

## Human development: from conception to maturity

### *Desenvolvimento humano: da concepção à maturidade*

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#### Abstract

The main objective of this review was to describe and emphasize the care that a woman must have in the period prior to pregnancy, as well as throughout pregnancy and after the birth of the baby, cares and duties that should continue to be followed by mother and child throughout the first years of the child's life. Such cares are of nutritional, behavioral and lifestyle natures, and also involve the father and the whole family. Human development, from conception to maturity, consists of a critical and important period due to the multitude of intrinsic genetic and environmental factors that influence, positively or negatively, the person's entire life. The human being, who originated and passed his/her first phase of development in the womb, receives influence from different factors: a) of parental origin (father and mother), including health and lifestyle of the father and mother, genetic inheritance, nutrition of the mother prior to and during pregnancy; b) events that affected the mother and hence the child under development in intrauterine life, at birth (delivery), during perinatal period, and throughout the early years of life. The fragility of development continues throughout the preschool, school and adolescent periods during which proper nutrition with a balanced lifestyle is essential and depends on guidance from the parents, caregivers and teachers.

**Keywords:** Human development; Nutrition; Health care; Genetic inheritance.

#### Resumo

O principal objetivo desta revisão é descrever – além de enfatizar – o cuidado que a mulher deve ter no período anterior à gravidez, bem como durante toda a gravidez e após o nascimento do bebê. Tais cuidados e deveres devem permanecer com a mãe e a criança nos primeiros anos de vida. Estes cuidados são de natureza nutricional, comportamental e de estilo de vida, e também envolvem o pai e toda a família. O desenvolvimento humano, desde a concepção até a maturidade, consiste em um período crítico e importante devido à multiplicidade de fatores genéticos e ambientais intrínsecos, que influenciam, positiva ou negativamente, a vida da pessoa em toda a sua longevidade. O ser humano, que é originário e tem sua primeira fase de desenvolvimento no útero, recebe influência de diferentes fatores: a) origem parental (pai e mãe), incluindo saúde e estilo de vida do pai e da mãe, herança genética, nutrição da mãe antes e durante a gravidez; b) eventos que podem ocorrer com a mãe e que afetam a criança em desenvolvimento na vida intrauterina, no parto (nascimento), no período perinatal e nos primeiros anos de vida. A fragilidade no desenvolvimento continua nos períodos pré-escolar, escolar e de adolescência, nos quais uma nutrição adequada, com um estilo de vida equilibrado, é essencial e dependente da orientação dos pais, cuidadores e professores.

**Palavras-chave:** Desenvolvimento humano; Nutrição; Cuidados de saúde; Herança genética.



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### ■ 1 Nutrition and human development

It is important to make the distinction between two terms that overlap in practice, namely, growth and development. Growth refers simply to the increase in body size, both weight and stature, while development represents changes in parameters that may or may not depend on growth, involving a very complex series of factors: genetic, epigenetic, nutritional, environmental and lifestyle, amongst others (HURLEY, 1980; STANNER et al., 2009). Development is the sequence of ordered alterations that occurs within the organism as from fertilization of the ovum formed in the ovaries, by sperm produced in the testicles, resulting in the oocyte (first diploid cell) of the new organism to be formed. The alterations are progressive and irreversible; they occur in a regular sequence with slight variations, and each change leads to an organism that is different from the previous one and unable to return to its original stage. These changes constitute the life cycle of the organism since, as part of the development process, theoretically a new adult will be formed, who will be able to produce ova or sperm which may originate the next generation.

There are three aspects involved in development, as follows: 1) growth, which differs from development, despite being one of its aspects; it is a basic phenomenon that has been extensively studied for a long time in several different modes and regulatory mechanisms are involved in its initiation and termination, as well as in its maintenance; 2) differentiation, which refers to the transformation of the cell originally formed by fertilization, and subsequent cell division (mitosis) that transforms it into specialized cells. From a single cell (oocyte), cells of many different types are originated, varying both in structure and function. Some important questions are still made concerning this phenomenon, as follows: what are the biochemical processes that occur in cell differentiation and what are the mechanisms that control these processes? The interest is not only due to the type of cell that is formed, but also due to the control of the number of cells of each type. This is a basic problem in research on cancer. If the mechanisms controlling the numbers and types of cells were known, then in the case of the development of cancers, where there is excessive cell production, the control of this carcinogenesis might be more effectively carried out; 3) morphogenesis, this process includes the growth and development of the anatomical structures of the organism, involving the establishment of specific patterns of structural shapes and being the process whereby the adult reaches his/her final form. However, at the same time, development is both morphological and functional. Functional development represents an important aspect of the fetal and neonatal period (HURLEY, 1980).

Amongst the most important discoveries in cell biology are those relating to chromosomes, the structures

containing all the basic genetic information of an organism. In most eucaryote organisms, virtually all somatic cells contain duplicate chromosomes (2n: diploid) while the reproductive cells contain half, or only one chromosome (1n: haploid). In the human species, the total number of chromosomes is 46 (23 pairs) and 1 differentiated pair, known as XY in males or XX in females. Therefore, the Y chromosome, which appears only in the male (sperm), transmits the male characteristics, and if on fertilization the ovum receives that chromosome from the sperm, the future embryo will be male. If it receives the X chromosome from the sperm, the future embryo will be female. The definitive expression of sexuality of the individual depends on the hormonal balance and homeostasis during prenatal development and during the subsequent stages of postnatal development. Almost all the DNA in the chromosomes of eucaryote cells is associated with a set of different proteins called histones. The interaction between histones and DNA is fairly regular; that is, for each sequence of 150 to 180 DNA base pairs, one molecule of histone H1 and two molecules each of the histones H2A, H2B, H3 and H4, appear to be linked. The amino acid sequence of some of these histones has been remarkably well conserved during evolution (DARNELL et al., 1986).

### ■ 2 Developmental periods

Table 1 briefly shows the periods of life in the human species prior to maturity. In the first trimester of prenatal life, the embryonic period, there is rapid differentiation and development of organs and systems. The initial fetal stage occurs during the second trimester. This stage is characterized by accelerated growth, the development of structures, and the start of functional activities, thus being a period of biochemical development; in the final stage of the fetal period considerable biochemical alterations occur. The period known as parturient consists exactly of the labor, and the neonatal period corresponds to the first month of postnatal life. The next stages correspond to what we call baby, toddler, preschool age, school age and adolescence. With sexual maturity the individuals acquire the ability to reproduce and can restart a new cycle.

#### 2.1 Curve of human perinatal growth

If we plot the development of human weight gain (kg) on a graph according to the pre- and postnatal age in weeks (56 weeks), we can see a tendency for a sigmoid curve (Figure 1). During the exponential growth phase, there is a doubling of the number of cells in each cell division (mitosis). The time required for postnatal doubling of the cell mass varies according to species, and for the human species it is approximately 180 days. In the growth of a multicellular organism, the parts of the body (organs) do not develop at the same speed, but overall the sigmoid curve is maintained, and in the same

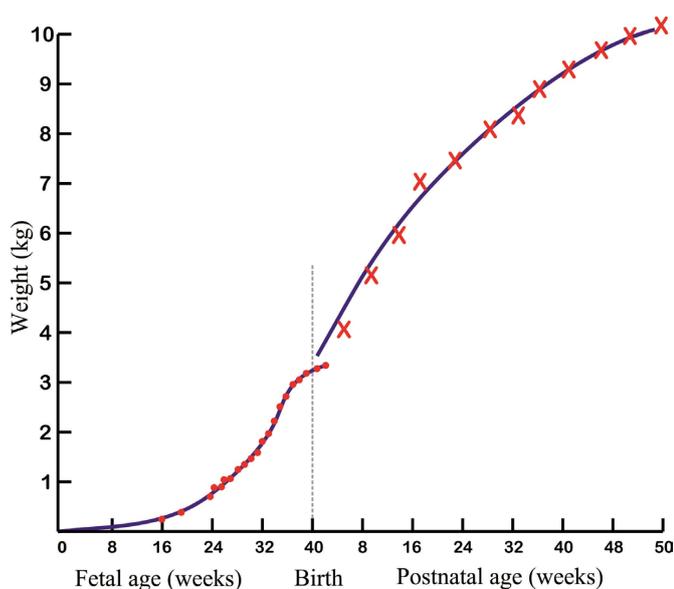
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**Table 1.** Periods of human development according to age group prior to maturity.

Designation of the Period	Age Group (approximate)	Some differentiating Characteristics
Embryonic	First trimester of prenatal life	- Rapid differentiation, Formation of organs and systems
Initial fetal	Second prenatal trimester	- Accelerated growth, development of structures, beginning of functional activities
Final fetal	Third prenatal trimester	- Rapid increase in body mass, end of preparation for postnatal experience
Mother	Period of childbirth and birth	- Risk of trauma and anorexia, end of placental functioning
Neonate and early childhood	First month of postnatal life	- Postnatal adjustment of circulation, commencement of breathing and other functions
Childhood	1 month to 1 year	- Rapid growth and maturation, maturation of functions, especially of nervous system
Late Childhood	1 to 2 years	- Deceleration of growth, progress in walking and other voluntary motor activities and in control of excretory functions
Preschool	2 to 6 years	- Slow growth, increase in physical activity, motor mechanisms and coordination, fast learning
School	Girls 6 to 10 years Boys 6 to 12 years	- Constant growth, development of intellectual processes and skills
Adolescent (pre-puberty)	Girls 10 to 12 years Boys 12 to 14 years	- Acceleration of growth, rapid weight gain, early changes in endocrine system and sex organs
Adolescent (Puberty)	Girls 12 to 14 years Boys 14 to 16 years	- Maturation of secondary sex characteristics
Post-puberty	Girls 14 to 18 years Boys 16 to 20 years	- Increase of postnatal growth to maximum, deceleration and terminal growth, rapid muscle growth and increase of skills, rapid growth and maturation and functions of sex organs, need for freedom and independence

Adapted from Timiras (1972).



**Figure 1.** Curve representing human development (0-56 weeks divided into three phases: (A) 0-16 weeks (“lag” phase) in which growth is practically imperceptible; (B) exponential growth, comprising the prenatal period (16 to 36 weeks) during which growth occurs mainly by cell multiplication; (C) final prenatal weeks and first postnatal year, cell division decelerates and body mass growth occurs mainly by increase in cell size (Widdowson, 1968).

way the parts do not stop growing at the same point in time. Once maturity is reached, the total size of the body remains relatively constant. Another characteristic of growth in a multicellular organism is that the growth of one part of the body is controlled by another part. For example, the growth of the skeleton can be controlled by the pituitary gland, which produces the necessary hormones. There is an integrative interaction between the parts to maintain the correct body proportions (HURLEY, 1980).

In an animal model (rat), Enesco and Leblond (1962) showed that cell multiplication and growth can also be divided into three distinct phases: the first is a period of rapid cell proliferation, during which there is virtually no increase in cell size. In the rat, this period extends for about 17 days after birth; in the second phase, cell proliferation decreases considerably, but cell size increases rapidly. In the rat, this period extends from 17 to 48 days after birth; in the third phase, there is almost no cell proliferation, but cell size increases rapidly. The authors demonstrated that in most rat organs the RNA content was proportional to that of the DNA during the first months of postnatal life, resulting in a constant value of RNA per nucleus; therefore the RNA/DNA ratio is immutable for each organ. Organs

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with high protein synthesis, such as liver, heart and muscle, showed higher RNA/DNA ratios.

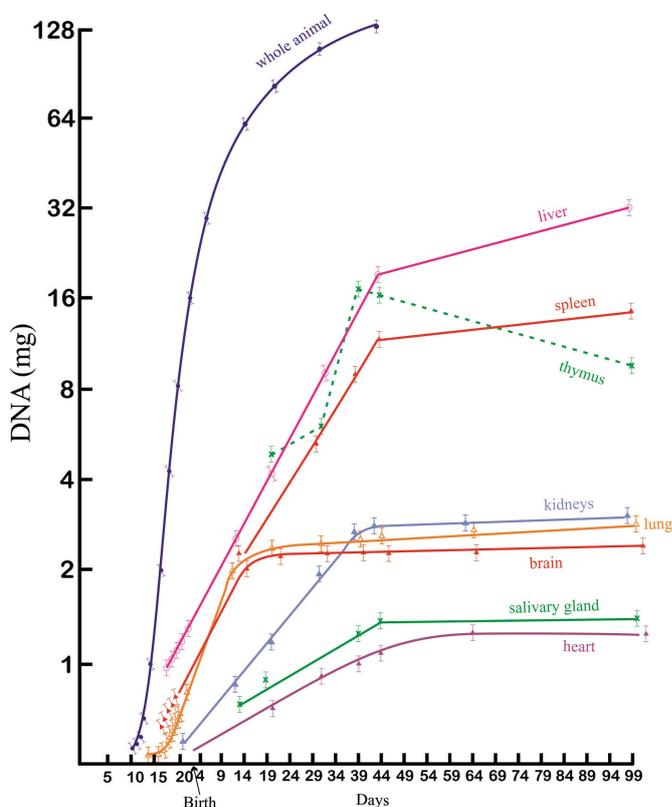
The organs in which DNA synthesis ended earlier were the lung and brain; and these were also the organs in which the cell proliferation stage ended earlier, which in the rat was observed about 9 days after birth. In the kidneys, the rapid cell proliferation phase ended 39 days after birth, and in the heart, 49 days after birth. Thus the various organs of the body presented different speeds of DNA synthesis and different times for the growth phases. This phenomenon is important in terms of the effects of nutrition on development. If the individual is submitted to malnutrition throughout the whole phase of rapid cell proliferation, the number of cells is diminished and cannot be reversed even with regular nutrition at a later stage. These discoveries concerning the stages of cell reproduction and growth were very important, because they demonstrated that precocious malnutrition, particularly in the stages of rapid cell proliferation, is detrimental to the future development of the individual, considering both physical and cognitive aspects, irreversibly in several species, including the human species (ENESCO; LEBLOND, 1962; WINICK; NOBLE, 1965; SUSSMAN, 1973; RICHTER, 1961; DOBBING, 1964, 1965; CRAVIOTO; ROBLES, 1962, 1965; CRAVIOTO et al., 1967; MONCKEBERG, 1968). These authors demonstrated that malnutrition in the intrauterine period and in the first phase of life (in humans, up to approximately 3 years of age) is detrimental not only to physical development (height, body weight) but also to learning and school performance, also impacting the physical and mental performance and sociability of these individuals in adulthood. Winick and Noble (1965) studied cell development in rats, in terms of (mgDNA) for different vital organs, showing the periods during which these organs were showing maximum cell reproduction activity, as well as the postnatal age around which some organs (heart, lung, kidneys, salivary gland and particularly the brain) stop producing new cells, and reach maturity. On the other hand, organs such as the liver and spleen continue to grow, while the thymus gland begins a process of partial atrophy around 39 days after birth (WINICK; NOBLE, 1965), Figure 2.

### 2.2 Evolution of clinical studies in humans

Under conditions of less severe malnutrition than those caused by a great lack of food, for example when the population is exposed to famine for prolonged periods, it is more difficult to assess the effects on prenatal development, and little information has been made available up to the present time, resulting from clinical studies in humans. Amongst the many issues involved, there is the difficulty in evaluating dietary intake, in establishing nutritional intake safely, and in controlling all the factors likely to affect development. However, thanks to the continuity of studies, currently the consensus indicates that the nature

of a pregnant woman's diet may affect fetal development in many ways.

A clinical study investigating the relationship of maternal nutrition to neonate development, with a well-controlled double blind, was published in the early 1940s by Burke et al. (1943). Dietary surveys were carried out with women who attended a prenatal care clinic at Harvard University (USA) in which the nutritional profile was evaluated. When the babies were born, they were examined by pediatricians who did not know the mothers' nutritional profiles. Mothers whose diets were classified as good or excellent gave birth to babies whose condition was classified as good or superior. A total of 42% of the mothers with diets considered good or excellent had babies classified as superior. For the rest of mothers with good or excellent diets, their babies were classified as good. In contrast, for mothers whose diets were considered regular, only 6% had babies classified as superior, 44.5% were considered good or regular, and 5% were considered inferior. Therefore, there was a well-defined correlation between the quality of the maternal diet during pregnancy and the condition of the babies at birth. It was concluded that the weight and length of the baby at birth correlated with the quantity of protein in the maternal diet. For a quantity of protein less than 45 g/day, the mean weight at birth was 2.63 kg; for diets ranging from 65 to 74 g



**Figure 2.** DNA content (mg) during normal rat growth. The points are mean values of at least 10 animals or organs. I, bars represent the range of variation. ↑ age from birth (age in days).

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of protein per day, the mean weight of the babies was 3.63 kg; while in diets with 85 g or more of daily protein, the unborns presented a mean weight of 4.173 kg. Similar results were presented by Jeans et al. (1955). In this study, the dietary habits of 400 rural low-income pregnant women were assessed and correlated with the condition of their babies at birth. Again it was observed that lower weights, decreased vitality and a greater number of newborn deaths correlated with mothers showing poorer nutritional profiles. In addition, this study showed that the incidence of premature infants increased significantly as the nutritional status of the pregnant woman worsened. In the case of women whose dietary habits were classified as acceptable to excellent, 4% of the babies were born prematurely, while for the pregnant women whose diets were considered poor or very poor, the incidence of premature infants was 9.6%. Even more serious were the conditions of these mothers' newborns (1 death in labor, 4 born with severe congenital abnormalities and 5 deaths in the neonatal period).

Primrose and Higgins (1971) carried out a study of nutritional intervention in Montreal (Canada). In this study, the dietary history of pregnant women was assessed, and poor women with deficient diets were provided with an extra supplement based on milk, eggs and oranges, as well as education on nutrition. Expectant mothers were also provided with a supplement containing mixtures of vitamins, iron and other essential minerals. In the group of pregnant women who received the nutritional supplements and education on nutrition, the incidence of deaths in labor, and perinatal and neonatal mortalities was significantly lower than those in the province of Quebec and in Canada as a whole, as observed in Table 2.

### 2.3 Fetal growth retardation in humans

Fetal malnutrition can occur in two different ways: 1) the nutritional status of the mother, before and during pregnancy, and the dietary intake can affect the supply of nutrients to the fetus; 2) abnormal or insufficient functioning of the placenta can deprive the fetus of essential nutrients due to inadequate transfer via the placenta. Furthermore, the functions of the placenta may be affected by factors such as diseases, drugs or abnormalities in the chromosomes. Poor fetal nutrition or malnutrition is usually studied in babies

with intrauterine growth retardation, which most specialists consider to be a sign of fetal malnutrition. Intrauterine growth retardation is defined as the child being born with size and weight below those considered normal for the gestational age. Metcoff (1973) published a study on fetal growth retardation as an index of malnutrition during pregnancy. In this study several biochemical parameters were analyzed in newborns, such as: the protein/DNA ratio (cell size) and the profiles of various enzymes in white blood cells isolated from umbilical cord blood. These results were compared with the same parameters obtained from white blood cells isolated from mothers who gave birth to children with normal sizes for their gestational age. The size of the leukocytes of infants who were submitted to fetal malnutrition and of their respective mothers was larger than those of any other group of newborns. Moreover, enzyme analyses showed alterations in the energy metabolism profiles of the leukocytes of the newborns. A reduced ATP content per cell was also observed, as well as for pyruvate and adenylate kinase. This profile was similar to that found in newborns with severe postnatal protein-calorie malnutrition, offering more evidence that fetal growth retardation may be taken as an index of prenatal malnutrition.

### 3 Metabolic programming

More recent research has introduced new concepts concerning the physiological, metabolic and genetic phenomena during pregnancy and after birth. The success of a pregnancy should not be defined only by the result obtained at birth, but also by the state of health throughout the life of the individual. Conditions in the intrauterine period and in the first months of life affect their general state of health, with increased risk of diseases in adulthood. Nutritional, hormonal and physiological alterations during pregnancy, in critical phases of development, may result in low birth weight, which is associated with metabolic diseases in adulthood, particularly type 2 diabetes (DM2) and cardiovascular disease (CVD) (BARKER 2007; BARKER, 1998). The hypothesis that came to be known as the "Barker hypothesis" assumes that fetuses that underwent intrauterine deprivation developed an energy saver phenotype ("thrifty phenotype") (BARKER et al. 1989; HALES; BARKER, 1992). A selective economy is assumed that prioritizes oxygen and nutrients for more vital organs, such as the brain, to the detriment of other

**Table 2.** Influence of nutritional intervention on births in the study of dietary supplementation in Montreal.

Events (Nature)	No./1000 live births		
	Study in Montreal (Dietary supplementation)	Province of Quebec	Canada (entire country)
Deaths in labor	8.7	11.8	11.4
Neonatal mortality (1st week)	5.7	16.2	14.4
Perinatal mortality	14.4	28.0	25.8

Adapted from Primrose and Higgins (1971).

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“less vital” organs such as the pancreas. If, after birth, the food deprivation is replaced by food abundance, the phenotype starts to develop obesity and the metabolic syndrome.

Dutch youth who underwent intrauterine exposition to a period of starvation or famine from 1944 to 1945 (The Dutch Famine, 1944-1945 apud WATERLAND; GARZA, 1999) were examined at the age of 19. The children of mothers subjected to famine during the first two trimesters of pregnancy showed a prevalence for overweight that was 80% higher than those borne to mothers who were not subjected to the same condition (WATERLAND; GARZA, 1999). Nutritional deprivation during the critical period for the differentiation of the hypothalamus, resulted in alterations in the development of the hypothalamus centers that regulate the appetite. On the other hand, the youths whose mothers were exposed to conditions of food scarcity during the last trimester of pregnancy or during the first five months after birth showed 40% less prevalence for overweight as compared to those who were subjected to food deprivation early in the pregnancy. In the latter group, the nutritional deprivation occurred during the critical period for adipocyte replication. Thus depending on the time of dietary deprivation during pregnancy, the effects may impact as alterations in the organs and systems under development at that moment, for example: 1) maternal malnutrition during pregnancy may affect the health of adult individuals without influencing their size at birth; 2) the occurrence of metabolic adaptations to allow fetal development (ROSEBOOM et al., 2001). In the latter case, the mechanisms by which this phenomenon occurs came to be known as metabolic imprints and occur via variations in the structure of organs, alterations in the number of cells and metabolic differentiation, such as, for example: 1) changes in vascularization, innervation or the juxtaposition of different cell types within the organ; 2) alterations in the expression of certain genes, leading to variations in the production of enzymes, hormones, hormone receptors, transporters, etc. (WATERLAND; GARZA, 1999).

In another survey carried out in China, Li et al. (2010) reported a study with 800 adults born in the period from 1954 to 1964, who were exposed to malnutrition at the intrauterine stage (“The Chinese famine from 1959 to 1961), with a high risk of negatively affecting the homeostasis of the glucose metabolism in adult life. In these studies in humans it is difficult to differentiate between the effects of stress and of malnutrition, since interfering effects, such as infections and stress, can both lead the individual to develop health problems which are similar to those caused by famine. Prenatal stress is recognized as capable of affecting the functioning of the hypothalamic-pituitary-adrenal (HPA) axis and, particularly, the secretion of cortisol. This could be a plausible explanation for the mechanism of association

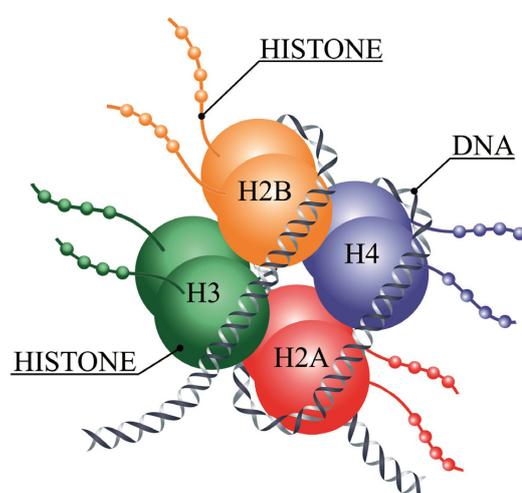
between prenatal programming and a higher prevalence of hyperglycemia in adult life.

## 4 From plasticity to epigenetics

The ability of the genotype to produce different phenotypes in response to different environments is known by the term of “plasticity”. The period of greatest plasticity seems to be during development. This ability of the organism to facilitate changes is called “adaptability” for the expression of a set of genes, particularly during developmental transitions, probably due to the fundamental plasticity of an organism. Developmental plasticity acts in order to adjust the expression of the genes to produce a more adequate phenotype for the predicted subsequent development (GLUCKMAN; HANSON, 2004). When the resulting phenotype is adjusted to its environment, the organism will remain healthy. When incompatibility occurs, the individual’s ability to respond to environmental changes may be inadequate and the risk of diseases increases. Therefore, the degree of genotypic/phenotypic incompatibility determines an individual’s susceptibility to chronic diseases (GODFREY et al., 2007).

### 4.1 The epigenome

Inheritance is not limited to the transmission of the genetic information contained in the DNA sequence. The DNA is packed in the form of chromatin, contained within the nucleus of each cell, and the DNA molecule is wrapped in a bundle in the three-dimensional structure of the chromosomes. In eukaryotes, the DNA molecules are wrapped in an octameric nucleus of histones consisting of two copies of each protein molecule: H2A, H2B, H3 and H4, as shown in Figure 3. These core particles or nucleosomes are the basic units of chromatin, and may form arrangements of higher structural levels due to the binding of histones



**Figure 3.** The structure of a nucleosome - A nucleosome showing a DNA strand comprising a histone octamer composed of two copies of each of the histones H2A, H2B, H3, and H4.

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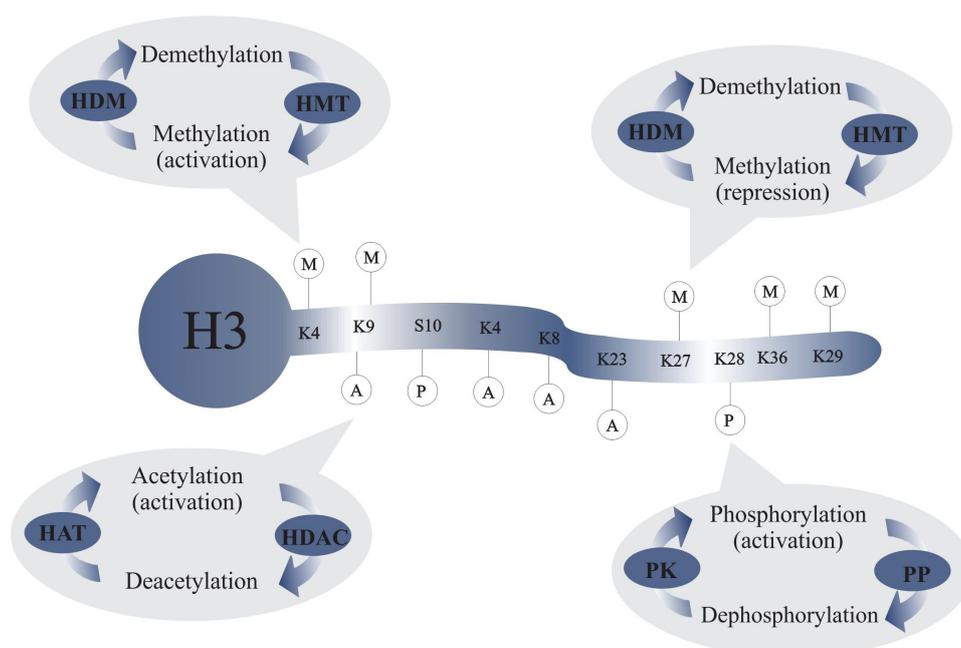
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H<sub>1</sub> and nonhistone proteins, as well as non-coding RNAs (PORTHA et al., 2014). The nucleosomes maintain the DNA-histone complex compacted, and the degree of compaction creates an additional layer of genomic activity. The configuration of the histone-DNA complex is maintained by electrostatic bonds between histones with (+) charges and DNA with (-) charges. Alterations to the profile of these charges regulate the gene expression. The nucleosomes are also subject to covalent modifications in their histones and in the DNA. These epigenetic modifications (markers) can determine whether portions of the chromosomes are strongly or weakly associated, which influences whether the gene can be “turned on” or “turned off”. Other epigenetic parameters are also important to modulation of the structure and genomic activity including histone variants, noncoding RNAs, remodeling of the chromatinic complex and spatial organization of the chromatin within the nucleus (PORTELA; ESTELLER, 2010). Currently, it is recognized that the epigenetic information is crucial for the dynamic interpretation of gene information, so the correct genes are expressed at the correct time during critical decisions of the cellular phase.

### 4.2 Modifications of histones

Each core histone features a terminal amine tail that protrudes from the nucleosome and may be subject to a series of post-translational covalent modifications (SANTOS-ROSA; CALDAS, 2005; MARGUERON; REINBERG, 2010). Chromatin is usually compartmentalized in two main

types of domain: heterochromatin, which is condensed and poor in genes, and euchromatin, which is decondensed and rich in genes (MARGUERON; REINBERG, 2010). These domains feature different profiles of histone modifications and are associated in different arrangements of nucleosomes, with higher structural order and nuclear organization. In general, heterochromatin is associated with marker histones that are repressive to DNA methylation, while euchromatin is associated with active marker histones (MARGUERON; REINBERG, 2010). Acetylation of histones is restricted to lysines (k) preserved in the core histones. It is considered that an open marker, with active chromatin domains, corresponds to actively transcribed genes with high levels of acetylation in their promoting regions, initial transcription sites, which are CpG islands and regulatory functional elements. Acetylation levels as chromatin are determined by histone acetyltransferases (HATs) which catalyze the addition of acetyl radicals to lysine (k) residues, and histone deacetylases (HDACs) that remove acetyl groups from the lysine residues. The balance of the activities of these two types of enzyme determines the state of acetylation of the histones, which influences the levels of expression of the associated genes. The acetylation of the lysine 9 (K9) residue at the terminal amino of the histone tail H<sub>3</sub> (H<sub>3</sub>K9ac), for example, neutralizes the positive charge of the histone tail, decreasing its affinity for the negative charge of the DNA, resulting in relaxation of the DNA which wraps around the histone octamer residues (Figure 4). Transcription factors and the transcription apparatus will



**Figure 4.** Posttranslational histone modifications: Common covalent modifications of histones including: (A) acetylation; (M) methylation; (P) phosphorylation – occurring on several amino acid residues. Acetylation is catalyzed by histone acetyltransferases (HATs) and reversed by histone deacetylases (HDACs); methylation, which can be both activator and repressor, is catalyzed by histone methyltransferases (HMTs) and reversed by histone demethylases (HDMs); and phosphorylation is catalyzed by protein kinase (PK) and reversed by protein phosphatases (PP). k = lysine residue; s = serine residue.

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have access to the DNA, and the corresponding gene expression is facilitated (CEDAR; BERGMAN, 2012). On the other hand, deacetylation is associated with gene silencing. In fact, HDACs are generally considered as transcriptional corepressors.

Compared with acetylation, histone methylation is far more complex (ZHANG; REINBERG, 2001). Methylation can occur in preserved lysine (K) and arginine (R) residues and via the four types of histone. Up to 3 methyl groups can be added to the amino group of lysine (mono-, di-, and trimethylation), while arginine can only be mono- or dimethylated. Histone methyltransferases (HMTs) are enzymes responsible for the addition of methyl groups to lysine or arginine residues. Until recently it was believed that histone methylation represented the most stable or permanent modification, because the “turnover” of this marking was lower than the highly dynamic acetylation. However, the recent identification of enzymes capable of removing methyl groups from histones has shown that this marking can be similarly dynamic (BLACK et al., 2012). Therefore, unlike acetylation, which affects the charge of the amino acid residue, directly impacting the histone-histone or histone-DNA bonds, the role of methylation can only be governed by the additional recruitment of regulatory factors (Figure 4).

### ■ 5 Epigenetic deregulation: molecular mechanism of the origin of diseases

The phenomenon of epigenetic deregulation is an example of plasticity in the development, through which alternative phenotypes are generated from a specific genotype, by adjusting the developmental program in response to persistent environmental factors (GLUCKMAN et al., 2007). Therefore, epigenetics, and particularly epigenetic deregulation, go against the simplistic interpretation of the phenotype as a result set by the genotype. This interpretation dominated the thinking about developmental and evolutionary biology throughout the 20th century. Based on the hypothesis that body disorders may result from an imbalance between environmental factors in the womb and in infancy, it has been proposed that the memory of fetal history and the adaptive responses in aging cells and organs may be mediated through epigenetic gene regulation mechanisms (WATERLAND; GARZA, 1999; OZANNE; CONSTANCIA, 2007). The still unanswered question is whether the identity of the genes likely to be involved in this increased susceptibility to deregulation by environmental factors. Many investigations are being carried out to identify these genes by employing amplified genomic approaches in monozygotic (identical) and dizygotic (non identical) twins and rodent lineages (pure or “inbred”), in order to study the impact of the epigenome without interfering effects from genetic variability, such as the effects of chemical substances (food, toxins, drugs) or

non-chemical effects (e.g. behavior) or of environmental factors, on the epigenetic marking of specific genes.

In a recent review by Portha et al. (2014), they concluded that the idea is becoming increasingly accepted that environmental substances can produce alterations in genomic activity which, although not altering the DNA sequence, can produce important and stable translational alterations in the phenotype. Epigenetic alterations, in particular DNA methylation, produce a developmental “memory” of plastic responses in their primordial environment, which can be decisive in the generation and stability of phenotypes throughout life. Their effects may manifest only during prenatal life, for example, in terms of altered responses to environmental challenges. Evidence has accumulated that endocrine or nutritional interventions in early postnatal life may reverse epigenetic and phenotypic alterations induced, for example, by an unbalanced maternal diet during pregnancy. The elucidation of epigenetic processes may enable the identification of individuals at greater risk of future cardiovascular and metabolic diseases, and enable researchers and practitioners to develop intervention strategies to reduce the risk.

### 5.1 Significance of low birth weight

In general, low birth weight is considered to be an important index of the newborn's condition and there is high correlation between birth weight and perinatal mortality (BERGNER; SUSSER, 1970). In addition, evidence from large-scale studies has shown that low birth weight is correlated with congenital abnormalities. Thus, fetal malnutrition, as evidenced by low birth weight seems to cause an increase in the incidence of birth defects. Newborns with fetal growth retardation, followed during an 8 year period after birth, presented lower heights and weights than siblings born with normal weight. On the other hand when the infant's birth weight was above normal, as in the case of diabetic mothers, there was an increase in neonatal mortality. The analysis of a variety of data concerning humans suggests that, in general, malnutrition or maternal malnutrition in the last phase of pregnancy decelerates the final growth of the fetus, and thus impacts the birth weight. Maternal malnutrition in the first part of pregnancy affects the rates of fetal development and mortality. The effect of the mother's nutrition during development and childhood, can also represent a crucial factor in the child's development. For example, a woman who had rickets in the first years of life can reproduce the damaging effects of the disease in her children. Regarding this issue, there is still a need for much research to obtain definitive proof. Direct proof of the influence of nutrition and malnutrition on human gestation is difficult to obtain, because of many factors that interact during this period and that impact fetal development and the outcome of the pregnancy. Socioeconomic factors are strongly

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influenceable. Low birth weight is correlated with race and poverty, which correlate with malnutrition and subnutrition. Other complicating factors include, for example, a lack of education, poor integration of family units, inadequate hygienic conditions and diseases. All these factors acting in conjunction form, apparently, the syndrome of poverty, disease and human underdevelopment.

Considering all the organs affected by malnutrition or subnutrition in humans during the prenatal period and first year of postnatal life, the impact on the brain is that which has been the greatest concern of those responsible for the areas of health and education. Similar to animals, in humans, the most vulnerable period in the development of the brain is the last stage of prenatal growth and the first postnatal period (approximately 12 months), periods in which there is rapid proliferation and initial cell growth and differentiation. Myelination occurs rapidly, at the same time as the exponential growth of the brain. When malnutrition or subnutrition is imposed during this period of rapid myelination, there is a decrease in the quantity and concentration of cholesterol. Cholesterol is an essential component for the formation of myelin, along with cerebrosides, phosphatidylethanolamine and sphingomyelin. All these components suffer reductions in conditions of malnutrition in the most vulnerable period of development, which results in a decreased speed of myelination and reduced amount of myelin in the brain. A reduction in the number and composition of all types of brain cells will occur as a result of precocious malnutrition.

In general, studies in humans are considerably outnumbered by studies in animal models; however, similar results have been obtained in children exposed to malnutrition and/or subnutrition in early periods of their lives. Some studies were carried out in Chile, a country that has undergone serious problems with child malnutrition. They examined the brains of children who died of malnutrition, specifically of protein-calorie malnutrition (marasmus). The graph in Figure 5 compares the composition of well-nourished Chilean children who died in accidents or of other causes not related to malnutrition and which were within the range of values considered normal, even for North American children. The concentrations of RNA, protein and DNA were significantly lower in children who died of marasmus, in different periods after birth (WINICK, 1969).

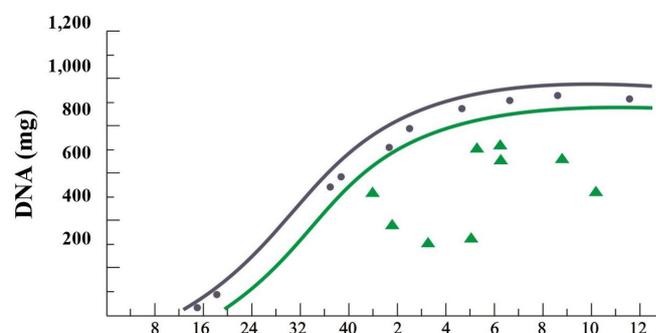
### 5.2 Influence of malnutrition on brain function

Malnutrition in early life can produce permanent effects on the size, number of cells and composition of the brain. This fact has been demonstrated in animals and in humans (Figure 5). The question that arose at the time was what these changes could mean in terms of brain function. Currently, there is significant evidence that malnutrition or subnutrition, in critical periods of development, produces alterations of a behavioral nature in experimental animals.

Various techniques have been used such as: learning tests, behavior tests and emotionality tests. There are still many important issues to be studied on the applicability to humans of the results obtained with animals.

The important question in terms of human society is the following: does early malnutrition have a negative effect on learning ability? The difficulty in answering this question lies in the fact that the malnutrition factor is never isolated from a number of other factors that can also affect the learning ability and intelligence quotient (I.Q.) of an individual. Malnutrition is rarely found as an isolated factor but rather in combination with poverty, low socioeconomic level, unfavorable home environment, absence of intellectual stimulus and other factors that are related to the development and low learning ability. What we can conclude is that subnutrition and malnutrition at an early age (prenatal and in the first year of postnatal life) permanently alter some structures and the chemical composition of the brain, which leads to the hypothesis that the IQ and learning ability should also be affected. However, the direct cause-and-effect relationship with the permanent and irreversible detriment to intellectual capacity in humans, still demands future studies which seek to eliminate interfering factors of a non-nutritional nature as much as possible.

The period from 1950 to 1970 was of great importance since much relevant medical and nutritional research was carried out. These studies demonstrated the need for greater care in the food area in relation to pregnant women and their gestational products, so that they could generate healthy children that might develop into intelligent and productive citizens. Based on the literature published in the areas of pediatric medicine, nutrition and food science, particularly concerning pregnant women, newborns and children in preschool and school age, there was greater motivation by the government agencies responsible for public health to direct greater investment to these areas. The ultimate goal



**Figure 5.** Reduction of the number of brain cells in nine children who died of malnutrition in Santiago, Chile. The lines of the graph delimit the range of normality adopted in the United States (USA): (●) DNA content of normal Chilean children; (Δ) Chilean children who died of marasmus (Winick, 1969).

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was to better preserve the human capital through special programs that enabled greater and coordinated care for pregnant women, newborns and children in preschool and school age, the most critical periods for the development of future citizens who are healthy and productive in society. In the 1960s, institutions such as INAN (National Institute of Food and Nutrition), COBAL (Brazilian Food Company) and PRONAN (National Program of Food and Nutrition) were created in Brazil in order to increase food and nutritional assistance so as to implement an improvement in the nutrition and nutritional status of these segments of the population, particularly in the most destitute. In Chile, the Chilean Government created INTA (National Institute of Food Technology) with the goals of developing foods that were adequate for those segments of the population. Due to these initiatives, in a few years maternal and child malnutrition and subnutrition were virtually eradicated in the country. More recently, research has continued to be carried out in Brazil and in virtually all countries (developed and developing) with the objectives of better explaining the dynamics of human development in its various stages.

### 5.3 Later effects of precocious malnutrition

An excellent review on the effects of maternal and child malnutrition and its consequences on the health of the individual as an adult, was published by Victora et al. (2008). They addressed the associations between maternal and child malnutrition and the human capital and risks of diseases in low- and middle-income countries. The analysis was carried out using data from five long cohort studies including Brazil, Guatemala, India, the Philippines and South Africa, after maternal and infant malnutrition indices had been collected. The following indices were evaluated: maternal height, birth weight and intrauterine growth restriction, in addition to the weight, height and body mass index when the child reached 2 years of age, in accordance with the new growth standard of the World Health Organization (WHO). These indices were considered in relation to the results for adults with respect to: height, educational level and economic power of the family, as well as birth weight, body mass index, blood glucose concentration and blood pressure. Systematic reviews of studies in low and middle family income countries were carried out for these same parameters and for indicators related to blood lipids, cardiovascular diseases, pulmonary and immune functions, cancers, osteoporosis and mental illness. Subnutrition was shown to be strongly associated with short stature, low educational level, reduced economic productivity and, for women, lower birth weights. Associations with disease indicators in adults were not so clear in this research. Higher weight at birth and in childhood was positively associated with the adults' body mass index, and, less clearly, with blood pressure values, but not with blood glucose concentrations.

Both in the analyses carried out by the aforementioned authors and in other published studies, lower birth weight and subnutrition appeared as risk factors for high blood glucose concentrations, blood pressure and undesirable lipid profiles. It was observed that adjustments were made to the body mass index and height, suggesting that rapid postnatal weight gain – especially after childhood – was connected to these unfavorable conditions.

The review of the studies published indicated an insufficiency of information on long-term alterations of immune function, blood lipids, or indicators of osteoporosis. Birth weight was positively associated with lung function and with the incidence of some types of cancers, and subnutrition may be associated with mental illness. The authors observed that the relationship with age (2 years) was the best predictor for the evaluation of human capital and that subnutrition was associated with inferior human capital. They concluded that the damage suffered at an early age lead to permanent losses which could even affect future generations. Prevention will surely bring improvements to health and education, in addition to economic benefits. Chronic diseases are especially common in malnourished children, who experience rapid weight gain after infancy. Although research on nutrition has advanced and solved a good part of the most pressing problems of maternal and child nutrition, it is known that many countries in Africa and in the Middle East have not progressed with respect to solutions for these problems that are critical to human development. Sub-Saharan African countries have shown very poor statistics regarding nutritional progress indices. The high incidence of maternal and child morbidity and mortality has been associated, directly or indirectly, with a high incidence of deaths in pregnancy and during childbirth (UNICEF, 2009). This has also been the major cause of low birth weight, which contributes significantly to the morbidity and mortality rates, with subsequent poor cognitive development. Problems related to child and maternal nutrition are still not considered a priority in many countries. Although nutrition is the main risk factor for childhood diseases, the attention that the problem deserves is still not universally recognized. Researchers have demonstrated that the nutritional status of the populations is influenced by the following interrelated factors: 1) political instability; 2) poverty/socioeconomic differences; 3) inefficient political programs; 4) climate and environmental changes; 5) inadequate food safety administration; and 6) inadequate food implementation and health support programs. Women and children with nutritional necessities are part, in particular, of a risk group with negative implications in terms of maternal health and well-being, as well as of the the survival, growth and normal development of the children. In conclusion, maternal malnutrition results in retardation of fetal growth and development of the newborn, in the first two years of

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life, and may result in irreversible detriment throughout the individual's life, such as a reduction in adult stature, poor school performance, reduced competitiveness at work as an adult and lower birth weight of descendants (VICTORA et al., 2008).

A child's brain volume doubles from birth to six months of life, triples from birth to 2 years of age, and reaches the adult volume by 5 years of age. The brain prototype is remodeled after birth, since unused neurons disappear and stimulated neurons increase in both number and quantity of connections, which results in a complex brain network. This fact illustrates the importance of stimuli during the early years, which are critical to brain development. Direct psychosocial stimuli by means of contact with parents are some of the most significant elements for brain development in early childhood. In the fetal period, the brain is well protected as long as the mother has correct and balanced nutrition. However, iodine deficiency can lead to mental retardation and a lack of folic acid in the first months of pregnancy can cause neural tube defects (GERMAN, 2007). When there is a low amount of iodine in the diet, as in some regions that are mountainous and far from the sea, the amount of iodine transferred to the fetus through the placenta and that which is contained in the breast milk may be insufficient. The addition of iodine to table salt (NaI) was the technological solution found to address this problem in several countries. A lack of iron is the main nutritional deficiency both in developed and developing countries. It is estimated that anemia caused by a lack of iron affects more than 25% of the children in the world and there is evidence that iron deficiency anemia is associated with the impairment of psychomotor and cognitive development. Children with iron deficiency anemia reach inferior levels of mental and motor development. Supplementation with ferrous sulfate improves both mental and motor performance in cases of established retardation; however, it is necessary to establish the needs of each child in treatment. Breast milk is adequate for the needs of babies because they are born with a reserve of iron. Infant formulas enriched with iron contain higher amounts of this mineral, but while the iron in breast milk is absorbed up to 70%, absorption of iron from formulas is only 11%. A child's need for iron changes during the first year of life. The fuel used by the brain is practically only glucose. The neuron membranes comprise a double thin layer composed primarily of fatty acid molecules, and glucose, oxygen and micronutrients pass through the membrane to nourish the neurons and provide the fuel required for nerve impulses. Myelin, the protective layer that surrounds the axons, is composed of 30% protein and 70% lipid. The brain requires lipids for its protection and to provide speed to neural transmissions (GERMAN, 2007).

## 5.4 Congenital abnormalities: significance of birth defects

A second type of abnormal development consists of congenital abnormalities, which are synonymous with birth defects. The word congenital means that the condition already exists at birth, be it caused by genetic or environmental factors. Birth defects are defined as structural or metabolic disorders present at birth, caused by factors that act during the prenatal period. Often, congenital abnormalities are not apparent at birth and are discovered later due to producing functional problems. Congenital heart disease, for example, is commonly discovered after birth, to the extent that cardiac function presents as abnormal and insufficient. The study of congenital abnormalities and their etiologies is the object of Teratology. There are two ways in which the development of the embryo can be affected by environmental factors, including nutrition: 1) by direct effect on the embryo itself; 2) indirect effect through the mother.

In 1910, the percentage of children who died because of congenital malformation was low, around 5%, while 30% of deaths during the first year of life were caused by enteritis, diarrhea, pneumonia and other infectious diseases. The methods of care intended for children and the hygienic conditions of hospitals improved, and, especially, antibiotics and other drugs have emerged, leading specific infectious diseases to decrease significantly. Around 1950, child deaths by infectious diseases dropped to approximately 5% and, proportionately, deaths due to congenital malformations increased.

In 1964, 19% of child deaths occurred due to congenital malformation. It is likely that, in absolute terms, the incidence of deaths due to congenital malformation did not change in the period 1950-1964, but it became more important as other causes of death decreased because of improved care and medical knowledge. According to research published by Apgar and Stickle (1968), the vital statistics for the United States in 1964 indicated that birth defects were the leading cause of infant death (1st year of life). They also found that at least 21,000 cases of pregnancy indicated that at least 7% of all children born showed structural or functional defects of prenatal origin, detected in the first years of life. Less than half (50%) of these defects are detectable at birth. The authors, Apgar and Stickle (1968), also found that at least 62,000 deaths at any age, in each year, could be attributed to birth defects (Table 3 and 4).

When the statistical data for the entire North American population was examined, it was found that 15 million people presented one or more birth defects that could affect daily life. Therefore, the occurrence of birth defects is an important public health problem. In most cases of children with birth defects, the causes of abnormal development cannot be established. According to Wilson (1972), the

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**Table 3.** Deaths caused by congenital conditions identified in the seventh revision of the international classification of diseases in the United States, 1965.

Cause of death	No. of deaths
Congenital syphilis	34
Neoplasms, with less than 28 days	91
Myxedema and cretinism	342
Diabetes mellitus	33,174
Cystic Fibrosis	610
Lipidosis (lipidic metabolic disorder)	158
Amyloidosis	171
Other metabolic diseases	672
Family jaundice	130
Sickle cell disease	358
Hemophilia	59
Chromosomal abnormalities	267
Hernia of abdominal cavity	3,277
Muscular birth defect	689
Congenital malformations	19,512
Neonatal disorders originated from diseases of the mother during pregnancy	717
Hemolytic disease of the newborn (erythroblastosis)	1,485
Hemorrhagic disease of the newborn	477
Other congenital conditions	8
Total	62,231

According to Apgar and Stickle (1968).

**Table 4.** Causes of the development of birth defects in humans (in %).

Causes	Birth Defects (%)
Known genetic transmission	20
Chromosomal aberration	5
Environmental causes:	
Radiation	<1
Infections	2-3
Maternal metabolic imbalance	1-2
Environmental chemicals and drugs	2-3
Combinations and interactions	(?)
Unknown	65-70

According to Wilson (1972).

known causes of birth defects amount to only 30-35% and include: genetic transmission, chromosomal aberrations, radiation, German measles and other viral infections, diabetes, drugs and environmental chemicals. Wilson estimated that 65-70% of all birth defects in humans are of unknown causes. It is possible that nutrition is involved in some of the factors in this unknown group, whether due to nutrition by itself or in interaction with some other factors, already known to affect development.

The dangerous effects of some environmental chemical contaminants have recently been described. Rubin and Soto (2009) describe a possible association between the intake of the compound Bisphenol A in perinatal period and weight gain. Bisphenol A (BPA) is a component of polycarbonate plastics and of the resinous lining on the

inside of the packaging of drinks and food. BPA is known for transferring to the product with which it is in contact (food or drink) and being routinely ingested with food and drink. In a recent study of a sectional cohort, BPA was detected in urine samples of 92.6% of the population examined, in the United States. BPA's potential influence on body weight was suggested by *in vitro* studies, showing effects of the substance on adipocyte differentiation, lipid accumulation, glucose transport and the secretion of adiponectin. Data from *in vitro* studies have demonstrated dose-dependent and sex-dependent effects on the weight of rodents exposed to BPA in the perinatal period. The mechanisms through which perinatal exposure to BPA produces persistent effect on body weight and increase of adiposity were not elucidated.

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Lu et al. (2006) determined the exposure of pre-school age children to organosulphur pesticides in 23 schools by way of urinary biomonitoring. The conventional diet of most children was replaced by organic farming food for 5 consecutive days, during which two samples of urine were collected daily in the morning and another before going to bed, during the 15 days of the study. It was found that the median urinary concentrations of specific metabolites for melation and chlorpyrophosphate decreased to undetectable levels immediately after introducing the organic diet, and remained undetectable until the conventional diet was reintroduced. The authors concluded that these children were exposed to organosulphur pesticides exclusively through their diets.

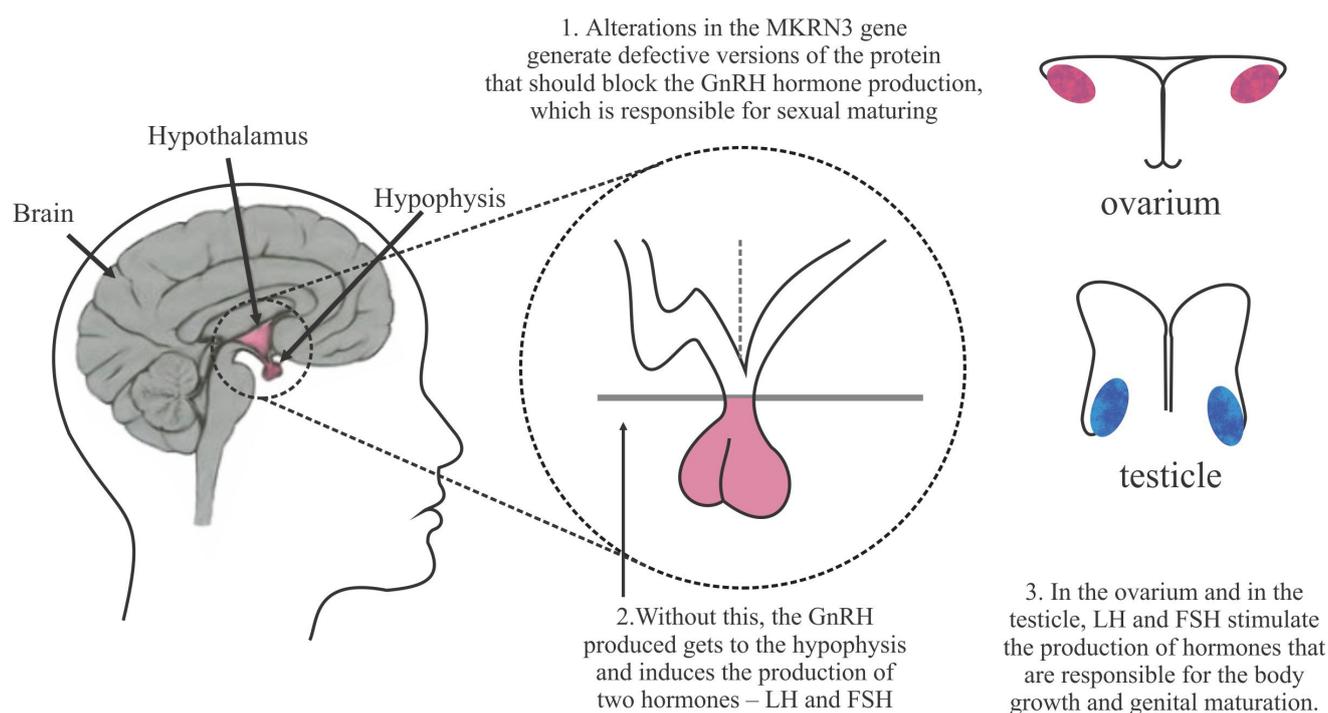
In recent years, there has been increasing concern about the potential role of chemicals that interfere with the endocrine system in the development of chronic diseases such as obesity and type-2 diabetes (CASALS-CASAS; DESVERGNE, 2011).

Recent experimental evidence suggests that prenatal exposure to chemicals that harm the endocrine system can increase the risk of postnatal obesity, and that these effects may be dependent on the diet and sex (VALVI et al., 2012). The authors explored the influence of the concentration of some organochlorine (OC) compounds such as polychlorinated biphenyl (PCB), dichlorodiphenyldichloroethylene (DDE) and dichlorodiphenyltrichloroethane (DDT), to determine if they associated with overweight in 6.5 year old children, and if the child's sex and fat intake would alter the results. A total of 344 Spanish children were studied from a cohort

established in 1997-1998. Overweight at 6.5 years of age was defined as a body mass index (BMI) with a score-Z  $\geq$  8.5%, according to the reference established by the World Health Organization (WHO). Concentrations of products in the umbilical cord blood were determined and treated as categorical variables. The childrens' diets were estimated using the food intake frequency questionnaire and the relative risks (RRs) estimated using generalized linear models. After multivariate adjustments, the authors found an increase in overweight RR in the third tertile for exposure to PCB [RR=1.70; 95% (CI): 1.9; 2.64] and in the second tertile for the DDE compound [RR=1.67; 95% (CI): 1.0; 2.55], but no association was found for exposure to DDT in the population as a whole. Associations between overweight and the PCB and DDE concentrations were stronger for girls ( $p=0.01$  and  $0.28$ ); DDT was associated with overweight only for boys. In the aforementioned study, the authors suggested that prenatal exposure to the chemicals PCB, DDE and DDT may be associated with overweight in children, and that sex and a high fat intake are factors that may influence the susceptibility to the phenomenon.

### 5.4.1 Central precocious puberty

An unusual heritage that affects the child in the first years of life is called central precocious puberty, caused by early activation of the hypothalamus-pituitary-gonads axis and occurring in both sexes, as illustrated in Figure 6. Several researchers from Brazil and from abroad have devoted themselves to this topic in the past decade,



**Figure 6.** Central Mechanism and glandular brain of human reproduction.

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according to Zorzetto (2014). In 12 Brazilian families and three foreign families, 32 individuals were shown to have entered puberty too early, generally at the age of 6 years, by way of clinical and hormonal tests. In all these cases, the accelerated development that marks the transition of the body to adulthood started ahead of time, due to a premature increase in the production of the hormone that releases the gonadotropins, the GnRHs, which are responsible for the sexual maturation of the organism. Produced in the brain by a small group of neurons in the hypothalamus, the GnRHs are released in faster pulses at puberty, inducing the pituitary gland to produce two other sex hormones: the luteinizing hormone (LH) and the follicle stimulating hormone (FSH). These hormones are released into the bloodstream and reach the ovaries and testicles, where they activate the release of other sex hormones that make the body grow and mature from the reproductive point of view (Figure 6). The researchers then decided to sequence the genetic material of the 32 participants, investigating alterations that could explain the early onset of puberty. Eight of the 32 individuals showed defects in the same gene, the MKRN3 gene, this being the first gene identified as responsible for this inherited form of precocious puberty. The high incidence of genetic defects in a single gene (33%) surprised the researchers, as alterations in genes affect less than 10% of individuals with a particular genetic disorder. In addition to being very frequent in the cases where precocious puberty was present in more than one generation in the same family, the MKRN3 gene mutations were also shown to be common in people with central precocious puberty of nonhereditary origin. Puberty is usually associated with a series of long-term physical and psychological phenomena and hence a greater understanding of what defines its onset could create an opportunity to address health issues such as cancer, risky behavior and drug abuse.

A group of researchers in São Paulo, Ribeirão Preto and Campinas (all in Brazil) and in Macedonia (Eastern Europe), followed 215 children who presented isolated, nonhereditary precocious puberty. The proportion of individuals with altered MKRN3 genes was considered high, approximately 3% (ZORZETTO, 2014). In the first phase of the research, it was established that alterations in the MKRN3 gene generated defectuous versions of the kisspeptin protein, which should block the production of the hormone GnRH, which controls sexual maturation. With the mutation, this block was absent and the GnRH that was produced reached the pituitary gland, inducing the production of the hormones LH and FSH. These hormones will act making the body grow and the genitals develop precociously. The group of international researchers continued to seek for an explanation for this phenomenon, and recently published the results of their research (TELES et al., 2008; ABREU et al., 2013). According to Teles et al. (2008) the central or gonadotropin-dependent

precocious puberty is caused by an early maturation of the hypothalamus-pituitary-gonad axis, and in girls, this condition is mostly nonhereditary. Recently, a G protein-coupled receptor, GPR54, and its ligand to the protein kisspeptin, were described as an excitatory neuroregulator system for the secretion of the gonadotropin regulating hormone (GnRH). In this study, the authors identified an autosomal dominant mutation in the GPR54 receptor, consisting of the replacement of arginine (R) by proline (P) in the code 386 for this receptor (R386P), in the genetic profile of a girl with precocious puberty. The authors reported the case study of a girl aged 8 years which attempted to evaluate her precocious puberty. Premature breast development had been observed as from birth. By 7 years of age, breast growth was accelerated as well as pilosity in the pubic region. The mammalian animal model suggests an important role for kisspeptin, since intermittent infusion of this protein results in early sexual maturation in rats and an early release of the hormone GnRH in primates (NAVARRO et al., 2004a; PLANT et al., 2006). In their study, Teles et al. (2008) identified a heterozygotic mutation in GPR54 (R386P) in the aforementioned girl with nonhereditary precocious puberty.

Data in the literature suggests that an increased hypothalamic expression of kisspeptin in puberty contributes to maturation of the reproductive axis (NAVARRO et al., 2004b; HAN et al., 2005). Teles et al. (2008) speculated that a decrease in sensitization of the receptor GPR54 because of the mutation (R386P) could be expected to increase the stimulatory effects of kisspeptin on the secretion of GnRH, thus accelerating the maturation of the reproductive axis. In addition, in this study the development of the patient's breasts in the neonatal period seems to be consistent with the kisspeptin-GPR54 system activity. The authors concluded they had identified a mutation in an autosomal dominant gene (R386P-GPR54), which prolonged the intracellular signaling of the GPR54 receptor in response to kisspeptin, and that all indications pointed to this being associated with the phenotype of central precocious puberty.

According to Abreu et al. (2013), the development of puberty is partly due to genetic factors, but in some cases, rare molecular defects have been identified, associated with central precocious puberty. The aforementioned researchers carried out the sequencing of a complete "exon" in 40 members of 15 families with central precocious puberty and the genetic variants were confirmed using the Sanger sequencing method. Quantitative tests using the polymerase chain reaction (PCR) in real time were also carried out so as to determine the levels of messenger RNA (m-RNA) in the hypothalami of different aged mice. The authors identified 4 new heterozygotic mutations in the MKRN3 gene, which encoded for the protein 3 macorina "RING finger" in 5 of the 15 families, both sexes being

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affected. A total of 4 mutations were identified, of which 3 involved encoding for truncated proteins and 1 was of the missense type that could block the production of the protein. The MKRN3 gene is located in a special region of chromosome 15 (15q11-q13) and all the affected individuals inherited the deficiency from their parents, a finding that indicates perfect segregation according to the expected inheritance from an imprint gene.

How puberty is initiated is still an enigma that defies an explanation from scientists. Much of the recent advance in the understanding of the mechanisms involved in reactivation of the central system, hypothalamus-pituitary-gonad, or reproductive axis in puberty, has been based on the characterization of genetic mutations associated with reproductive disorders in humans. Most mutations were identified in patients with hypogonadotropic hypogonadism, a disorder which is much less common than central precocious puberty (SEMINARA et al., 2003; ROUX et al., 2003). It is believed that the onset of puberty results from the reduction of factors that inhibit GnRH release combined with an increase in stimulatory factors. Studies on hypogonadotropic hypogonadism have resulted in the identification of genes that encode factors that have stimulatory action (BIANCO; KAISER, 2009; SEMPLE; TOPALOGU, 2010). In contrast, MKRN3 seems to have an inhibitory role in humans, a role that disconnects as a result of the mutation that occurs in the GRP54 receptor, activating the central axis of precocious puberty.

### 5.4.2 Etiology of infantile leukemia

Another serious problem that affects human development and originates in the womb, are the infantile leukemias. Acute leukemias amount to approximately 30% of all malignant diseases that affect children in the western world. The peak incidence of B-cell precursors that transform into leukemic cells or acute lymphoblastic leukemia (ALL) emerged as a result of improved socioeconomic conditions in numerous countries throughout the world. In studies on twins and blood analyses in newborns, it has been possible to reproduce the first genetic events in hematopoietic cells that are critical for the "in utero" fetal development of the B-cell precursors to ALL, and, in some cases, of the precursors to AML or acute myelogenous leukemia (FORD et al., 1993; GALE et al., 1997; WIEMELS et al., 1999; WIEMELS et al., 2002; MORI et al., 2002). These events may occur as a normal part of fetal development, but it is not clear if other factors (constitutional or environmental) are involved and if they may increase the probability that the first events occur. For some leukemias (e.g.: ALL), the first event seems sufficient to create a clone of malignant cells; however, for most cases of ALL and AML, other genetic alterations are required, probably in the postnatal period.

Many environmental factors have been proposed as causes for leukemia, but only ionizing radiation and

certain chemicals (e.g., cytotoxic alkylating, benzene and topoisomerase II inhibitors) have been confirmed, especially for AML. It seems increasingly probable that delayed and unregulated responses to common infectious agents play a very important role in the conversion of preleukemic cell clones into B-cells that are precursors to ALL, the most common form of childhood leukemia. Polymorphic allelic variants, constitutional in genes of the immune response (especially HLA class II proteins) and cytokines, may play a role in determining the type of immune response. High-penetration mutations similar to germs are involved in only approximately 5% of childhood leukemia (more in AML and ALL). There is very little evidence supporting the participation of viruses as the cause of leukemia in humans. However, there is evidence for the role of other environmental factors such as nonradiating electromagnetic radiation and electric fields, although their mode of action on the genesis of leukemia remains unclear. Childhood leukemia has no single cause and for most individuals it is the result of a combination of factors; all involving gene-environmental interaction. To date, few preventive measures have emerged except completely avoiding x-ray exams in the first trimester of pregnancy; a healthy diet with an adequate amount of folic acid, both in the preconception period and in early pregnancy. It is important that the child has contact with other children outside the home environment for stimulus and maturation of the immune system (EDEN, 2010). A summary of the main genetic and environmental factors involved in the development of the main childhood leukemias is presented in Table 5.

### 5.4.3 Normal birth versus surgical birth

In a study coordinated by WHO (World Health Organization) and funded by the World Bank, epidemiologists and specialists in female reproductive health evaluated the outcome of nearly 100 thousand childbirths carried out from September 2004 to March 2005 in 8 Latin American countries (Argentina, Brazil, Cuba, Ecuador, Mexico, Nicaragua, Paraguay, and Peru). According to Zorzetto (2006), the result confirmed what was feared: the unnecessary surgical births (cesarean section) are more harmful than beneficial. When the rate of Cesarean section in a hospital exceeds 10 to 20% of total deliveries, the risk of complications for mother and baby is greatly increased. There is greater probability that the women may die during surgical birth, have serious bleeding or acquire an infection requiring hospitalization in the intensive care unit. There is a greater risk that the child be born with less than 37 weeks gestation (preterm) due to medical miscalculation, may die during the birth or in the first week of life and may require intensive care. While WHO establishes that 75 to 80% of births should occur through natural means, in Brazil the opposite has occurred in recent decades, with approximately 80% of births by

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**Table 5.** Major genetic and environmental factors involved in the development of infantile leukemia.

<p><b>&gt; Genetic Factors</b></p> <ul style="list-style-type: none"> <li>• Genetic mutations (~5% TP53, NF<sub>1</sub>, AT, etc)</li> <li>• Down's Syndrome considerably increases risk (ALL and AML)</li> <li>• Twins, no interference in prenatal period but postnatal influence may occur</li> <li>• Polymorphic metabolic variants, immune response and gene repair may play important role (e.g.: NQO1, MTHFR, HLA class II)</li> <li>• The profile of genes and protein expression may identify other susceptible genes</li> </ul>
<p><b>&gt; Environmental factors</b></p> <ul style="list-style-type: none"> <li>• Ionizing radiation causes leukemia if exposure is high and/or involves vulnerable individuals (fetal DNA damage, defects in the repair system)</li> <li>• Irradiation of the environment in most cases does not affect childhood leukemia</li> <li>• Parents' occupation/exposure to diagnostics (controversial, unclear mechanism)</li> <li>• Avoid: x-rays in the first trimester, care in selection of imaging tests in childhood</li> </ul>

Adapted from Eden (2010).

caesarean section, with greater risk for mother and baby, in addition to unnecessary expense as a detriment to the national health system.

### 5.4.4 Viroses

Dengue, chikungunya, microcephaly (Zika virus). The virus of Zika, known in Brazil and in the media as the Zika virus, was first identified in 1947 in a "*rhesus*" monkey used by British scientists as sentry for the detection of yellow fever, while they researched in a laboratory located in the forest named Zika, in Uganda, Africa - hence the name "Zika virus" for the newly discovered virus. The first human infection was described in 1954 in Nigeria, Africa. Only in 2007 was there a massive infection of 75% of the population of a small island (Yap) between the Philippines and New Guinea, Western Pacific Ocean, followed by an even larger epidemic in 2013, in French Polynesia (CHANG et al., 2016).

There are two known strains of the Zika virus, one African strain and one Asian strain (DAFTY et al., 2009; HADDOW et al., 2012). Initially associated only with mild clinical symptoms, subclinical or even asymptomatic disease, the virus, at present, has come to be associated with multiple cases of neurological damage in the newborns of mothers infected with the Zika virus, even the Guillain Barré Syndrome, in epidemic areas of the virus. Initially, it was thought that the virus could only be spread by mosquitoes, but more recently it was found that individuals could also be infected by sexual contact, blood transfusion, saliva and other physiological fluids (MUSSO et al., 2015; VENTURI et al., 2016).

The pathogenesis of infection by Zika virus, in particular the more severe complications, are as yet unknown. Distinct cellular mechanisms may be at work, including autophagia, the balance between cytokines

and molecules as adhesion receptors that facilitate viral penetration. Interferon inhibitors have been shown to be effective against the Zika virus infection *in vitro* and may be an alternative (HAMEL et al., 2015). While the Zika virus infection spreads, the need to develop a vaccine is vital.

The main challenges of the research aimed at combating the Zika virus are:

- 1) Establishing clearly the connection between neurological sequelae and infection by the Zika virus and, in case of confirmation, determine the risk factors (genetic and/or environmental) associated with the complications;
- 2) Define tests that identify the Zika virus infection during pregnancy;
- 3) Determine the molecular signatures of the virus that are associated with the virulence and/or mechanisms of the neurological complications associated with microcephaly and the Guillain-Barré Syndrome;
- 4) Determine if the Zika virus isolated from its natural host in Africa differs from that isolated from natural vectors in the West.

Microcephaly is associated with multiple causes, including: genetic disorders (e.g., autosomal recessive microcephaly, Aicardi-Goutières Syndrome, chromosomal trisomia, Rett syndrome, and X-chromosomal microcephaly); intoxication of pregnant mother with drugs and chemicals (e.g., use of alcohol, cocaine, antiepileptic drugs, lead, mercury or radiation poisoning); malnutrition and any transplacental infection by virus or bacteria (VON DER HAGEN et al., 2014); maternal infections, including rubella, Cytomegalovirus, herpes simplex, varicella (Zoster Virus), HIV

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and arbovirus such as chikungunya have been associated with microcephaly in newborns (GÉRARDIN et al., 2014).

Several species of mosquito have been identified as vectors of the Zika virus, including: *Aedes africanus*, *Aedes luteocephalus*, *Aedes hensilli*, *Aedes polynesiensis*, *Aedes dalzielii*, *Aedes albopictus*, *Aedes apicoargenteus* and *Aedes aegypti*, amongst others. *Aedes aegypti* is by far the predominant mosquito species in Brazil and is also associated with the transmission of other types of virus that cause dengue and chikungunya. The first case of infection by the Zika virus in Brazil was confirmed in May 2015 (ZANLUCA et al., 2015). The incidence of microcephaly in Brazil in 2015 was 20 times higher than in previous years. After a complete study of the genetic sequencing of the Zika virus by Calvert et al. (2016) and a comparison with genetic banks of the same virus found and studied in several continents, it was concluded that the Zika virus found in Brazil was probably closer to that found in French Polynesia of the Asian strain than that of the African strain. The determination of the Zika virus genome and the Zika virus IgM in the amniotic fluid of pregnant women and unborn children with microcephaly had not been reported in detail in the scientific literature (CALVERT et al., 2016).

Other severe neurological complications such as Guillain Barré Syndrome have been described in patients infected with the Zika virus (OEHLER et al., 2014). A perfect understanding of the range of neurological diseases which may be caused by the Zika virus is important not only for affected individuals but also to establish care plans for the health of the population. The Japanese experience with encephalitis in Asia has shown that the development of a vaccine is not sufficient. Public health planners must

understand the full extent of the disease to complement the implementation program with a vaccine (SOLOMON, 2006; CAROD-ARTAL et al., 2013), and such development will take a few years. For the moment, there is urgent priority in understanding the scale and complete range of the neurological problems associated with the Zika virus infection.

## 6 Nutrition in the perinatal period

### 6.1 Nutrition in pregnancy

The subject of nutrition in pregnancy is complex due to the fact that it involves multiple factors that interfere with the health of mother and child, some of which were presented briefly in specific topics in this review. Special care should be exercised with some micronutrients as suggested in Table 6 according to the recommendations of Rauber and Vitolo (2012).

In the first trimester of pregnancy, the maternal energy intake should be similar to that of the pregestational period, that is, approximately 2,000 Kcal per day, considering a diet with a proper balance of nutrients. In the second and third trimesters, an additional intake of 300 Kcal is recommended, considering a diet such as that recommended by the RDA. Table 6 illustrates the recommended intakes of some nutrients for the different ages of pregnant women. Some of the nutrients mentioned in Table 6 are critical for the development of the fetus and newborn; therefore, they should be evaluated with criteria.

**Calcium.** Hormonal alterations that occur in pregnancy promote adjustments to the calcium metabolism, so as to promote increased biological use of that element during this period. Therefore, despite the calcium requirements being greater in pregnancy, dietary recommendations remain

**Table 6.** Dietary intake of the most important micronutrients in pregnancy for the different ages of pregnant woman.

Recommendations	EAR	RDA ou AI	UL
Pregnant women < 18 years			
Calcium (mg)	1,000	1,300	2,500
Iron (mg)	23	27	45
Folate (µg)	520	600	800
Vitamin A (µg)	530	750	2,800
Vitamin B <sub>12</sub> (µg)	2.2	2.6	-
Vitamin C (mg)	66	80	1,800
Zinc (mg)	10.5	12	34
Pregnant women 19-50 years			
Calcium (mg)	800	1,000	2,500
Iron (mg)	22	27	45
Folate (µg)	520	600	1,000
Vitamin A (µg)	550	770	3,000
Vitamin B <sub>12</sub> (µg)	2.2	2.6	-
Vitamin C (mg)	70	85	2,000
Zinc (mg)	9.5	11	40

EAR = Estimated Average Requirement; RDA = Recommended Dietary Allowance; UL = tolerable upper level intake. Sources: IOM (2006, 2011).

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the same as for non-pregnant women. The recommended values can be obtained by the ingestion of two glasses of milk (150 ml), one slice of fresh cheese (30 g), and one unit of yogurt (150 g). Although some vegetables are good sources of calcium, in general its bioavailability is much smaller in products of plant origin, suggesting the need to eat larger quantities.

**Vitamin C.** As vitamin C is not stored by the body, consumption should be daily. The plasma concentration of this vitamin tends to decrease during gestation, probably during hemodilution and transfer to the fetus. However, the recommendations for vitamin C are easily met by the daily consumption of fruits and vegetables. The recommendation for the tolerable upper level intake (UL) is 2 g daily.

**Iron.** At the beginning of pregnancy it is very important that a woman has an iron reserve of approximately 500 mg in her organism in order to maintain an adequate hematopoietic balance (SCHUMAN et al., 2007). Considering that, on average, 6 mg of Fe is obtained from every 1,000 Kcal of healthy food, a mean daily intake of 2,000 Kcal will provide approximately 12 mg of iron. Therefore it was concluded that it is practically impossible to achieve the daily recommendation of 27 mg (RDA) only by means of normal feeding, and there is a need to increase the consumption of foods high in bioavailable iron or use supplementation (VITOLO, 2008; BRASIL, 2006). The iron form with high bioavailability is heme Fe, found in foods of animal origin, particularly in red meat and offal, with liver being the richest source (1 steak weighing 100 g contains more than 10 mg of Fe). Non-heme Fe, found in plant foods, shows low bioavailability (~5%) and its absorption can suffer the influence of factors that facilitate absorption (ascorbic acid, carotenoids, fructose, citrates and some amino acids such as cysteine, histidine and lysine) or that inhibit absorption (phytates, fiber, oxalates, caffeine, phenolic compounds, calcium, phosphorus and zinc). Therefore, nutritional education should prioritize the intake of heme iron and/or improve the bioavailability of heme iron.

In the practice of iron supplementation, it is recommended that all pregnant women take an iron supplement of 30 to 40 mg daily during the last trimester of the pregnancy, as a prophylactic measure to ensure maintenance of the iron reserves, while continuing to meet the other nutritional requirements (WHO, 2001). In the case of anemia or iron deficiency, supplementation with 60–80 mg is recommended, but supplementations with even greater doses should be avoided. Very high doses of iron can cause zinc deficiency in the presence of a marginal intake of this mineral, and excessive drug supplementations may produce side effects that are detrimental to treatment adherence (RIOUX; LEBLANC, 2007).

**Folic acid.** Despite the variety of foods containing folate (PINHEIRO et al., 2005), it has been shown that

only 8% of American women consume the recommended amount of this nutrient daily (LOCKSMITH; DUFF, 1998). A balanced diet providing 2,000–2,200 Kcal provides approximately 250 µg of folate a day. According to dietary recommendations, women of childbearing age should consume 400 µg/day of folic acid by way of fortified foods and/or supplements, in addition to a diet with natural sources of folate, and in the same way, pregnant women should consume 600 µg/day, since these values are difficult to reach from a basic diet. Most prenatal supplements contain 1 mg of folate (1,000 µg), a sufficient amount to meet the needs and restore stocks in the case of a deficiency of this vitamin. However, in cases of hemolytic disorders, such as sickle cell disease, the recommendation is to supplement with 5 mg/day. It is noteworthy to observe the difference between physiological doses of folate (below 1,000 µg) with prophylactic purposes, and pharmacological doses (over 1,000 µg) for therapeutic treatments, for example, for patients with megaloblastic anemia (RAUBER et al., 2011).

In Brazil, corn and wheat flours have been fortified with iron and folic acid since 2004; 100 g of flour must provide 4 mg of Fe and 150 µg of folic acid. For pregnant women, such an amount would correspond to only one-seventh of her requirements, indicating the need to consider an adjustment to this level of supplementation. Other trace minerals may also be a cause for concern, particularly in certain regions of the globe, which is the case of zinc and iodine.

**Zinc.** The occurrence of zinc deficiency in humans was well established in Egypt and Iran in the 1960s and 1970s, respectively, resulting in dwarfism and hypogonadism in male (Egypt) and female (Iran) adolescents. More recently, zinc deficiency was found in children in the United States (PRASAD, 1976a, b; PRASAD et al., 2007). Since these abnormalities may occur in humans, it has been suggested that Zn deficiency may also be a factor in congenital abnormalities in the human species, which has already been thoroughly demonstrated in rodents (HURLEY, 1980). There is some evidence that Zn deficiency functions as a teratogenic factor in humans, and data from epidemiological studies seem to support an association between zinc deficiency and malformations of the central nervous system in humans, since a high incidence of malformations has been found in the populations of both countries showing Zn deficiency (Egypt and Iran). Another type of evidence has been found in women with acrodermatitis enteropathica, a genetic disorder of Zn metabolism. In the early 1970s, it was demonstrated that the signs and symptoms of this condition could be cured through oral therapy with zinc, and patients treated with drugs containing Zn both survived and grew, but were unable to maintain normal plasma levels of the mineral. Thus women carrying this genetic factor that became pregnant presented abnormally low Zn concentrations

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in the blood plasma, and the results of their pregnancies were significantly negative. The numbers of abortions and of children with malformations were much higher than in the normal population: of seven pregnancies, two presented neonates with serious congenital deformities and one resulted in miscarriage.

In Sweden a correlation was found between low levels of Zn in pregnant women and various complications in pregnancy. Women who gave birth to children with malformations, had delayed birth, or an abnormal delivery, presented significantly lower serum Zn levels as compared to women whose deliveries and children were normal or whose children presented low birth weights.

**Iodine.** Iodine has an important function as part of the structure of the thyroid hormone, thyroxine. Iodine deficiency results in hypothyroidism due to an insufficient production of thyroxine. When this happens to an individual in growth or to an adult, the condition is known as goiter. Due to the fact that the deficiency occurs in certain geographical areas and is related to a deficiency of iodine in the soil or in the environment in general, the problem is known as endemic goiter. Endemic goiter occurs in defined areas and refers to an increased volume of the thyroid gland when the iodine intake is insufficient. In certain areas of endemic goiter there is also a high frequency of cretinism, which is a disease known for many years, having been described since the 16th century. However, the association of cretinism with goiter only occurred in the early 19th century. Currently, it is well known that endemic goiter results from iodine deficiency, but the causes of the coexistence of endemic goiter and cretinism are still under discussion, the main question being that endemic cretinism does not always occur in areas where there is an incidence of endemic goiter. Endemic cretinism represents only one of the types of cretinism, the other forms being: 1) congenital thyroid aplasia; 2) genetic defects of the thyroxine metabolism; and 3) hypothyroidism in teenagers. The child born with cretinism presents clinical aspects of mental and physical retardation, with a protruding abdomen, large tongue taking up almost the entire oral cavity, facial features similar to those of Down's syndrome and skin that is rough and thick. Neurological disorders such as an inclined stance, strabismus and spasticity are often observed. The development of the bones is abnormal, delayed dentition and delayed development of the epiphyses being characteristic. Deafness and speech impairment occur frequently and mental retardation, which may reach an extreme level, is also observed with some frequency. In the highlands of Ecuador, where iodine deficiency is severe, a clinical study of the patterns of cretinism indicated a wide range of variation regarding the signs and symptoms of the disease. In regions where the incidence of endemic cretinism was high, there was a significant decline in the disease after the introduction of iodine (NaI) into certain

foods as a prophylactic measure. In some valleys of the Swiss Alps, for example, where both goiter and cretinism were endemic, endemic cretinism virtually disappeared after the introduction of iodized salt (NaCl).

## 7 Probiotics and bioactive substances

In addition to micronutrients, other components of the diet have aroused great interest with respect to both pregnant woman and the newborn. A few of the possible components of the diet of both pregnant woman and the newborn, such as: probiotics; polyunsaturated fatty acids; prebiotics; polyphenols, and bovine milk, will be briefly discussed.

### 7.1 Probiotics and prebiotics

Russell and Murch (2006) recommended the controlled use of probiotics for both pregnant woman and neonates. For pregnant women, the following beneficial effects were observed: 1) decreases in the transfer of antigens to the fetus; 2) strengthening of the immune system; 3) preparation of the intestinal and vaginal microbiota for childbirth. For neonates, the following beneficial effects were observed: 1) decreases in the risk of allergies, atopias and upper respiratory tract infections in childhood; 2) decreases in the risk of autoimmune diseases and metabolic diseases in adulthood.

The effect of the probiotics *Lactobacillus rhamnosus* and *Bifidobacterium lactis* in the regulation of blood glucose during and after pregnancy for a period of up to 12 months postpartum was presented by Laitinen et al. (2009). This was a randomized, double-blind, placebo-controlled study and the pregnant women were normoglycemic with a controlled diet for the placebo group. Two experimental groups were used, namely: 1) controlled diet with the addition of probiotic as from the first gestational trimester; 2) controlled diet with the addition of probiotic in the last gestational trimester. The group that received probiotic in the last trimester showed lower blood glucose levels and a lower concentration of circulating insulin. A recently published article (MILLION et al., 2012) tested the hypothesis that the species of *Lactobacillus* or *Bifidobacterium* found in the human intestine could be associated with obesity or with the absence of overweight and obesity. The authors analyzed the feces of 68 obese individuals and 47 controls, testing for the following microorganisms: Firmicutes, Bacteroidetes, *Methanobrevibacter smithii*, *Leucococcus lactis* and *Bifidobacterium animalis* and seven species of *Lactobacillus* were analyzed by quantitative PCR (qPCR) and cultured in a selective medium for *Lactobacillus*. The authors concluded that reduced levels of *M. smithii* were associated with obesity. In addition, high levels of *B. animalis*, *L. paracasei* or *L. plantarum* were associated with normal weight, while high levels of *L. reuteri* were associated with obesity. These results suggested a possible

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interrelation between certain probiotic species marketed for human consumption and obesity. According to the authors, these results should be considered with caution, since to date, it is the first study associating specific species of lactobacilli with obesity in humans. This matter is of critical importance for management of the obesity epidemic throughout the world, particularly considering the growing market for probiotics. Recent studies can also be found in the literature describing beneficial effects during pregnancy, such as in the reduction of postprandial blood glucose levels and improvements in the occurrence of constipation, and the influence of the microbiota in children, reducing the risk of atopic dermatitis, and contributing to an increase in folate and maturation of the immune system in both mother and child.

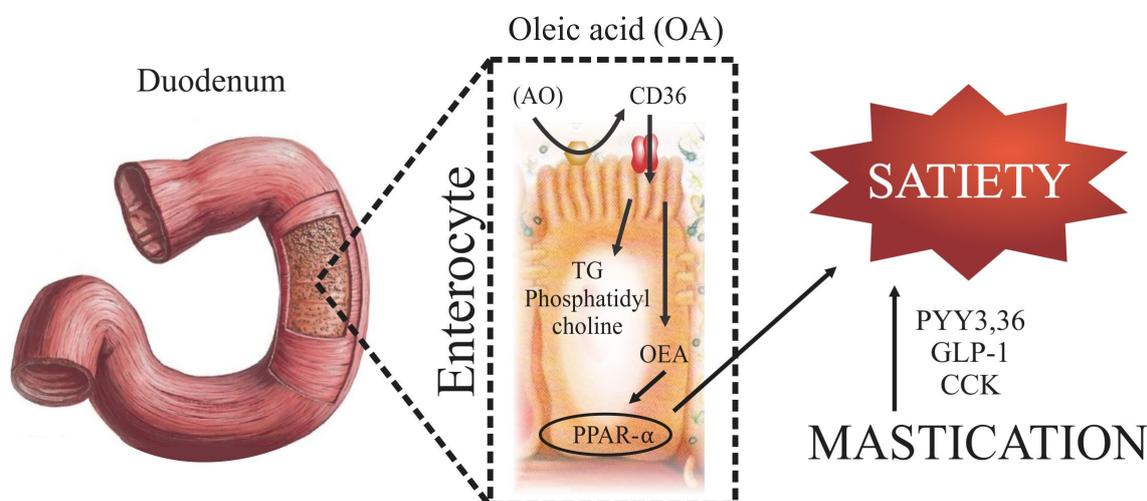
### 7.2 Lipids: oleic (OA) and Docosahexaenoic (DHA) acids

Oleic acid, the main lipidic component of the Mediterranean diet, has proven effectiveness as a bioactive component in modulation of the lipid metabolism, and in the control of blood cholesterol, the circulatory lipoproteins, atherosclerosis and cardiovascular diseases, in addition to its importance in the formation and function of the central nervous system. Figure 7 illustrates graphically the transformation of oleic acid (OA), which is absorbed by the enterocytes with the aid of the CD36 protein and metabolized inside the enterocyte into triglycerides (TG), phosphatidylcholine (PC) and oleoylethanolamide (OEA), the latter (OEA) acting as an activator of the nuclear receptor PPAR- $\alpha$  producing satiety. Other satiety-stimulating peptides (PYY 3,36; GLP-1 and CCK) produced during mastication act synergistically in the phenomenon of satiety, helping to curb food intake. This mechanism is stimulated by cerebral branches of the vagus nerve.

The requirements for Omega-3 fatty acids, especially for docosahexaenoic acid (DHA), during pregnancy, have received significant attention; however, evidence as to the effect on the characteristics of the baby at birth is very limited. Ramakrishnan et al. (2010) published the results of a double-blind, randomized, placebo-controlled trial carried out in Cuernavaca (Mexico) with 1,094 pregnant women aged 18 to 35 years. The intake of DHA from algae ranged from 55 to 400 mg/day in the experimental group, for a period of 18 to 22 weeks of gestation up to birth. The results of the births were followed and certified in the hospital as 968 live births and 5 stillbirths, 24 hours after birth. The results showed no statistical difference ( $p > 0.05$ ) between the experimental group and the placebo group. The conclusion was that DHA supplementation during the second half of pregnancy showed no benefits as far as gestational age or birth size. The authors stated that, according to their knowledge, this was the first comprehensive study on the potential benefits of DHA supplementation in a developing country such as Mexico, which is undergoing a period of nutritional transition characterized by the coexistence of subnutrition and obesity problems (OLAIZ-FERNANDEZ et al., 2006).

### 7.3 Bovine milk

Milk has been recognized as a functional nutrient system that is active in promoting the growth of neonates in mammals. According to Melnik et al. (2013), cell growth is regulated by nutrient-sensitive kinase, whose mechanism targets the activation of the rapamycin complex 1 (mTORC1). There is still a lack of information about the stimulation mechanisms (+ regulation) of this system by milk consumption. According to the aforementioned authors, milk works as a maternal-neonatal valve system by transferring preferential amino acids that promote increased levels



**Figure 7.** Satiety-stimulating mechanism exercised by oleic acid by way of oleoylethanolamide (OEA), the nuclear receptor (PPAR- $\alpha$ ) and the peptides (PYY 3,36; GLP-1 and CCK), generated during the mastication process.

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of glucose-dependent insulinotropic polypeptides (GIP), glucagon-like peptide 1 (GLP-1), insulin, growth hormone (GH) and insulin-like growth factor 1 (IGF-1), for activation of the rapamycin complex 1 (mTORC1). It is important to observe that milk contains exosomes (particles) that regularly contain microRNA-21, which probably represents a gene transfection system, enhancing the metabolic processes carried out by mTORC1. Although human milk is the ideal food for newborns, enabling adequate postnatal growth and species-specific metabolic programming, persistent signalling of high bovine milk intake during adolescence and adulthood may promote diseases of civilization caused by mTORC1 (MELNIK et al., 2013). Also according to Melnik et al. (2012a, b, c; 2013), the routine consumption of bovine milk, which was stimulated by the introduction of cooling technology in the early 1950s, has become a revolutionary feeding habit that can have long-term adverse biological consequences (MELNIK et al., 2012a). Milk is not just a food, but also seems to represent an endocrine signaling system that is very sophisticated and able to activate mTORC1 via special maternal dietary messengers derived from milk and controlled by the lactation genome in mammals. These are the branched chain amino acids (BCAAs) of the milk proteins, and exosomes containing microRNAs (miRs) produced by the mammary glands, which seem to increase the mTORC1 signaling for postnatal growth. Therefore the concern that the persistent increase in the consumption of bovine milk by children in the postnatal period has been recognized as a fundamental driving force for the development of civilization diseases stimulated by m-TORC1, is crucial (MELNIK et al., 2012b, c).

Thus future research in nutrition science should focus special attention on the role of the branched chain amino acids (BCAAs) derived from dairy products. Moreover, it should clarify the potential role of the microRNAs (miRs) transferred by exosomes, in the metabolic regulation of a milk-consuming individual. The potential intake of marked miRs, contained in the exosomes of commercial milk, should be studied in greater detail in both animal and human models.

### 7.4 Polyphenolic substances

Phytochemicals considered as non-nutrient, including polyphenols, are often discussed due to the great interest that these compounds have stimulated in researchers, due to a series of bioactive properties that are considered beneficial to animal and human health. Among such bioactive properties, the most researched have been the high antioxidant, anti-inflammatory and anti-stress powers of these compounds, whose functions can extend to the control of blood cholesterol, of atherosclerosis, of hypertension and the combat against cardiovascular disease and some cancers.

Pregnancy requires adjustments in the maternal organism due to an increase in the production of hormones such as progesterone, estrogen and prolactin, in addition to several placental hormones. The gestational period is a phase during which the nutritional needs are high, because of physiological adjustments of the pregnant woman and of demands for nutrients for fetal growth. At physiological concentrations, polyphenols can also bring cardiovascular benefits to pregnant women, helping prevent preeclampsia due to mediating vasodilation, and isoflavones seem to have importance in the regulation of the maternal-fetal blood flow (SPERONI et al., 2009). However, it is important to understand that the amount of phenolic compounds consumed during pregnancy should be controlled, since they can cross the placental barrier and get into the fetal tissues, interfering with development (SCHRÖDER-VAN DER ELST et al., 1998). However, intake assessment is hampered by the scarcity of data in food composition tables. A study of pregnant women who consumed the juice *Mona Vie*®, rich in anthocyanins and proanthocyanidins, which inhibit the cyclo-oxygenase and nitric oxide synthase enzymes, showed that the babies, at birth, presented hypertrophy and dysfunction of the right ventricle and pulmonary hypertension (KAPADIA et al., 2010).

#### 7.4.1 Childhood leukemia

The high consumption of flavonoids during pregnancy appears to increase the risk of acute childhood leukemia. This is because the phenolic compounds (quercetin, fisetin, apigenin, luteolin, and genistein) can cross the placenta and inhibit the activity of the DNA topoisomerase II (topo II) enzyme, promoting aberrational chromosomal recombinations and transcriptions in genes of leukemic cells. A series of studies have recommended that supplements containing flavonoids be controlled during pregnancy. However, the procyanidin present in cocoa and the catechins exert no significant effect on the top II enzyme since they do not interact with them (LANOUE et al., 2010; VANHEES et al., 2011).

#### 7.4.2 Fetal development

A study on rats showed that the consumption of epigallocatechin gallate (EGCG) during pregnancy can adversely affect embryonic development, increasing the number of viable cells and apoptosis in malformed embryos (WANG et al., 2007). However, nothing is known about the possible reproducibility in humans of the experimental results found in animals.

#### 7.4.3 Effect on thyroid hormones

The gestational period represents stress to the thyroid gland, with changes in the metabolism of the thyroid hormones due to deiodization by the placenta. Thyroid

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dysfunction is closely related to gestational hypertension and low fetal weight (COSTA et al., 2004). Flavonoids consumed during pregnancy can affect thyroid function and secretion of the T3 and T4 hormones, due to inhibition of the deiodinase enzymes and their availability to the fetal tissues (VAN DER HEIDE et al., 2003). Transient deficits (of up to 3 intrauterine days) of thyroid hormones can permanently alter the cerebral cortical architecture, causing autism. Soy isoflavones (genistein and daidzein) also inhibit the thyroid peroxidase, which catalyzes the iodization and biosynthesis of thyroid hormones, and may contribute to the onset of autism (VAN DER HEIDE et al., 2003). The addition of 400 mg of bittersweet chocolate to the diet of pregnant and lactating rats affected embryonic angiogenesis, caused disturbances in bone mineralization and significantly altered the morphometric structure of the kidneys. The authors were unable to identify which component of the chocolate was responsible for these effects, but suspicion fell on the high content of polyphenols, including catechins.

In short, during pregnancy the phenolic compounds can cross the placental barrier and penetrate into fetal tissues, interfering with child development. Due to their content of antioxidants, polyphenols could reduce the oxidative stress of pregnancy and reduce the detrimental effects to the fetus caused by the mother's use of antiteratogenic drugs. However, polyphenols can also cause poor absorption of iron and folic acid, constriction of the fetal arterial duct, childhood leukemia and hormonal changes, putting in doubt the possible benefits from the extra-physiological intake of these compounds for pregnant women and lactants, until new studies in animal and humans models can clarify these still highly controversial issues.

### ■ 8 Importance of breastfeeding

Recent research reported by Zorzetto (2011) emphasized the importance of breastfeeding in the first year of a child's life. According to the report, the chance of a child being born and growing healthy starts at conception and continues for only 1,000 days, the 270 days of pregnancy plus the 730 of the first two years of his/her life. In principle, the possibility of a child who is born with good health growing up this way and remaining so for decades, requires the adoption of measures that are apparently simple: proper nutrition of the mother during pregnancy, exclusive breastfeeding for the first six months of life, and, as from this age, breastfeeding in conjunction with water, juices, teas, baby foods and solid foods, rich in protein, vitamins and minerals, as recommended by the World Health Organization (WHO).

Experiments with rodents (rats) indicated that replacing breast milk with other foods, including other types of milk, at this stage of development, can change the child's taste and install a hormonal imbalance in the body that can last

the lifetime and promote weight gain, whilst the correct nutrition reduces the risk of developing adulthood obesity and cardiovascular diseases, as concluded by several populational studies carried out in five developing countries (Brazil, South Africa, Guatemala, Philippines, and India). According to these studies, exclusive breastfeeding also favors intellectual performance. For some decades, research teams in these countries, including that of the Brazilian epidemiologist Cesar Victora, regularly evaluated the growth of 10,912 children. Children who started receiving other foods before 6 months of age, which occurred before the third month in 69% of the babies in the Brazilian sample, accumulated more body fat throughout life. Moreover, the earlier they consumed juices, baby foods and other types of milk, the more fat accumulated, increasing the risk of subsequent heart problems and strokes, which account for 30% of deaths throughout the world. According to Victora et al. (2008), the most influential factor in the accumulation of fat was not the duration of breastfeeding, but the precocity of introducing other foods into the child's diet. The same researchers claimed that only 41% of Brazilian mothers exclusively breastfed their children for the first six months of life.

In studies with experimental animal models, Moura et al. (2009) caused early weaning by applying a compound that prevents the production of prolactin, the hormone that induces the secretion of milk, to the female rat. The animals that weaned earlier reached adulthood with 10% more weight, 40% more total fat and up to 300% more visceral fat (that formed within the organs and hence the most harmful). Confirming the deleterious effect of visceral obesity, rodents weaned before time had higher glucose, cholesterol and triacylglycerol blood levels and lower HDL contents (the protein that removes cholesterol from the blood and prevents the formation of fat in the blood vessels). These alterations constitute that which physicians designate as the metabolic syndrome, a condition that enhances the risk of developing diabetes and cardiovascular problems. As adults, the animals that were breastfed for a shorter postnatal period also showed blood leptin levels (a hormone produced by adipose tissue and which acts by inhibiting the appetite and causing satiety) that were three times higher than normal. Despite the huge amount of this hormone, the leptin produced no effect in these animals. After fasting for 12 hours, the researchers administered leptin to two groups of rats: one breastfed for the usual time and one whose breastfeeding had been interrupted. As expected, the rodents in the first group ate less, but those in the second group continued feeding, which indicated they showed no response to the hormone. Moura et al. (2009) observed another hormonal imbalance: rats weaned prematurely developed hypothyroidism. They presented 50% lower blood levels of the hormone thyrotropin, whose function is to activate the thyroid gland, which produces

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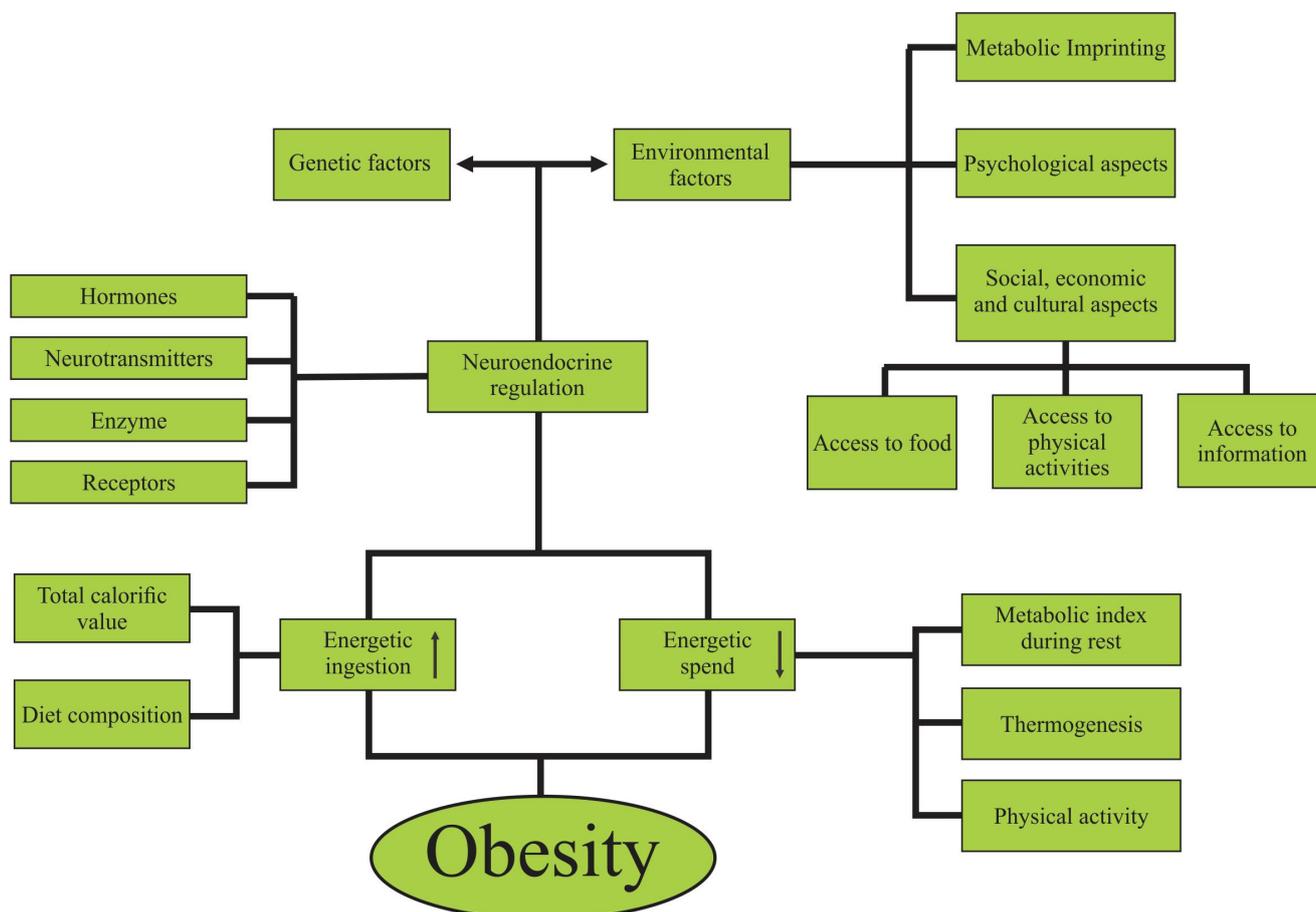
hormones that stimulate energy consumption. According to the researchers, hypothyroidism can be a consequence of leptin resistance. As leptin acts on the hypothalamus, a region of the brain that controls the production of other hormones, amongst which thyrotropin, insensitivity to leptin can affect the functioning of the thyroid.

These hormonal and metabolic alterations are apparently a phenomenon of epigenetic programming (alterations in gene functioning), which must still be proven (MOURA et al., 2009). However it has been proven that maternal malnutrition induced by the inhibition of prolactin during the final phase of lactation, promoted the metabolic programming for obesity, dyslipidemia and insulin resistance as adults, increasing the risk of developing the metabolic syndrome. Metabolic programming is defined as a biological phenomenon that determines the relationship between the chemical and physical stimuli in early life and the future functional state (MOURA; PASSOS, 2005; MOURA et al., 2008). In fact, there is an association between low birth weight and an increased risk of postnatal diseases, both in the child and in the mother (BARKER, 1995; FALL et al., 1995).

An interesting review was published by Balatan and Silva (2004) about the protective effect of breastfeeding

against childhood obesity. The authors stated that obesity affects 20-27% of children and adolescents in the United States (SCHONFELD-WARDEN; WARDEN, 1997). Monteiro et al. (1995) reported a prevalence of obesity in children under 5 years of age at the national level in Brazil, ranging from 2.5% amongst the poorest children to 10.6% in the most economically favored group. A secular trend study carried out in the Brazilian Northeast, showed an upward trend for the prevalence of overweight and obesity in male teens in all states, from 1980 to 2000 (VASCONCELOS- CHAVES, 2001). In the city of Recife, a 17.4% prevalence of obesity was observed in preschool children from high-income families and 10.1% in those from low-income families (SILVA et al., 2005).

According to Balatan and Silva (2004), most of the studies reviewed reported a protective effect of breastfeeding against childhood obesity, although some studies found no association between breastfeeding and obesity. Different definitions of exposure and outcome made the comparison between studies difficult. Metabolic “imprinting” was suggested as a potentially involved mechanism, in order to explain the association, and behavioral aspects may also be involved. The authors presented, graphically, a causal model that is quite interesting, as shown in Figure 8.



**Figure 8.** Genetic, epigenetic and environmental factors in action in the origin and progress of obesity. Source: Balatan and Silva (2004).

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The potentially involved mechanisms still need to be clarified. Breastfeeding involves various aspects, including the amount of food ingested (both from the point of view of nutrients and of non-nutrient bioactive compounds), the age when solid foods were introduced, the development of the regulatory food intake mechanisms, as well as behavioral aspects associated with the mother-child relationship and with the constitution of the child's feeding habits. The metabolic "imprinting" mechanism is an interesting explanation. However, this phenomenon requires development to clarify at what level breastfeeding would act, if by altering the number and/or size of adipocytes, by interfering with the hypothalamic regulatory mechanisms, by modulating the endocrine responses, by interfering with gene expression or by some other mechanism as yet undetermined. Obesity, with its multiple causes and consequences, represents a challenge for pediatricians and for other professionals interested in human health problems. It represents a major call for the uniting of the efforts of many professional classes in seeking alternative solutions for such a serious public health problem throughout the world. The transformation underway in the framework of the health problems of children and adolescents is forcing pediatricians to review their role in the disciplines of medicine. In addition to continuing to attend the acute conditions of infection and malnutrition, they will also have to worry about their small patients not developing the so-called chronic degenerative diseases. Problems that arise in childhood and even in the womb advance silently for decades and only show their effects 30, 40 or even 50 years later, affecting the quality of life of the adults and limiting their longevity. The new pediatrics should undergo a redefinition in order to provide care for children who could reach 100 years of age and become the elderly of the 22nd century. Zorzetto (2006) reported a series of research projects that demonstrated serious problems relating to childhood obesity that had already begun in the formation of the fetus. This suspicion arose from the observation that poor regions of England, with high mortality rates in the early 20th century, also had higher heart disease rates than the means for the 1970s and 1980s. Based on this information, Barker (1995) formulated the theory of fetal programming, according to which the baby organism subjected to abnormal conditions during pregnancy, such as a lack of nutrients due to placental defects or maternal malnutrition, would undergo physiological adaptations in order to save energy during deprivation. The long-term result of this would be the propensity to accumulate fat in times of abundance and the probable future development of obesity, a risk factor for increased cholesterol, diabetes and cardiovascular diseases. Several reports from recent studies carried out in Brazil (MONTEIRO et al., 1995; SILVA et al., 2005;

VASCONCELOS-CHAVES, 2001; ZORZETTO, 2011) seem to confirm these same findings abroad.

## ■ 9 Nutrition and health: trends and prospects

More than a scientific discipline, the study of nutrition is an extremely complex area of human knowledge, due to being multi-disciplinary and multi-sectoral. The practice of nutrition is an even more complex domain, since it depends on equally important factors such as: food availability, composition, conservation and safety, involving sectors such as agriculture, food science and technology and government policies as well as socioeconomic, cultural and environmental aspects related to the target population.

### 9.1 Some historical milestones

In the second half of the 19th century the onsets of certain diseases such as scurvy and beriberi were already attributed to some deficiencies in the diet of unknown nature, which were designated as accessory food factors, later identified and called vitamins. In the early 20th century, foods were considered as sources of just a few nutrients such as protein, carbohydrate, fat and a few minerals, with no detailed knowledge of their chemical structures, essentiality and specific functions within the human organism.

It was in the period from 1906 to 1912 that the essential character of certain amino acids was established. During this period systematic studies were initiated focusing on identifying, isolating and establishing the structures and functions of substances today recognized as essential for growth and for the maintenance of health in the human species.

The study of almost all vitamins aimed at comprehending their structures, functions and the pathologies caused by their lack or deficiency in the diet, extended from 1900 to 1940, except for folic acid and vitamin B12, for which the study of the structures, functions and importance in the treatment of anemia was only completed after the end of World War II (1945).

Methodologies to quantify raw energy and its use at the metabolic level, as well as to determine the composition of foods by way of chemical, biochemical and biological methods, were developed and refined from 1950 to 1970. In the same period, information making it possible to combat, if not eliminate, some of the main nutritional deficiencies that undermined the physical and intellectual development of the Brazilian children and youth in pre-school and school age, became available. Here one must highlight energy-protein deprivation (EPD) which manifests itself and still occurs in much of the population in the form of "Kuachiorkor and/or marasmus". Research from that period, already mentioned in the preceding pages of this review,

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was opportune, such that researchers and national and international organizations mobilized to intensify and enhance research and programs to better serve pregnant women, lactants, preschoolers and schoolchildren in addressing nutritional problems that compromised school learning and impacted the future human capital of Brazil and of other nations on the planet, especially in the underdeveloped world but also in the developing world.

Concomitant with the advances in nutrition, food science and food technology, the medical and pharmacological sciences advanced in the diagnosis and control of infectious and communicable diseases.

In the decade from 1990 to 2000, there were profound transformations in the concepts of human nutrition. This was the concept of healthy or functional nutrition and foods, which was initiated in Japan (1980s and 1990s) and rapidly spread to several countries on different continents.

Very important discoveries were made that nutrients already known for their nutritional functions, and other food components considered non-nutrient, could have important functions in stimulating and/or controlling the metabolism, and in decreasing the risks and controlling the worsening of various types of disease, thus contributing to a better quality of life and longevity.

### 9.2 Current trends and future prospects

Despite advances in knowledge in the areas of nutrition, food science and technology, medicine and pharmacology that were able to satisfactorily manage some infectious diseases and some diseases related to deprivation, there is still the so-called "hidden hunger", which manifests itself as the deficiency (marginal or not) of one or several trace elements, and impacts negatively on the development and health of the Brazilian population in various age groups.

The concept of functional foods and diets has enabled new advances to be made, and provided new challenges in comprehending the causes and consequences of some

chronic non-communicable diseases that are increasingly affecting younger age groups. At this point, it is worth mentioning two major challenges to researchers and agencies engaged in providing answers to the serious problems of public health in this country: The first is the current outbreak of viral infections (in particular of the Zika virus), which we referred to in previous pages; the second is the pandemic of overweight and obesity that has been growing exponentially in Brazil and in most civilized countries. At present obesity is considered as the origin of many chronic non-communicable diseases (NCDs), which are currently called the diseases of civilization by some authors, with the aggravating factor that nowadays obesity is affecting children at a very early age.

Although the scientific and technological knowledge to address, and eventually solve, all these food, nutrition and health problems in developing countries is available, in the medium and long term, the initiative is hindered by two sets of problems: the first is the relative lack of resources and exact understanding of the problem by financing agencies (governmental or private); and the second is the lack of a networked research approach and development (innovation) to attack the problem at the national level.

Within this new approach and perspective of enhancing nutrition, the inclusion of education programs on nutrition as part of the strategies to improve the availability of functional diets and foods at a populational level, still seems indispensable, as suggested in Table 7 and Figure 9 (SGARBIERI et al., 2012).

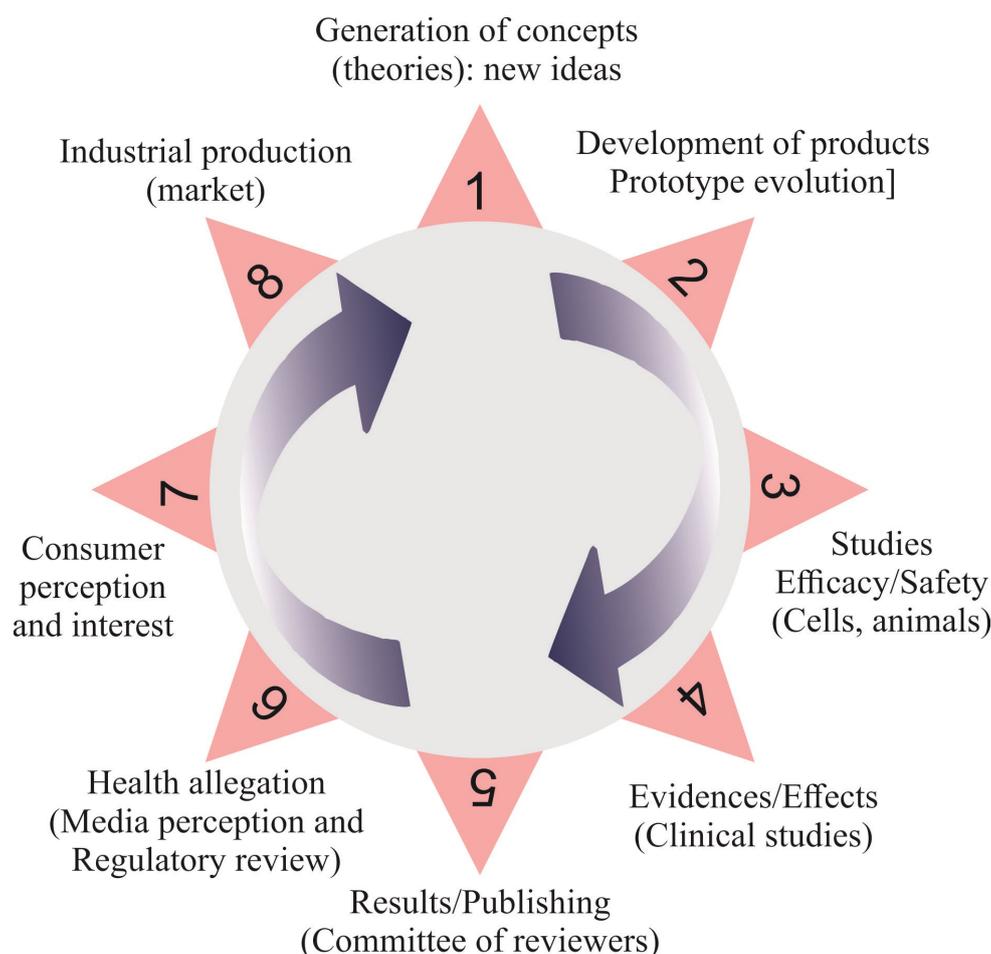
Therefore, strong leadership and a focused effort will be required to convince researchers in the areas of Food Science and Technology from Universities and Institutes involved in research, food industries interested in improving and innovating their production, and also fostering agencies, that investments in the food area are the shortest and most effective way of obtaining better results.

**Table 7.** Strategies to improve the availability of food and functional diets for the population.

1. EDUCATION
Introduction of food education at all levels of formal education
Informal education via the provision of information supplied by professionals in the areas of medicine, food science and technology, and the media (properly guided)
2. SCIENCE AND TECHNOLOGY
Basic research
Applied research
Technological research
Development of products for specific groups and purposes

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**Figure 9.** Cycle for the innovation of functional foods.

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