers to hyperandrogenism, anovulatory menstrual cycles or oligomenorrhea, hirsutism, and the appearance of polycystic ovaries on ultrasonography.[26] Insulin resistance and elevated serum luteinizing hormone levels are also common features of PCOS. Polycystic ovary syndrome is associated with an increased risk of type 2 diabetes and cardiovascular events. Insulin resistance, in conjunction with altered regulation of the HPA axis, promotes a hyperandrogenic state at the level of the ovary and adrenal gland.[23] Obese adolescents with PCOS have an increased prevalence of impaired glucose tolerance, insulin resistance, and atherogenic lipid profiles compared with lean counterparts with PCOS.

Precocious puberty

Another factor of health and social importance is precocious puberty (i.e., early sexual maturation in female children). There is evidence that girls are maturing at an earlier age and that precocious puberty is increasing.[27]

Precocious puberty affects 1 in 5,000 children and is 10 times more common in girls. Statistics indicate that girls in the United States are maturing at an earlier age than they did 30 years ago and that the number of girls with diagnosed precocious puberty (i.e., the appearance of secondary sex characteristics before the age of 8 years or the onset of menarche before the age of 9 years) is increasing. Early menarche has been linked to a greater risk of breast cancer as an adult. Therefore, a precocious onset would seem to increase that risk.

Responsible factors included genetic and ethnic background, pediatric obesity, and environmental variables that disrupt endocrine function (i.e., chemicals, toxins, plasticizers, infant feeding methods, skin and hair products, and assisted reproductive technologies), psychosocial stress, and early exposure to a sexualized society.[27] The role of obesity is often cited in association with the earlier onset of puberty. The number of overweight children aged 6 to 11 years has more than doubled in the past 20 years (from 7.0% in 1980 to 18.8% in 2004), and the rate has more than tripled among adolescents aged 12 to 19 years (from 5.0% in 1980 to 17.1% in 2004).

Conclusions

There is increasing evidence that genetic and epigenetic factors (i.e., early-life environmental influences) can affect prenatal development and cause structural and functional changes that may be responsible for the onset of diseases in childhood and adulthood. This concept of early-life physiological programming or imprinting[1] has been examined for prenatal and postnatal exposure to endogenous factors (e.g., sex hormones) and exogenous agents (including toxins and drugs). Certain windows of vulnerability are identified, in which different tissues, signaling pathways through the HPA axis, and more important, the immune system, are sensitive to these challenges. Many chronic diseases with an increasing incidence (e.g., childhood asthma, allergies, neurologic syndromes, and metabolic syndrome) are triggered through early-life environmental risk factors and immune dysfunction. Therefore, the identification of and protection against risk factors for the developing immune system and resulting immune dysfunction and tissue damage provide a major opportunity to reduce health risks for the most prominent chronic diseases of children and adults.

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