ABSTRACT

Fetal developmental potential is determined at the moment of conception by genetic inheritance. However, this development is modulated by environmental factors. It is important to recognize that both, the mother and the fetus, actively participate in the maintenance of the physiological intrauterine environment. Unfortunately, the fetus is not entirely protected from harmful influences of the external factors. By altering the intrauterine environment, these factors can have a long-term effect on fetal health.

Keywords: Physiological intrauterine environment, Genetic inheritance, Environmental factors.

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INTRODUCTION

Human life does not begin with birth. Normal development of the human being lasts 280 days before parturition. In prenatal growth and development, the placenta plays a key role. It has numerous functions essential for maintaining the pregnancy and promoting normal fetal development. During intrauterine period, the fetus gradually begins to perform many vital physiological functions. Furthermore, through 9 months of gestation, a repertoire of fetal functions and activities constantly expands. Development of modern imaging methods has revealed the existence of a full range of fetal movement patterns, even facial movements similar to emotional expressions in adults. Indeed, the world in utero is fascinating. Therefore, the birth is not the beginning, but only a new chapter in the story of human life.

PLACENTA

‘The vessels join to the uterus like the roots of plants, and through them the embryo receives its nourishment.’ Aristotle, De Generatione Animalium, Book II.

DEVELOPMENT OF THE PLACENTA

The placenta is an organ that is indispensable for the transfer of nutrients and gases from the mother to the fetus and the removal of fetal waste products. Placenta can be defined as a fusion of fetal membranes with the uterine mucosa. The development of the placenta starts with the implantation, in the moment when the blastocyst begins the invasion of the endometrium, about the 6th day after conception. Prior to implantation in the uterine lining, blastocyst consists of an external, single-layer, cellular component named the trophoblast and the inner cell mass, embryoblast. After the trophoblast has attached to the endometrial epithelium, rapid cellular proliferation occurs and the trophoblast differentiates into two layers consisting of the inner cytotrophoblast and an outer syncytiotrophoblast, a multinucleated mass without cellular boundaries. Syncytiotrophoblast processes extend through the endometrial epithelium to invade the endometrial stroma. Stromal cells surrounding the implantation site become laden with lipids and glycogen, develop into polyhedral shape, and are referred to as decidual cells. These decidual cells degenerate in the region of the invading syncytiotrophoblast and provide nutrition to the developing embryo.

At day 7 and 8 after conception, the blastocyst has completely crossed the epithelium and is embedded within the endometrium. At day 8 and 9 postconception, the syncytiotrophoblast generates a number of fluid-filled spaces within its mass. These spaces flow together forming larger lacunae and are finally separated by parts of the syncytiotrophoblast (trabeculæ) that cross the syncytial mass from the embryonic to the maternal side. The development of the lacunar system leads to the division of the placenta into several compartments. The embryonically oriented part of the trophoblast will become the chorionic plate, the lacunae will develop into the intervillous space (Fig. 1), while the trabeculae will become the anchoring villi, with the growing branches developing into floating villi. Finally, the maternally oriented part of the trophoblast will develop into the basal plate.

At day 12 after conception, the process of implantation is completed. The developing embryo with its surrounding extraembryonic tissues is totally embedded in the endometrium and the syncytiotrophoblast surrounds the whole surface of the conceptus. Mesenchymal cells derived from the embryo spread over the inner surface of the trophoblast, thus generating a new combination of trophoblast and mesoderm, termed chorion. Starting on day 12 postconception, proliferation of cytotrophoblast pushes trophoblast cells to penetrate into the syncytial trabeculæ, reaching the maternal side of the syncytiotrophoblast by day 14. Further proliferation of trophoblast cells inside the trabeculæ (day 13) stretches the trabeculæ resulting in the development of syncytial side
branches filled with cytotrophoblast cells (primary villi). Shortly after, the mesenchymal cells from the extra-embryonic mesoderm too follow the cytotrophoblast and penetrate the trabeculae and the primary villi, thus generating secondary villi. At this stage there is always a complete cytotrophoblast layer between the penetrating mesenchyme and syncytiotrophoblast. Around day 20 and 21, vascularization within the villous mesenchyme gives rise to the formation of the first placental vessels (tertiary villi). Only later, the connection to the fetal vessel system will be established. The villi are organized in villous trees that cluster together into a series of spherical units known as lobules or placentones. Each placentone originates from the chorionic plate by a thick villous trunk stemming from a trabecula. Continuous branching of the main trunk results in daughter villi mostly freely ending in the intervillous space.  

In normal pregnancies, decidual and myometrial segment of the spiral arteries (Fig. 2), undergo changes to convert them into large vessels of low resistance (Figs 3 and 4). Two types of migratory cytotrophoblast cause this—endovascular and interstitial cytotrophoblast. Endovascular cytotrophoblast invades spiral arteries on the decidua and myometrium and replaces arterial endothelium, destroying muscle and elastic tissues in the tunica media. Interstitial cytotrophoblast destroys the ends of decidual blood vessels, promoting the flow of blood into the lacunae. The maternal arteries are opened up and functionally denervated so that they are completely dilated and unresponsive to circulatory pressor substances or autonomic neural control. Behind this, at uterine radial artery level, local prostacyclin maintains vasodilatation. Free transfer of maternal blood to the intervillous space is established at the end of the first trimester of pregnancy.  

**ABNORMAL PLACENTAL DEVELOPMENT AND ULTRASOUND**

Trophoblast invasion is a key process during human placentation. Failure of trophoblast invasion and spiral artery...
transformation leads to reduced perfusion of the placenta and fetus, and inadequate fetal nutrition and oxygenation. This condition is called uteroplacental insufficiency because the metabolic demands of the fetus and placenta exceed the uteroplacental transport capacity. It is considered that there are two phases of trophoblast invasion. The first wave of trophoblastic invasion converts the decidual segments of the spiral arteries between 6 and 10 weeks of the pregnancy. The second wave converts the myometrial segments between 14 and 16 weeks of the pregnancy. As a result of these physiological changes, the diameter of the spiral arteries increase from 15 to 20 mm to 300 to 500 mm, reducing impedance to flow and optimizing fetomaternal exchange in the intervillous space. In pregnancies complicated by pre-eclampsia and IUGR, trophoblast invasion is limited to the decidualized endometrium, which results in failure of the spiral arteries to become low-resistance vessels. Using Doppler ultrasound, uteroplacental and fetal vessels conversion of the uterine spiral arteries and placental development may be assessed.

Successful trophoblast invasion results in loss of early diastolic notching in the uterine artery Doppler waveform by the end of the first trimester. The failure to undergo physiological trophoblastic vascular changes is reflected by the high impedance to the blood flow at the level of the uterine arteries and with the characteristic waveform of early diastolic notching (Fig. 5). In normal pregnancies, due to progressive maturation of the placenta, impedance to flow in the umbilical artery decreases and end-diastolic velocity establishes by the end of the first trimester. Doppler indices continue to fall toward term as umbilical blood flow resistance decreases (Fig. 6). In cases of placental insufficiency, because of inadequate ramification of villi and increased degradation due to degenerative processes, surface of the capillary network is reduced and blood flow resistance in the placenta is elevated. These conditions reflect in the abnormal umbilical artery blood velocity waveforms. However, pathological studies have demonstrated that increased impedance in the umbilical arteries becomes evident only when at least 60% of the placental vascular bed is obliterated. In pregnancies with reversed or absent end-diastolic flow in the umbilical artery, compared to those with normal flow, mean placental weight is reduced and the cross-sectional diameter of terminal villi is shorter. Absent diastolic velocity or retrograde diastolic velocity in the umbilical artery indicate extremely increased placental vascular impedance (Fig. 7).

Endangered by placental insufficiency, fetus activates compensatory mechanisms. Fetal response to placental dysfunction evolves from early compensatory reactions to late decompensation in multiple organ systems.
responses to hypoxia, which include modification of the heart rate, an increase in arterial blood pressure and redistribution of the cardiac output toward vital organs, are probably the most important adaptive reactions responsible for maintaining fetal homeostasis. The redistribution of blood flow toward the fetal brain is known as the ‘brain-sparing effect’ (Figs 8 and 9). Doppler assessment of the fetal cerebral and umbilicoplacental circulations can detect fetal blood flow redistribution toward the brain during hypoxia and quantify the degree of this redistribution using the C/U ratio. In normal pregnancies, cerebral vascular resistance remains higher than placental vascular resistance. Therefore, the cerebrombical (C/U) ratio, expressed as the cerebral resistance index/the umbilical remains resistance index, remains higher than 1. This ratio becomes less than 1 in case of blood flow redistribution in favor of the fetal brain.

Previous experimental studies on animal models have shown that the C/U ratio decreases in proportion to fetal pO₂. Although, the brain-sparing effect attempts to compensate for the reduced oxygen delivery to the fetal brain, it has recently become clear that this phenomenon cannot always prevent the development of brain lesions. Our studies have demonstrated the existence of several phases in the hemodynamic response of the fetal brain to chronic hypoxia. During the early phase of Doppler surveillance, cerebrovascular variability was still observed; this was followed by a loss of cerebrovascular variability and finally an increase in cerebrovascular resistance with a reduction in brain perfusion. Maximal redistribution of blood flow in favor of the fetal brain was reached 5 to 8 days prior to the onset of fetal heart rate abnormalities.

FUNCTIONS OF THE PLACENTA

The placenta has multiple roles in fetal metabolism and growth. The major function of the placenta is to provide diffusion of nutrients and oxygen from the mother’s blood into the fetus’s blood and diffusion of excretory products from the fetus back into the mother. The placenta also produces hormones that affect fetal growth. The placenta is usually fully formed and functional as a nutritive, respiratory, excretory and endocrine organ by the end of the third month of pregnancy. However, well before this time, oxygen and nutrients are diffusing from maternal to embryonic blood, and embryonic metabolic wastes are passing in the opposite direction. Most of the early nutrition is due to trophoblastic digestion and absorption of nutrients from the endometrial deciduas. This is the only source of nutrients for the embryo during the first week after implantation. The embryo continues to obtain at least...
some of its nutrition in this way for another 8 weeks, although the placenta also begins to provide nutrition after about the 16th day after fertilization (a little more than 1 week after implantation). Molecules of low molecular weight, such as blood gases, sodium, water, urea, fatty acids, nonconjugated steroids, pass through placental membrane by simple diffusional exchange between the circulations. Hexose sugars, conjugated steroids, amino acids, nucleotides, water-soluble vitamins, plasma proteins, cholesterol will not gain access to the fetal circulation unless either special transport mechanisms exist or the integrity of the barrier is breached. In the early months of pregnancy, the placental membrane is still thick because the placenta is not fully developed. Therefore, its permeability is low. Further, the surface area is small because significant placental growth has not occurred yet. In later pregnancy, the permeability increases due to the thinning of the membrane diffusion layers and the multiple expansion of the surface area, giving way to a tremendous increase in placental diffusion (Figs 10A and B). In addition to the placental thickness, the factors that will influence exchange between the mother and the fetus include the maternal and the fetal blood flow; the fetal and the maternal concentrations of the substances to be transported; and the types of transport mechanisms available. The exchange of more freely diffusible molecules such as $O_2$ is to a larger extent dependent on the blood flow than placental thickness.

**Fetal Growth and Metabolism**

As soon as within the 1st month following the fertilization of the ovum, all the organs of the fetus have already begun to develop and in the next 2 to 3 months, the fine anatomic structures of the organs will be formed. After the 4th month, the organs of the fetus, including the majority of their substructures, are for the most part the same as those of the neonate. However, the development of the cells in the structures is still far from complete and will require the remaining 5 months of pregnancy to complete development.

Normal fetal growth requires macronutrients—carbohydrates, lipids, proteins and micronutrients—vitamins and minerals. Also, other factors influence growth, like growth factors and hormones. The main ingredient of the fetal diet is carbohydrate. The fetus has a low capacity for gluconeogenesis, largely because the necessary enzymes, although present, are inactive due to a low fetal arterial $pO_2$. The fetus must therefore obtain its glucose from the maternal blood. The growing fetus requires approximately 87 kcal/kg/per day. About half of the calories needed for fetal growth and metabolism come from the mother’s glucose, and the other half from her amino acids and placental lactate. The fetus has a high ability of storing proteins and fats. Protein accumulation occurs early in fetal development, to reach its maximum by week 35. Protein deposition precedes fat deposition. Fetal fat content is low at 26 weeks. Fat acquisition starts sometime between the 26 and 32 weeks and continues intensively thereafter, being a result of glucose utilization rather than placental fatty acid uptake. By term, about three times as much energy is stored as fats than as proteins. In addition, glucose is also stored as glycogen in the fetal liver. Glycogen is an important nutrient in the period immediately after birth, before nutrients from breast milk are used.

Fetal metabolism shows some particularity in relation to calcium, phosphate, iron, and some vitamins. About 22.5 gm of calcium and 13.5 gm of phosphorus are accumulated in an average fetus during gestation. About one-half of these accumulate during the last 4 weeks of gestation, which is coincident with the period of rapid ossification of the fetal bones and with the period of rapid weight gain of the fetus. Iron accumulates in the fetus even more rapidly than calcium and phosphate. Most of the iron is in the form of hemoglobin, which begins to be formed as early as in the third week after fertilization of the ovum. Small amounts of iron are concentrated in the mother’s uterine prostegational endometrium even before implantation of the ovum. This iron is used to form the early red blood cells. About one-third of the iron in a fully developed fetus is normally stored in the liver. Interestingly, the fetus needs an equal intake of vitamins as the adult. The B vitamins, especially vitamin $B_{12}$ and folic acid, are necessary for formation of red blood cells and the nervous tissue, as well as for the overall growth of the fetus. Vitamin C is necessary for appropriate formation of intercellular substances, especially the bone matrix and fibers of connective tissue. Vitamin D is needed for normal bone growth in the fetus. The mother needs it for adequate
absorption of calcium from her gastrointestinal tract. If the mother has plenty of this vitamin in her body fluids, large quantities of the vitamin will be stored by the fetal liver to be used by the neonate for several months after birth. Vitamin E, although the mechanisms of its functions are not clear, is necessary for normal development of the early embryo. In its absence in laboratory animals, spontaneous abortion usually occurs at an early stage of pregnancy. Vitamin K is used by the fetal liver for formation of blood coagulation factors. Prenatal storage in the fetal liver of vitamin K derived from the mother is helpful in preventing fetal hemorrhage, particularly hemorrhage in the brain when the head is traumatized by squeezing through the birth canal.19

The fetus actively participates in endocrine regulation of its metabolism and growth by synthesis and secretion of hormones. For instance, the rate at which glucose is utilized by growing fetal tissues is probably determined largely by the actions of fetal insulin. The storage of glucose as fat is also regulated primarily by fetal insulin. Fetal adrenocorticotropic hormone (ACTH) and glucocorticoids stimulate the storage of glucose as glycogen.21 Hormonal regulation of fetal growth differs from hormonal regulation of growth during postnatal life. Furthermore, fetal growth hormone (GH) has a small role in stimulating fetal growth. Although pituitary begins to produce and secrete GH during the 5th week of gestation, fetal GH does not significantly affect fetal growth, possibly due to the lack of functional GH receptors on fetal tissues.23 Data have shown that pituitary aplasia and congenital hypopituitarism do not cause severe IUGR.24,25 On the contrary, fetal insulin significantly stimulates fetal growth. It is a known fact that pancreatic agenesis is associated with severe growth restriction26 and that fetal hyperinsulinemia leads to fetal mass overgrowth. It is believed that insulin-like growth factors (IGFs or somatomedins) produced by a large range of fetal cell types and particularly by the fetal liver, provide a major endocrine stimulus to fetal growth.21 They have the potent effect of increasing all aspects of bone growth in postnatal life.19 IGFs are present in human fetal tissue extracts after 12 weeks gestation.22 IGF-1 has the most important role in stimulation of fetal growth.21 Its levels in fetal and cord circulation directly correlate with the fetal length and mass.27 Reduced plasma concentration of IGF-1 has been reported in intrauterine growth restriction (IUGR).28 Furthermore, maternal starvation leads to a rapid decrease in fetal plasma IGF-1 concentration, which is generally associated with the cessation of intrauterine growth.29 It is considered that glucose is the major regulator of fetal IGF-1 secretion.30 Maternal IGF-1, IGF-2 and insulin do not cross the placenta, and do not have a direct effect on fetal growth, but may have an effect on placental function, thus altering the nutrient exchange between the placenta and the fetus.31 It has been found that maternal plasma IGF-1 concentration correlates with fetal growth.32 Production of fetal IGFs is stimulated by prolactin, insulin and human chorionic somatomammotropin (HCS).33 In the fetus, HCS acts via lactogenic receptors to stimulate growth, regulate intermediary metabolism and stimulate the production of IGFs, insulin, adrenocorticotropic hormones and pulmonary surfactant.23 Fetal thyroid hormones also stimulate growth, especially in the later stage of pregnancy, but their most significant role is the one they have in the central nervous system development.21

Additional factors that affect birth weight include parity (primiparous mothers have smaller babies than multiparous mothers), maternal size, multiple pregnancy.21 Maternal nutrition is also of great significance for fetal growth and the adverse effects of severe malnutrition on fetal well-being and neonatal survival have been long known. Recent data have confirmed a great impact of maternal diet during pregnancy on fetal growth and development, as well as on postnatal development and health.34-43 It is during intrauterine life that the diet has significant effect on the brain development. It has been known for some time that folic acid plays a protective role in neurodevelopmental processes. Periconceptional use of folic acid has been proven to significantly reduce the risk of neural tube birth defects.34 Such, birth defects can cause death or permanent physical disability. Periconceptional use of folic acid decreases the occurrence of anencephaly and spina bifida by at least 50%.35 Hence, some countries (USA, Canada) have decided to fortify food with folic acid. A recent study on the prevalence of congenital abnormalities following folic acid fortification of grain in the United States found a modest, yet statistically significant decrease in prevalence of transposition of the great arteries, cleft palate, pyloric stenosis and omphalocele.35 Yet, other studies provide no evidence of folate being an important factor in the prevention of birth defects other than neural tube defects.36 Furthermore, a significant protective effect was seen with large doses of folic acid (approximately 6 mg/d) and iron (150-300 mg/d of ferrous sulfate) during the first gestational month against Down’s syndrome.37

Numerous findings have shown a favorable impact of essential fatty acids on prenatal development.38-40,42,43 Omega-3 and omega-6 fatty acids are necessary for human growth and development. Since, their endogenous synthesis is impossible, they need to be taken into the body through diet. The arachidonic (AA) and docosahexanoic acids
(DHA) are the key components of all membranes and are incorporated into the structural lipids of the developing brain. Fetal demand for essential fatty acids is at its peak during the third trimester of pregnancy. A recent study has demonstrated that DHA supplemented during pregnancy plays a role in the maturation of the visual system and benefits infant visual acuity at 4 but not 6 months of age. Also, results of a recent study indicate that DHA consumption in pregnancy significantly affects problem solving abilities at the age of 9 months, but does not affect memory processes. Additionally, children’s mental processing scores at 4 years of age correlated significantly with maternal intake of DHA during pregnancy. Seafood (especially sardine and tuna) is a rich source of omega-3 fatty acids. Essential fatty acids can be also found in linseed oil, walnut oil and soy. In the USA, women are advised to limit their seafood intake during pregnancy to 340 gm per week. According to a recent study published in an esteemed journal, maternal seafood consumption should be more than 340 gm per week. A lower seafood intake during pregnancy was in the study associated with an increased risk of suboptimum developmental outcome. Further, the findings suggest a protective effect of fish intake during pregnancy against the risk of atopy and asthma. Consumption of apples during pregnancy may also have a protective effect against the development of childhood asthma and allergic diseases.

Healthy and varied diet during pregnancy is required for normal fetal growth and development. Most pregnant women need 2200 to 2900 kcal a day. If appropriate nutritional elements are not present in a pregnant woman’s diet, a number of maternal deficiencies can occur, especially in calcium, phosphates, iron and vitamins.

**Fetal Cardiovascular System**

The cardiovascular system is the first embryonic system to start functioning. The need for substrates which facilitate fast growth and development of the embryo requires an early development of the mechanism that supplies the cells with nutrients and removes the metabolic products from them. Cardiovascular development begins when the process of diffusion becomes inadequate to supply the fetus with nutrients and oxygen. Blood circulation can be observed in the ‘body’ of the embryo as early as at the end of the third week of the intrauterine life. Between the 27 and 35th day of intrauterine life, during which the embryo grows from 5 mm in length to about 16 to 17 mm, cardiac septum and endocardial cushions begin to form. The endocardial cushions will give rise to mitral and tricuspid valves. By the end of 7th week, they are short and thick, but over the next few weeks they are becoming longer and thinner, and achieve their final shape. Impairments in cardiac septum development lead to the existence of pathological communication between the heart chambers (Fig. 11), which can be more or less life-threatening condition for newborn child. Some of these anomalies, such as ventricular septal defect, are among common congenital anomalies and can occur independently or as a part of different syndromes. Fetal echocardiography is a powerful tool and many cardiac malformations can be successfully diagnosed before birth.

The human heart starts beating between the 21 and 23rd day after fertilization, at a heart rate of 65 beats/min. In that period, the heart is a tube-like structure with a single lumen. Between the 5 and 9th week of gestation the heart rate accelerates from 80 beats/min to 165 beats/min. It has been shown that a continuous decrease in the heart rate during this period is associated with miscarriages occurring in the first trimester. By the 10th week after fertilization, the heart rate has reached its highest value (approximately...
170/min), it starts decreasing (Fig. 12). Before birth, the human heart contracts at a rate of about 140 beats/min.

The fetal circulatory system operates much differently than the circulatory system of the newborn baby, which is not surprising considering the specific features of fetal environment. After the birth, the individual components of the circulatory system are in serial connection. However, the fetal circulatory system is organized in parallel circle. Further, fetal values of cardiac output and blood pressure are significantly different from values in adults.

During intrauterine life, blood returning from the placenta through the umbilical vein passes through the ductus venosus, mainly bypassing the liver. Then most of the blood entering the right atrium from the inferior vena cava is directed in a straight pathway across the posterior aspect of the right atrium and through the foramen ovale directly into the left atrium. Thus, the well-oxygenated blood from the placenta enters mainly the left side of the heart, rather than the right side and is pumped by the left ventricle mainly into the arteries of the head and forelimbs. The blood entering the right atrium from the superior vena cava is directed downward through the tricuspid valve into the right ventricle. This blood is mainly deoxygenated blood from the head region of the fetus and it is pumped by the right ventricle into the pulmonary artery. Since, the pressure in the pulmonary artery is about 0.7 kPa higher than the pressure in the aorta, almost all the blood from the pulmonary artery goes through the arterial duct (ductus Botalli) into the descending aorta, then through the two umbilical arteries into the placenta, where the deoxygenated blood becomes oxygenated. Only a small portion of blood from the descending aorta portion goes to the visceral organs and lower extremities.

Blood carrying the highest oxygen saturation goes to the fetal heart, the brain, the upper extremities while the other parts of fetal body receive blood with lower oxygen saturation. Also, fetal blood pO₂ is much lower than maternal blood pO₂. At term pO₂ of fetal blood after the oxygenation in the placenta amounts 30 mm Hg. Such, low pO₂ levels can be observed in adults at altitudes between 6000 and 8000 meters, at which human life is barely possible. Therefore, fetal environment has long been considered the Mount Everest in utero. Despite the low pO₂ in the fetal blood, the fetus does not live in hypoxic environment. Due to adaptive mechanisms, the amount of oxygen delivered to the fetal tissue is similar to the amount of oxygen delivered to maternal tissue by maternal blood.

In addition, the hemoglobin concentration of fetal blood is about 50% greater than that of the mother. Furthermore, fetal hemoglobin can carry more oxygen at a low than it can at a high pCO₂. The fetal blood entering the placenta carries large amounts of carbon dioxide, but much of this carbon dioxide diffuses from the fetal blood into the maternal blood. Loss of the carbon dioxide makes the fetal blood more alkaline, whereas the increased carbon dioxide in the maternal blood makes it more acidic. These changes cause the capacity of fetal blood to combine with oxygen to increase and that of maternal blood to decrease. This forces more oxygen from the maternal blood, while enhancing oxygen uptake by the fetal blood. Thus, the Bohr shift operates in one direction in the maternal blood and in the other direction in the fetal blood. These two effects make the Bohr shift twice as important here as it is for oxygen exchange in the lungs; therefore, it is called the double Bohr effect. These mechanisms, as well as a large cardiac output, ensure adequate supply of oxygen of fetal tissues, despite its low partial pressure.

Maintenance of normal cardiovascular function, blood pressure, heart rate, and the flow distribution through the placenta and fetal tissue are influenced by the local vascular and reflex mechanisms. Further, the autonomic nervous system and hormones also have an effect on the fetal heart and circulation. The potential regulators can be identified by measuring their concentration and dynamics of secretion in states in which a redistribution of the blood flow occurs, such as fetal hypoxia. The first line of supervision over the circulation of the fetus are the carotid chemoreceptors, but not the aortic chemoreceptors. They mediate the fetal cardiovascular response (redistribution of circulation in favor of vital organs like the heart, brain and adrenal glands to acute hypoxemia). Slower regulators, the second line of control, are hormones antidiuretic hormone (ADH), angiotensin II, catecholamines and cortisol. ADH and angiotensin II are released independently of the carotid chemoreceptors, whereas the secretion of cortisol and catecholamines is partially under the control of these neural mechanisms. After carotid sinus denervation or splanchnic blockade, rapid secretion of cortisol in response to hypoxia or a sudden drop in blood pressure, is decreased. While the secretion of ACTH does not change and occurs about 15 minutes after stimulation. Thus, the rapid rise in cortisol secretion is the result of neural mechanisms and not as a result of ACTH stimulation. However, the role and purpose of such regulation is unclear. Medullary, hypothalamic and cerebral cortical activity also affect fetal cardiovascular function. Furthermore, in control of fetal circulation autocrine and paracrine mechanisms play important role. Some of the possible regulators of the peripheral resistance, at least in the sheep fetuses, are endothelin-1 and nitrogen-(II)-oxide (NO). They allow...
an increase of cerebral flow in fetal hypoxia. Several other factors, such as sleeping of the fetus or uterine contractions, can also have a temporary influence on the cardiovascular system. A

One of the most important events after the delivery is the adjustment of the circulation of new conditions. The transitional period of circulation, which lasts 4 to 12 hours after birth, is characterized by a large increase of the blood flow through the lungs and by the establishment of the pulmonary circulation. The primary change in the circulation at birth is loss of the tremendous blood flow through the placenta, which approximately doubles the systemic vascular resistance at birth. This increases the aortic pressure as well as the pressures in the left ventricle and left atrium. Furthermore, in the unexpanded fetal lungs, the blood vessels are compressed because of the small volume of the lungs. After birth, the pulmonary vascular resistance greatly decreases as a result of expansion of the lungs. Also, in fetal life, the hypoxia of the lungs causes considerable tonic vasoconstriction of the lung blood vessels but when aeration of the lungs eliminates the hypoxia, the capillary endothelial cells produce vasoactive substances such as NO and prostaglandin I2, which have a strong vasodilatory effect and vasodilation takes place. All these changes together reduce the resistance to blood flow through the lungs as much as fivefold, which reduces the pulmonary arterial pressure, right ventricular pressure and right atrial pressure. Changes in pulmonary and systemic resistances at birth cause blood now to attempt to flow from the left atrium into the right atrium, through the foramen ovale. Consequently, the small valve that lies over the foramen ovale on the left side of the atrial septum closes over this opening, thereby preventing further flow through the foramen ovale. Arterial ductus begins to close around 4 hours after birth and is usually completely closed after 24 hours. Its closing marks the end of the transitional period of the newborn circulation. After birth, blood begins to flow backward from the aorta into the pulmonary artery through the ductus arteriosus, rather than in the other direction as in fetal life. However, after only a few hours, the muscle wall of the ductus arteriosus constricts markedly. This is called functional closure of the ductus arteriosus. Then, during the next 1 to 4 months, the ductus arteriosus ordinarily becomes anatomically occluded by growth of fibrous tissue into its lumen. The cause of ductus arteriosus closure relates to the increased oxygenation of the blood flowing through the ductus. In fetal life, the pO2 of the ductus blood is only 15 to 20 mm Hg, but it increases to about 100 mm Hg within a few hours after birth. Furthermore, many experiments have shown that the degree of contraction of the smooth muscle in the ductus wall is highly related to this availability of oxygen. The reason for the closure of the venous duct is still unknown. Immediately after birth, blood flow through the umbilical vein ceases, but most of the portal blood still flows through the ductus venosus, with only a small amount passing through the channels of the liver. However, within 1 and 3 hours the muscle wall of the ductus venosus contracts strongly and closes this avenue of flow. As a consequence, the portal venous pressure rises from near 0 to 6 to 10 mm Hg, which is enough to force portal venous blood flow through the liver sinuses. Although the ductus venosus rarely fails to close, we know almost nothing about what causes the closure. Knowing the characteristics of this transitional phase of circulation is very important because the postnatal increase of the resistance in the pulmonary capillaries, for example caused by hypoxia or respiratory distress syndrome, if exceeds the value of systemic resistance, can restore conditions as they existed in the fetal life, greater resistance in the pulmonary circulation than in systemic and pulmonary-aortic or right-left flow of blood through the arterial duct.

**Fetal Gastrointestinal System, Development of Appetite and Satiety Mechanisms**

The primitive gut forms during the fourth week of the embryonic development. The primitive gut is divided into three parts: The foregut, midgut and hindgut. The derivatives of the foregut are the pharynx and its derivatives, the lower respiratory tract, the esophagus, the stomach, the duodenum, proximal to the common bile duct, and the liver, biliary tract, gallbladder, and pancreas. The derivatives of the midgut are the small intestines (except for the duodenum from the stomach (Fig. 13) to the entry of the common bile

![Fig. 13: Transverse scan of the fetal abdomen showing the stomach, liver and intrahepatic part of the umbilical vein](image-url)
duct), cecum and appendix, ascending colon, and proximal one-half to two-thirds of the transverse colon. The derivatives of the hindgut are the distal one-third to one-half of the transverse colon, descending colon, sigmoid colon, rectum and upper portion of the anal canal, and part of the urogenital system. Activity of the gastrointestinal system begins during an early stage of pregnancy. By 10 weeks, peristalsis begins in the large intestine and by 11 weeks in the small intestine. Also, fetal swallowing activity was observed from the 11th week of gestation. Swallowing amniotic fluid reflects fetal CNS maturation and has numerous, although not entirely understood roles (Fig. 14). Fetal swallowing activity contributes to somatic growth, development and maturation of the fetal gastrointestinal tract. It has been estimated that swallowing of amniotic fluid proteins provides 10 to 15% of nitrogen requirements in the normal fetus. Upper gastrointestinal tract obstructions in human fetuses are associated with significantly greater occurrence of fetal growth restriction as compared with lower gastrointestinal obstructions. Studies have demonstrated that impairment of fetal swallowing in rabbits near term induces weight decrease. Esophageal ligation of ovine fetuses during midgestation induces a 30% decrease of small intestine villus height and a reduction in the liver, pancreas and intestinal weight. Fetal swallowing is an important, yet not the only mechanism of amniotic fluid volume regulation. Altered fetal swallowing has been associated with both a decrease and an increase in the amniotic fluid volume. These conditions are associated with a higher risk of perinatal morbidity and mortality. Furthermore, in some fetuses with esophageal atresia, the volume of amniotic fluid is increased. It is important to note that this is the case in some, but not all fetuses with esophageal atresia. Namely, this anomaly is often accompanied by tracheoesophageal fistula, a shortcut to the gastrointestinal tract. Therefore, intake of liquid during the respiratory movements might explain the nonappearance of polyhydramnios in some of these cases. Polyhydramnios sometimes, although not always, develops in anencephalic fetuses. Some of these fetuses have an intact swallowing reflex. Cases of a normal amniotic fluid volume and reduced fetal swallowing have also been described. Assessment of fetal swallowing using gray-scale and color Doppler sonography has demonstrated that there is a fetal trend toward the development of more coordinated swallow-related movements and more functional nose-mouth flow with the advancement of gestational age. These investigators have postulated that knowledge of the physiologic mechanism involving swallowing development could contribute to identification of altered swallow-related movements in fetuses with malformations of the gastrointestinal tract or with neurological disorders. Our recent investigation, performed by 4D ultrasound, has shown that swallowing pattern displays a peak frequency at the end of the second trimester. At the beginning of the third trimester, a decreasing incidence of this pattern was recorded. Some studies have shown that fetal swallowing activity may be modulated in accordance with neuro-behavioral state alterations (stimulation of swallowing with shifts from quiet to active sleep). Furthermore, fetal swallowing is influenced by the volume of amniotic fluid, hypoxia, hypotension and plasma osmolality changes. Experiments in fetal lambs have indicated that dipsogenic mechanisms begin to regulate swallowing during intrauterine life. Swallowing and arginine–vasopressin (AVP) secretion increase, following the central administration of hypertonic saline solution and angiotensin II. However, the fetus seems to have an extensively reduced sensitivity to osmotic stimuli when compared to the adult, despite the intact dipsogenic nuclei. The fetus swallows about six times more liquid in comparison to the adult. Mechanisms underlying the high rate of human fetal swallowing are regulated, in part, by tonic activity of central angiotensin II, glutamate N-methyl-D-aspartate receptors and neuronal production of the nitric oxide. A reduced NMDA receptor expression within the forebrain dipsogenic neurons contributes to observed differences in drinking activities between the fetus/neonate and the adult. Reduced swallowing activity during the systemic hypotension, despite elevated renin levels in plasma, provides further evidence that the fetal dipsogenic response is markedly different from that of the adult. It is possible that dipsogenic responses develop in utero in the human fetus to provide thirst stimulation for appropriate water intake during the immediate neonatal period. According to some studies, altered intrauterine osmotic environment may modulate not only fetal swallowing activity, but also the

**Fig. 14:** A sequence of images of the fetus recorded by 4D sonography showing swallowing movements
development of adult sensitivities for thirst, AVP secretion and AVP responsiveness.67,68,78 An animal study demonstrated that extracellular dehydration during pregnancy (commonly observed during pregnancy after vomiting or diarrhea) can enhance the natriophilic propensity in offspring and suggested that vomiting during pregnancy may contribute to the epidemiological factors of hypertension.78 Furthermore, mothers consuming excessive amounts of salt and water during pregnancy increase salt preference in adult offspring.79 Similar to dipsogenic mechanisms, peripheral and central fetal orexic mechanism also develop during intrauterine life. Prenatal ingestive behavior is manifested as swallowing and intake of amniotic fluid. By swallowing amniotic fluid, the fetus explores a wide variety of tastes even before birth. By the 7th week of gestation, taste buds develop in human embryos.80 Fetal taste bud cells are spread over a wider surface than in the neonate or the adult.81 It has been shown that sweet taste, such as that of a low-concentration sucrose solution, stimulates swallowing in the human fetus, whereas the incidence of swallowing movements decreases following the injection of Lipiodol—a bitter extract of poppy seeds used as a contrast—into the amniotic fluid.81 Sweet taste is already in utero the favorite taste. It has been found that although oral sucrose significantly stimulates near term ovine fetal ingestive behavior, sweet taste adaptation or habituation does not occur, in contrast to that observed in adult animals and humans. Absence of taste adaptation in the fetus/newborn may facilitate increased neonatal food intake and accelerated growth.82 Increased or decreased glucose level in the serum does not affect the swallowing activity.81 The main feeding regulatory factors, neuropeptide Y (NPY) and leptin, are secreted in the human fetuses as early as at 16 to 18 weeks respectively.83-85 NPY is the most potent known inducer of food intake and leptin is a satiety factor. In some animal experiments, increased fetal swallowing has been demonstrated upon central NPY administration.86 The role of leptin in regulating ingestive behavior is interesting because, as opposed to its function in adults, leptin does not suppress fetal ingestive behavior.88 Fetal swallowing was significantly increased following the injection of leptin.87 Therefore, some investigators have postulated that the absence of leptin-inhibitory response potentiates feeding and facilitates weight gain in newborns, despite high body fat levels.88 Some findings suggest a possible role of leptin in the development of the fetal gastrointestinal tract.89 Apart from determined high leptin concentration in amniotic fluid and in the gastrointestinal mucosa at the time when the fetus starts swallowing an early presence of Ob-Rb (functional receptor of leptin) has been found in mucosa. This suggests a possible role for leptin, exerted endoluminally and in a paracrine pathway, in the developmental process (growth and/or maturation) of the human digestive tract.89 According to some other studies, the potential in utero imprinting of appetite and satiety mechanisms may affect infant, childhood and ultimately adult appetite ‘set-points’. An adverse intrauterine environment, with altered fetal orexic factors, could change the normal set-points of appetitive behavior and potentially lead to programming of adulthood hyperphagia and obesity.68,88 In a recent paper, prenatal exposure to over or undernutrition, rapid growth in early infancy, an early adiposity rebound in childhood and early pubertal development have all been implicated in the development of obesity.90 Further investigations are needed to delineate precisely the relationship between the intrauterine environment and the development of the set-points of adult appetite and thirst.

It is important to note that the function of the fetal digestive system also begins at an early stage of pregnancy. Water, electrolytes and other small molecules, such as glucose are absorbed through the small bowel.21 By 13 weeks, the intestine starts to absorb glucose and water swallowed by the fetus.85 Salivary amylase activity was found in the amniotic fluid in the late first-trimester pregnancies. Enzyme activity breaking down peptone is present in the small intestine of 7 to 10 week old fetuses and rises slightly after the 14th week of gestation. Lipase was found in the stomachs of fetuses in the 4th month of gestation, its activity increased with subsequent development. In addition, the pH of the gastric fluid in newborns is usually neutral or slightly acidic and the acidity increases shortly after birth, within several hours. The first traces of gastric acidity appear in 4 months old fetuses.91 Generally, during the last 2 to 3 months, fetal gastrointestinal function approaches that of the normal neonate. However, if the infant is more than 2 months premature, the digestive and absorptive systems are almost always inadequate. The absorption of fat is so poor that the premature infant must have low-fat diet.19 Insufficient fat absorption can cause problem to newborns that were fed milk that contains more fat than breast milk, such as undiluted cow milk.81

**Fetal Respiratory System**

Fetal lungs begin to develop in the 4th week after fertilization. At this time, the respiratory diverticulum (lung bud) appears ventrally to the caudal portion of the foregut. Angiogenesis in the lungs begins at the 5th week after fertilization. From the 16 to 26th week of pregnancy, formation of early respiratory units occurs and pneumocytes types II appear. From 26th week until birth, thinning of the
respiratory membrane takes place, primitive alveoli dilate and establish close relationship with the capillaries. From 36th week onward, secondary alveolar septa, with rich capillary network, develop. Hence, respiratory surface enlarges. Further thinning of the respiratory membrane happens. Mature neonate has 50% lower number of alveoli than an adult. Final number of alveoli is reached at 2nd year of postnatal life. Normal fetal lung development requires the presence of lung liquid as well as fetal movements, like breathing. In the regulation of the lung liquid volume fetal breathing-like movements have a very important role. Other functions of breathing-like movements (Fig. 15) during intrauterine life are the development of respiratory muscles, widening of the alveolar spaces, maintenance of the lung liquid volume and lung organogenesis. Animal investigation has shown that absence of respiratory movements (due to destruction of the brainstem nuclei above the phrenic nucleus) leads to hypoplasia of the lungs. Breathing-like movements appear at the 10th week. Early in gestation, fetal breathing activity is variable and isolated event but the frequency and complexity of the breathing patterns change over the following weeks and months. Changes in breathing-like patterns are consequences of the maturation of the fetal lungs as well as the respiratory and sleep centers in the CNS. During the 38 to 39th week of gestation, the frequency of movements decrease to 41 respirations per minute and the movements become as regular as in the postnatal period. A number of internal and external factors can influence fetal breathing-like movements during the second half of pregnancy. At 24 to 28 weeks, the fetal respiratory rate can rise as high as 44 inhale/exhale cycles per minute. This rate changes according to maternal carbon dioxide (CO$_2$) levels, strongly suggesting that respiratory center in the brainstem of the fetus already detects and responds to changes in CO$_2$ levels in the blood. This respiratory response to CO$_2$ is similar to that seen in newborns and adults. Furthermore, an increased number of fetal respiratory movements following the elevation of the glucose concentration in the maternal blood have been observed at the 34th week of gestation. Recent investigation has shown that intermittent maternal fasting is connected with a considerable alteration in the frequency and pattern of fetal breathing-like movements from the 30th week of gestation onward. Following premature rupture of membranes, during the 3 days prior to the initiation of labor, a decrease in fetal breathing-like has been recorded. However, similar maturation patterns in breathing and spontaneous fetal body movements were demonstrated among low-and high-risk fetuses threatening to deliver prematurely, which suggests normal functional development in the high-risk fetal group. Some studies have shown that maternal consumption of alcohol, methadone, as well as cigarette smoking decrease the incidence of breathing-like movements. On the contrary, aminophylline, conjugated estrogens and betamethasone are responsible for an increase in its frequency.

One of the most important events in the lung development is production and secretion of surfactant. At the end of 6th month, alveolar cells pneumocytes type II appear and begin to secrete surfactant. These cells differ from pneumocytes type I by the presence of numerous surfactant containing granules, lamellar bodies. By adsorbing to the air-water interface of alveoli during the first breath, with the hydrophilic head-groups in the water and the hydrophobic tails facing toward the air, the main lipid component of surfactant, dipalmitoyl-phosphatidylcholine, reduces surface tension. In this way, surfactant prevents the closure of the alveoli, with each expiration. The composition of surfactant changes during fetal life. Mature surfactant, rich with dipalmitoyl-phosphatidylcholine, is detectable after 35 weeks of gestation and indicates the functional maturity of fetal lungs. It is important to emphasize that the secretion of pulmonary surfactant in the lung liquid occurs only in the last weeks of fetal life. Besides phospholipids, surfactant contains proteins. Four types of surfactant-associated proteins have been described, SP-A, SP-B, SP-C and SP-D. They differ in structure, as well as in the function. SP-A and SP-D are hydrophilic molecules, they stimulate the secretion and removal of phospholipids and participate in maintaining of the homeostasis of surfactant. SP-B and SP-C are
hydrophobic molecules as they enable the spreading of the phospholipid bilayer along the alveoli and improve the stability of surfactant. However, most important role of all proteins is the defense as they are participating in innate immune defense of the lung. In addition, they bind and react with many microorganisms, allergens and mitogens, and their receptors have been detected in alveolar macrophages. Various hormones and inflammatory mediators affect the synthesis and secretion of surfactant. There are convincing data to support the use of antenatal corticosteroids in improving the respiratory outcome of newborn infants, especially those at greatest risk of developing respiratory failure. The current data suggest that this improvement may be due to enhanced expression of proteins and phospholipids of the surfactant system and enzymes of the antioxidant systems. Nevertheless, caution is needed, as the scanty data that are available in animal models suggest that lung growth, especially the development of capillary network and secondary alveolar septa, as well as somatic growth may be adversely affected. The existence of receptors for triiodothyronine, thyroid hormone in the fetal lung, as well as certain studies conducted in animal models, suggest that this hormone also participates in the development of the fetal lung. Data have shown that thyroid hormones promote morphogenesis of lung histotypic structures but have a negative effect on surfactant synthesis. However, it seems that the role of prolactin, which increases in the serum of fetuses just before birth, is important for lung maturation. It is known that children of mothers who are heroin abusers have lower incidence of neonatal respiratory distress syndrome and heroin stimulates prolactin secretion. Studies conducted on experimental animals have shown that estrogen also stimulates the synthesis of surfactant in the fetal lungs too. Insulin and androgens play a role in inhibition of surfactant secretion. Higher incidence of neonatal respiratory distress in children of diabetic mother and in normal male neonates has been confirmed. Insulin and androgens inhibit synthesis of the surfactant. Chronic hyperglycemia with hyperinsulinemia have been connected with the delayed appearance of surfactant in the fetal lung tissue. The hypothesis that insulin achieves its inhibitory effect primarily by disruption of protein synthesis of surfactant was confirmed by studies on cell cultures of human pneumocytes type II. However, it is interesting, that insulin, administered together with cortisol stimulates the synthesis of surfactant more than cortisol alone. Respiratory distress syndrome of newborn is more common in male than in female children, possibly due to later start of surfactant production in male fetuses. This difference could be influenced by androgen effects, but definitely genetic factors have a certain role in it. Further, powerful modulators of lung maturation are inflammatory mediators, particularly interleukin 1, tumor necrosis factor- and bacterial endotoxin. Maternal chorioamnionitis, in which the fetus is exposed to inflammatory agents, is a common cause of premature birth. However, these children, rarely suffer from respiratory distress syndrome. Still, although these cytokines enhance the maturation of the lungs and allow the survival of the child, their long-term effect is negative because they affect lung growth and development, especially vascularization. Therefore, in these children the respiratory surface is decreased. In addition, due to insufficient vascularization, vascular resistance in the lungs remains high after birth. This prevents the increase in flow through the lungs and leads to pulmonary arterial hypertension.

Although the fetal lungs are functionally inactive during the entire period of intrauterine life, respiratory function becomes essential for survival of the infant immediately after birth. Breathing is initiated by sudden exposure to the exterior world and it is a consequence of slightly asphyxiated state due to the birth process and sensory impulses that originate from the suddenly cooled skin. If an infant does not begin to breathe immediately, progressive hypoxia and hypercapnia develop, and additionally stimulate the respiratory center. At birth, the walls of alveoli are collapsed due to the viscous fluid that fills them. More than 25 mm Hg of negative inspiratory pressure is required to oppose the effect of surface tension. First inspirations of the neonate are extremely powerful and capable of creating as much as 60 mm Hg negative pressure in the intrapleural space. During first inspiration, about 40 milliliters of air enters the lungs. To deflate the lungs, considerable positive pressure is required because of viscous resistance offered by the fluid in the bronchioles. Expansion of the alveoli and increased concentration of oxygen in them stimulates the release of vasodilator substances from the endothelium of capillaries. This, together with the mechanical stretching of the alveoli, leads to the dilatation of the lung capillaries and the resistance to blood flow in the pulmonary circulation decreases several fold. Development of a nearly normal compliance curve and normal postnatal breathing establishes within 40 minutes after birth.

In addition to allowing gas exchange, increased blood flows through the lungs probably accelerate reabsorption of the lung liquid. Although the existence of lung liquid is necessary for the development of the lung, it must be quickly removed during delivery to allow normal breathing of the newborn. Most of the lung liquid reabsorbs in the pulmonary circulation and only a small part of it removes through the
upper airway during passage through the birth canal. Infusions of norepinephrine in concentrations, similar to those present at the delivery, prevent the lung liquid secretion. Hormones and factors that facilitate the removal of liquid from the lungs are arginine–vasopressin, catecholamine, prostaglandin-E₂, prolactin, surfactant, some growth factors and increase of the concentration of oxygen in the lungs, originating from the first breath.¹⁹

**Fetal Urinary System**

At the beginning of the fourth week, the intermediate mesoderm forms the nephrogenic cords. From the nephrogenic cords, three successive sets of excretory organs develop: The pronephros, the mesonephros and the metanephros. The first two, i.e. the pronephros and mesonephros, persist over a period of time and then regress, while the third, the metanephros, forms the definitive kidney. The permanent adult kidney, the metanephros, begins to develop early in the fifth week and is functional 2 to 3 weeks later. The ureteric bud develops as an outgrowth from the mesonephric duct. The ureteric bud forms the ureter, renal pelvis, calyces and collecting tubules. The nephrons are derived from the metanephric blastema.⁶³ First nephrons appear in the kidney medulla, around 20 to 22 weeks of gestation, later they can be found in the periphery of the kidney. Formation of nephrons ends around the 35th week of gestation and further development occurs due to the growth of existing nephrons.¹²⁹ At birth, the nephrons, approximately one million in each kidney, are formed but are still short. No new nephrons are formed after birth. During infancy, the nephrons complete their differentiation and increase in size until adulthood.⁶³ Enlargement of the glomeruli, enlargement and elongation of the tubules, as well as enlargement of the vascular and connective tissue contribute to the growth of kidneys.¹³⁰ Failure in the maturation of the primitive kidneys can lead to the abnormal development of the genital system, adrenal glands and lungs.¹²⁹ Various anomalies of the urinary tract can be caused by developmental disorders of pronephros and mesonephros. Developmental anomalies of the urinary tract account for about 40% of all anomalies. Frequent occurrence of the urinary tract anomalies is due to complicated ontogenesis of this system.¹³⁰ Recently, attention has been given to less noticeable but potentially very harmful consequences of impaired kidney development, such as a congenital nephron deficit. Since the lack of nephrons after birth is unrecoverable, numerous studies have been conducted to detect factors that in some way may impair the process of nephrogenesis.¹³¹ Studies conducted on the cell cultures of the fetal kidney showed that retinoids, metabolites of vitamin A, have a significant impact on the number of nephrons and that this effect is dose-dependent. Vitamin A deficiency in pregnant women is rare in developed countries but is more frequently observed in underdeveloped countries as a result of insufficient food intake. Even in a healthy population, concentrations of vitamin A and retinoids in the plasma considerably vary. Habits that are most commonly associated with its low plasma values are cigarette smoking, alcoholism and unbalanced diets.¹³¹ Unfortunately, lack of vitamin A is not the only factor that can lead to a nephron deficit. Experiments on animals have proved that fetal growth retardation,¹³² maternal hyperglycemia¹³³ and some medications, such as gentamicin,¹³⁴ cause a reduced number of nephrons, which cannot be fully compensated for after birth. If we remember that nephrogenesis in the humans ends before birth, we can assume that the harmful effects of these factors on the human fetus may be even more dangerous. Even a slight deficit of nephrons, often unrecognized after the birth, could be associated with diseases that occur later in the life, such as renal failure or hypertension. Therefore, more and more scientists believe that congenital nephron deficit could be a ‘missing link’ in understanding of the etiology of essential hypertension.¹³¹

For many years, data on fetal renal function have been insufficient and indirect. Investigations were carried out mainly in experimental animals and aborted fetuses. The insertion of a catheter into the fetal blood vessels and bladder allowed the testing under physiological conditions, and brought new insights about the function of the fetal kidneys, and the application of ultrasonic methods, enabled the non-invasive and easy way to study the physiology and pathophysiology of fetal urinary tract. Glomerular filtration rate in term-fetuses, measured by ultrasound and biochemical measurements, is 0.73 to 5.25 ml/min, which amounts to 1/29 to 1/4 values in adults. After birth, during the first 4 days of life, glomerular filtration rate rapidly increases.¹³⁴ It was found that the time of umbilical cord ligation influences on the value of glomerular filtration rate. In the newborns in which umbilical cord ligation was performed relatively late after the birth, a circulating blood volume and glomerular filtration was 40 to 50% greater than in the newborns in which the umbilical cord ligation was done immediately after birth.¹²⁹ Further, values of tubular reabsorption in fetal kidneys at term range between 55 and 97% of the adult values.¹³⁵,¹³⁶ Although histologically, kidney tubules seem well developed, at the time of delivery, the surface of transporting cells and the number of transporters is small. Reabsorption and excretory function are not completely developed. Immature cells
tubules have low concentration of Na⁺/K⁺ ATP-ase, an enzyme that provides energy for active transport of sodium. Therefore, capacity of renal tubular cells for sodium transport is limited. Consequently, reabsorption of bicarbonates, glucose and phosphates is also limited. Due to low glucose threshold, tendency of excretion of glucose and consequently of the water and sodium is increased. Because of that in neonate, dehydration can develop more rapidly than in an adult. Further, it was found that term-fetus is not capable to respond on dehydration or hypertonic solution by creating concentrated urine, like adult. Sodium overload of the mature newborn and increase of plasmatic concentration of sodium can cause increase of the body mass due to generalized edema. If the newborn gets a cow’s milk, which contains four times more sodium, protein and phosphate than mother’s breast milk, signs of salt and fluid retention may occur. The fetus usually produces hypotonic urine and in case of dehydration, ability to concentrate urine does not exceed the limit of 600 to 700 mOsm/l. Antidiuretic hormone (ADH), whose role is to preserve water in the body by concentrating the urine, the fetus begins to produce in the 11th week of pregnancy and its concentration in fetal blood is almost equal to the concentration in adults. Infusion of hypertonic NaCl solution, hypoxia or hypovolemia can increase concentration of ADH in fetal plasma. Therefore, we cannot talk about lack of ADH, as a cause of low osmolarity of fetal urine. However, it is possible to assume that the kidney is insensitive to ADH. The fetus cannot concentrate urine before appearing of specific water channels called aquaporin. They occur in human fetuses in the 12 to 15th weeks of pregnancy but their expression in the fetus and newborn is much lower than in adults. Insensitivity of the fetal kidney to ADH could be explained by the slow emergence of these water channels. Further, hydrogen ion secretion in the fetus and newborn is sufficient to allow bicarbonate reabsorption and excretion of metabolic acids. Filtered phosphate and synthesized ammonia are in quantities sufficient for buffering excessive hydrogen ions. However, it is important to note that the fetal kidneys do not play a major role in the regulation of acid-base balance. Even in fetuses with renal agenesis, acid-base balance may be normal. In fetus, the acid-base balance is regulated by maternal lungs and kidneys. CO₂ is quickly removed through the placenta into the mother’s bloodstream and then mother exhaled it. Large amounts of CO₂ can be effectively removed if the mother’s respiration, the uteroplacental flow and the umbilical flow are normal. Somewhat, more slowly, metabolic acids are transferred through the placental barrier and they are excreted through the mother’s kidneys. Thus, regulation of fetal acid-base balance depends on many interrelated factors, which include state of the mother, placenta and the fetus.

Fetal kidneys (Fig. 16) excrete urine from the 3rd month of pregnancy. This can be confirmed by the existence of urine in the bladder of the fetus (Fig. 17). Urine extracted from the fetal kidney is hypotonic and that is not surprising because the main excretion function is performed by the placenta. Due to this fact, electrolyte composition of fetal urine is poor. The pH of fetal urine is about 6. By the midgestation, fetal urine becomes the main source of amniotic fluid and swallowing the main way of its removal. These two processes are essential elements in the production and regulation of amniotic fluid in the middle trimester. The term-fetus excretes in the amniotic fluid about 400 to 1200 ml of urine daily. The fact that fetal urine is the main component of the amniotic fluid in the second half of pregnancy, allows us to determine the concentrations of electrolytes, creatinine, protein or glucose. Further, recording of their changes enables us to study the functional development and maturation of the fetal kidney during this
After birth, the kidneys are still immature, more accurately, their functional capacity is limited. Due to this, disorders in the maintenance of homeostasis can easily develop. Exchange of fluid in the newborn is very large and the intensity of metabolism and acid production are higher than in the adult. Taking into account immaturity of the kidney, we can easily understand that in this period acidosis, dehydration and sometimes excessive hydration frequently develop. The disruption in the maintenance of homeostasis is more often if the child is born before term, in hypoxia or infection. Fetal kidneys and kidneys of newborn do not perform their functions poorly, indeed, they work impressively, but they need time to achieve the perfect harmony of their functions.

Fetal Central Nervous System

Development of the human CNS begins in the early embryonic period and proceeds through a sequence of very complicated processes long after delivery. CNS develops from the embryonic ectoderm. Cells that will become neurons and glial cells originate from the neural plate, which is located within the ectoderm and contains about 125,000 cells. The neural plate is formed in the early third week of pregnancy. Its lateral edges are gradually rising and approaching one another, forming first a concave area known as the neural groove and then the neural tube. Cranial and caudal opening of the neural tube are closing between the 25 and 27th day of pregnancy. Failure of these openings to close contributes a major class of neural abnormalities. Further development is characterized by changes in size, shape and internal structure of the neural tube wall, which reflect the complex histogenetic processes. Since, some parts of the neural tube grow and develop at different speeds and intensities, it bends and changes its shape, forming the major subdivisions of the CNS. There are three subdivisions of the cranial part of the neural tube: prosencephalon, the mesencephalon, and the rhombencephalon. They will each eventually develop into distinct regions of the central nervous system: The forebrain (the cerebral cortex and basal ganglia), midbrain and posterior brain (the cerebellum, pons and medulla oblongata). From the caudal part of the neural tube develops the spinal cord.

Early embryonic development is characterized by its immobilization. Prerequisite for fetal movements is the existence of interneuronal and neuromuscular connections. The earliest interneuronal connections—the synapses, can be detected in the spinal cord shortly before the onset of embryonic motility, at 6 to 7 weeks of gestation. Therefore, the neural activity leading to the first detectable movements is considered to originate from the spinal motoneurons. Another important prerequisite for the motility is the development and innervation of muscular fibers. It is well known that primitive muscle fibers (myotubes) are able to contract as soon as they are innervated by motor neurons. Between 6 and 8 weeks of gestation, muscle fibers have formed by fusion of myoblasts, efferent and afferent neuromuscular connections have developed, and spontaneous neural activity causing motility can begin. The first spontaneous embryonic movements are gross body movements and they can be observed at the 7 to 7.5th weeks of gestation. They consist of slow flexion and extension of the fetal trunk, accompanied by the passive displacement of arms and legs. These, so called, ‘vermicular’ movements appear in irregular sequences. Simultaneously, with the onset of spontaneous movements, at the 7.5th week of gestation, the earliest motor reflex activity can be observed, indicating the existence of the first afferent–efferent circuits in the spinal cord. The first reflex movements are massive and indicate a limited number of synapses in a reflex pathway. General movements are the first complex, well-organized movement pattern, which involve head, trunk and limb movements. This pattern has been interpreted as the first sign of a supraspinal control on motor activity and can be recognized from 8 to 9 weeks of gestation onward (Fig. 18).

The brainstem is fashioned around the 7th week of gestation and basic structures of the diencephalon and cerebral hemispheres are formed by the end of the 8th gestational week. The remarkable expansion of the cerebral hemispheres follows during the remainder of
The development of synapses in the human cerebral cortex begins after the formation of the cortical plate, at the end of the 10th week of gestation. The brainstem consists of the medulla oblongata, pons and midbrain. It forms and matures in a caudal to rostral direction. That means that the filogenetically older structures, such as the medulla oblongata, will form and mature earlier in the gestation. In addition to its many subnuclei, the medulla gives rise to a variety of descending spinal motor tracts which reflexively trigger limb and body movements. It also hosts the five cranial nerves (VIII-XII), which exert tremendous influences on gross body movements, heart rate, respiration and the head turning. As the medulla matures in advance of more rostral structures of the brainstem, reflexive movements of the head, body, extremities, as well as breathing movements and alterations in heart rate, appear in advance of other functions.

The formation of pons begins almost simultaneously, but its maturation is more prolonged. The structures of the pons include the V and VIII cranial nerves (vestibular nuclei of the nerve VIII) and the medial longitudinal fasciculus (MLF), pontine tegmentum, raphe nucleus and locus coeruleus, which exert widespread influences on arousal, including the sleep-wake cycles. Facial movements, which are also controlled by V and VII cranial nerve, appear around 10 to 11 weeks. The brainstem gradually begins to take the control over fetal movements and behavioral patterns during the first trimester and continues its maturation in the second trimester, resulting in expansion and complexity of the behavioral repertoires.

From 10 weeks onward, the number and frequency of fetal movements increase and the repertoire of movements begins to expand. Qualitative changes in general movements can be also observed. These movements, which are slow and limited amplitude during 8 to 9 weeks, become more forceful at 10 to 12 weeks. After the 12th week, they become more variable in speed and amplitude. Using four-dimensional (4D) sonography, Kurjak and collaborators have found that from 13 gestational weeks onward, a ‘goal orientation’ of hand movements appears and a target point can be recognized for each hand movement. According to the spatial orientation, they classified the hand movements into several subtypes: Hand to head, hand to mouth (Fig. 19), hand near mouth, hand to face, hand near face, hand to eye and hand to ear. Our recent longitudinal study, performed by 4D ultrasound in 100 fetuses from all trimesters of normal pregnancies, has shown increasing frequency of various movement patterns, such as general movements, isolated limb movements, stretching, as well as head movements, during the first trimester. Using 4D sonography, general movements were found to be the most frequent movement pattern between 9 and 14 weeks of gestation. From 14 to 19 weeks of gestation, fetuses are highly active and the longest period between movements last only 5 and 6 minutes. In the 15th week, 16 different types of movements can be observed. Besides the general body movements and isolated limb movements, retroflection, anteflection and rotation of the head can be easily seen. Moreover, facial movements such as mouthing (Fig. 20), yawning, hiccups, suckling and swallowing, can be added to the wide repertoire of fetal motor activity in this period. The earliest eye movements appear as sporadic movements with a limited frequency, at 16 to 18 weeks of gestation. The delayed onset of eye movements can be explained with later onset of midbrain maturation.

Although the midbrain begins to form at almost the same time as the pons, its maturation does not even begin until the
second trimester. It consists of the dopamine producing substantia nigra, the inferior auditory and superior visual colliculus, and cranial nerves III and IV, which, together with MLF and cranial nerve VI, control eye movements.\textsuperscript{166,167}

Fetal human brain has a number of transitory structures, which cannot be observed in the adult human brain. One of the very important zones in the developing cortex is the subplate zone, that is a site for transient synapses and neuronal interactions. The development of subplate zone, between the 15th and 17th week of gestation, is accompanied with an increase in the number of cortical synapses, which probably form the substrate for the earliest cortical electric activity at 19 weeks of gestation.\textsuperscript{168} Subplate zone can play a major role in the developmental plasticity following perinatal brain damage.\textsuperscript{169}

The second half of pregnancy is characterized by organization of fetal movement patterns and increase in complexity of movements. The periods of fetal quiescence begin to increase and the rest-activity cycles become recognizable. Hardly any new movement pattern emerges in this period. The number of general body movements, which tends to increase from the 9th week onward, gradually declines during the last 10 weeks of the pregnancy.\textsuperscript{170-172} Although this decrease was first explained as a consequence of the decrease in amniotic fluid volume, it is now considered to be a result of cerebral maturation processes. As the medulla oblongata matures, myelinates and stabilizes, these spontaneous movements are less easily triggered, and begin to be controlled by more stable intrinsic activities generated within the brainstem.\textsuperscript{157} It is very important to point out that general movements are characterized by large variation and complexity in the third trimester.\textsuperscript{173}

Revolutionary improvement in the study of fetal facial movements came with the development of 3D and 4D sonography. Our results confirmed the potential of 3D/4D sonography for the investigation of structural and functional development of the fetal face.\textsuperscript{174} The application of 4D sonography in the examination of fetal facial movements has revealed the existence of a full range of facial expressions, including smiling, crying and eyelid movements,\textsuperscript{164,175} similar to emotional expressions in adults, in the 2nd and 3rd trimesters. Other facial movements, such as yawning, suckling, swallowing and jaw opening can also be observed in this period by 4D ultrasound. Recent study demonstrated that the most frequent facial movement patterns in the 2nd trimester were isolated eye blinking, grimacing, suckling and swallowing, whereas mouthing, yawning, tongue expulsion and smiling could be seen less frequently. Mouthing was the most frequent facial movement during early third trimester\textsuperscript{176} (Figs 21A and B).

Our longitudinal analysis of the frequencies of different facial movements in the 2nd and 3rd trimester revealed some interesting results. Contrary to the declining trend of head movement and hand movement patterns from the beginning of the second trimester to the end of the third trimester, a constant increase in the frequencies of almost all facial movement patterns was observed during the 2nd trimester. Various types of facial expression patterns displayed a peak frequency at the end of 2nd trimester, except eye blinking pattern (Fig. 22), which displayed a peak frequency at 28 weeks of gestation. During the remainder of pregnancy, decreasing or stagnant incidence of facial expression patterns was noted.\textsuperscript{164} Obviously, this developmental trend provides yet another example of the maturation of the medulla oblongata, pons and midbrain, or perhaps even the establishment of control of more cranial structures. The facts that even in the embryonic period same inductive forces that cause the growth and reshaping of the neural tube influence the development of facial structures and that many genetic disorders affecting the CNS are also characterized by dysmorphology and dysfunction of facial structures, emphasize the importance of structural and functional evaluation of the fetal face.\textsuperscript{159,177} Our recent study has demonstrated that there were no movements observed in fetal life that were not present in neonatal life. Furthermore, prenatal—neonatal continuity exists even in subtle, fine movements such as facial mimics.\textsuperscript{178}
In addition to morphological studies of the development of the central nervous system and studies about fetal behavior that provide insight into the functional development of central nervous system of fetuses, attention of researchers attracts the development of the fetal senses. For a long time, experts from different fields of science debate about whether the fetus feels pain. In humans, it is possible to distinguish several different reactions to pain. The simplest is reflex motor reaction, removal of stimulated body parts from painful stimuli. Next unconscious reaction involves the secretion of the so-called stress hormones—cortisol and catecholamines. The most complex reaction is conscious perception of pain and emotional reaction to it. We can claim with certainty that the first two are already present in the fetal period. The earliest reactions to painful stimuli are motor reflexes, resembling withdrawal reflexes. They appear early in gestation. Reflex threshold is remarkably low and various kinds of stimuli may induce very holistic and unspecific reactions. It is important to emphasize that these reactions are completely reflexive, directed by the spinal cord, and higher perception or processing of painful sensation does not exist at this stage.179

Further, as early as 16 to 18 weeks of gestation, fetal cerebral blood flow increases during invasive procedures.180,181 This increase of blood flow toward the brain may be mediated by the sympathetic system or by other undetermined mechanisms.181 With regard to the autonomic and endocrine responses to pain, an elevation of noradrenaline, cortisol and beta-endorphin plasma levels, in response to needle pricking of the innervated hepatic vein for intrauterine transfusion, was registered in a 23-week-old fetus. Pricking of the noninnervated placental cord insertion for the same purpose had no effect.182,183 Obviously, painful stimuli trigger a wide spectrum of reactions, such as activation of the hypothalamo-hypophysial axis or autonomic nervous system, without reaching the cortex. It has been suggested that neither motor reflexes nor hormonal stress responses to invasive procedures prove the existence of fetal pain.184 It is unknown whether and when the fetus begins consciously to feel pain. Functional thalamocortical connections are required for fetal awareness of noxious stimuli. Thalamocortical path is formed between 22 and 26 weeks and after this period, the fetus is probably capable of consciously perceiving painful stimuli. Evidence for conscious pain perception during intrauterine life is indirect, but evidence for the subconscious incorporation of fetal pain into neurological development and plasticity is incontrovertible.185 Despite the great interest in conscious experience and memory of pain, unconscious reactions like the secretion of stress hormones and their far-reaching detrimental effect, are probably more dangerous for the development of fetus than terrifying memories.

Reflex arcs involving the brainstem, such as vestibular, auditory and olfactory, mature early in fetal life. Vestibular nerve cells mature earlier than neurons of the lateral and inferior vestibular nuclei, which begin to function during the 9th week of pregnancy. It is believed that vestibular stimulation has a role in the emerging fetal movements. Nearly weightless state of the fetus in the uterus provides a particularly convenient medium for the vestibular reflexes. According to electrophysiological examinations of evoked potentials in prematurely delivered healthy infants, cochlear function develops between 22 and 25 weeks of gestation and its maturation continues during the first 6 months after delivery.186-188 However, fluid in the fetal ear as well as the immaturity of the cochlea, complicate the sound transmission, so that only strong acoustic stimuli can be registered by the fetus.157 Due to this reason and because of the immaturity of the cochlea, a very strong stimuli is needed for fetus to notice it. Maternal heartbeats and motility of gastrointestinal tract during digestion appear to generate 60 to 90 decibels of sound in utero, which is comparable to noise of the busiest street.189 During the last weeks of pregnancy, from the 36th gestational week onward, the fetus reacts to extremely loud sounds and even the mother’s voice with reflex movements of the body, by turning his head, and increased heart rate. More fascinating is the notion that a fetus at this age not only hears sounds but also can discriminate between different sounds. This finding is explained by the tonotopic organization of the cochlear nuclei and by the maturation of the brainstem during the last weeks of pregnancy. It was noted that the development of the auditory system can be disrupted by the influence of adverse factors (cigarette consumption) and also in some pathological conditions (intrauterine growth retardation, maternal hypertension).190-192 It is important to mention also that development of the auditory system affects the subsequent learning of speech and language acquisition.

Animal experiments have indicated that the intrauterine environment is not completely deprived of light. Although the developing fetus cannot distinguish objects clearly, the intensity of light is equal to the splendor that occurs through the cheek when mouth is highlighted by the powerful batteries. Furthermore, according to some experimental results, the development of visual and auditory organs could not be possible without any light or auditory stimulation.193,194 The structural development of sensory pathways is a prerequisite for functional development, but the final organization of the brain circuitries depends mainly on guidance from external inputs.169 A histological study
of the human visual pathway has shown that thalamic projections reach the visual cortex between 23 and 27 weeks of gestation. The primary visual cortex can be clearly delineated in the occipital lobe by immunohistochemical staining even before the 25th week. In this cortical area, synaptogenesis persists between 24 weeks of gestation and 8 months after delivery, while myelination of the optical tract begins at 32 weeks of gestation. Cortical visual evoked potentials indicate the development and maturation of the primary visual cortex. Maturation of the visual cortex is characterized by the appearance of surface-positive evoked potentials, which occurs between the 36 and 40th weeks. New data have shown that the amplitude of visual evoked potentials, which occurs between the 36 and 40th weeks, can be used in the assessment of fetal and neonatal habituation to light stimuli. Flash stimuli evoked responses can be used in the assessment of fetal and neonatal habituation to light stimuli over the maternal abdomen can cause the visual evoked brain activity in the human fetus, recorded by magnetoencephalography. The latency of the fetal response falls with increasing gestational age and begins to approach the adult latency near term. Recent experimental findings have demonstrated the importance of fetal eye motility in retinal (neuronal) cell differentiation, as well as eye functional maturation.

Fetal life in utero is organized in cyclical patterns. From the midgestation onward, periods of activity begin to alternate with the periods of rest. Between 30 and 38 weeks of pregnancy the difference between quiet and paradoxical, ‘active’ sleep can be seen. In advanced pregnancy, the fetus usually sleeps at the same time as the mother. In fetal animals, simultaneous measurements of fetal electrocortical activity, eye and body movements have shown that deep sleep, characterized by high-voltage waves and decreased fetal activity, occurred during 54% of a day. The total length of the REM sleep period, characterized by low-voltage waves and rapid eye movements, lasted 40% of a day. The wakeful state (6% of a day) is characterized by low-voltage waves. In human premature newborns, born 4 weeks prior to term, 60 to 65% of the total sleeping period is REM sleeping, whereas in term-newborns, the REM sleeping period includes 50% of the total 16 hours of sleep. During delivery, fetal EEG shows waves characteristic for quiet sleep, active sleep and wakeful-ness of the newborn. It is thought that REM sleep plays a role in the development of the nervous system, similar as physical activity helps to develop muscles. REM sleep is probably caused by intense activity of neural circuits and thus participates in the development of the central nervous system.

The human brain is intricately designed to execute cognitive functions, such as perception, attention, memory and learning. Psychobiologic investigations inspired the hypothesis that the acoustically rich environment in the uterus contributes to fetal learning. The intrauterine origin of learning and memory processes has been investigated extensively employing habituation methods, classical conditioning or exposure learning to assess fetal learning.

It was also found that the fetus has the ability to remember tastes to which it was exposed during the intrauterine period. Flavors from the mother’s diet during pregnancy are transmitted to amniotic fluid and are swallowed by the fetus. Consequently, the type of food eaten by the mother during pregnancy is experienced by the infants before their first exposure to solid food. For instance, garlic ingestion by pregnant women significantly alters the odor of their amniotic fluid, barely 45 minutes after ingestion. Prenatal experience of taste greatly affects the newborn child. It prepares it for the taste of the mother’s milk, whose taste also depends on the mother’s diet. Prenatal and early postnatal exposure to a flavor enhances the infant’s enjoyment of that flavor in solid foods during weaning. A study has shown that the infants who have been exposed to the flavor of carrots in either amniotic fluid or breast milk behaved differently in response to that flavor in food than did the nonexposed control infants. Specifically, previously exposed infants exhibited fewer negative facial expressions while being fed the carrot-flavored cereal compared to the plain cereal, whereas control infants whose mothers drank water during pregnancy and lactation exhibited no such difference. According to recent data, the neonate strongly reacts to fragrant signals of mother’s breasts. In the close proximity of mother’s breasts, in the first minutes after birth, the newborn spontaneously turns toward the breast and starts making the movement of sucking even before coming in the direct contact with the breast. In the first days of life, it demonstrates a similar reaction to its own amniotic fluid. To some extent, the chemical profile of breast secretions overlaps with that of amniotic fluid. Therefore, early postnatal attraction to odors associated with the nipple areola may reflect prenatal exposure and familiarization.

The development of human brain is not completed at the time of delivery. Only subcortical formations and primary cortical areas are well developed in a newborn. Associative cortex, barely visible in a newborn, is scantily developed in a 6 months old infant. Postnatal formation of synapses in associative cortical areas, which intensifies between the 8th month and the 2nd year of life, precedes the onset of first cognitive functions, such as speech. Following the 2nd year of life, many redundant synapses are eliminated. Elimination of synapses begins very rapidly and continues slowly until puberty, when the same number of synapses as seen in adults is reached.
Fetal Stress

A large number of environmental factors can trigger the fetal stress response. For instance, maternal undernutrition or placental insufficiency can alter the intrauterine environment, causing fetal stress. Painful stimuli also lead to the fetal stress response. Even severe maternal emotional stress or stressful life events, according to some investigations, may influence the fetal environment. The primary role of stress is the protection of organism but fetal exposure to stress may affect neurodevelopment, as well as the development of many other organ systems and have lifelong consequences. Many adaptive changes induced by fetal stress increase the chance of fetal survival by creating a short-term protection. However, these changes can leave profound alterations in the structure and functions of the organism. It is a known fact that fetal cardiovascular adaptation to hypoxia is manifested by the redistribution of blood flow primarily toward the fetal brain. However, our latest investigations have shown that severe brain damage can develop despite the fetal blood flow redistribution and increased brain perfusion, even earlier than it was previously thought. The neuroendocrine stress axis includes the production of the corticotropin releasing hormone (CRH), adrenocorticotropic hormone (ACTH) and cortisol. Fetal CRH has been shown to influence the timing of birth. These findings have pointed to an active role of the fetus in the initiation of parturition. Furthermore, ACTH impairs motor coordination and muscle tonicity, reduces attention span and increases irritability. Recently, epidemiological and experimental investigations have shown that chronic exposure to high levels of cortisol during intrauterine life, occurring either as a result of its exogenous application or the fetal stress, has a very adverse effect in the long run. Unfortunately, it has been recently established that cortisol, which accelerates lung and brain maturation and enables survival of premature infants, may have an adverse effect on growth of the lungs, development of the secondary alveolar septa and even on the growth of the whole organism. Accelerated maturation of the brain is also associated with the structural as well as behavioral changes. Stress induces structural changes of the hippocampus that are associated with memory impairment and learning disabilities. Behavioral changes associated with accelerated maturation of the brain include hyperalertness and impaired fetal responsiveness to novel stimuli. Retrospective studies on children whose mothers experienced severe psychological stress or adverse life events during their pregnancy have suggested long-term neurodevelopment effects on the infant. Such children exhibited symptoms of attention deficit hyperactivity disorder, sleep disorders, unsociable and inconsiderate behavior, as well as psychiatric disorders, including schizophrenic episodes, depressive and neurotic symptoms, drug abuse and anxiety. Increased maternal stress during pregnancy seems to influence infant temperament and cognitive functions. Moreover, stressful maternal life events measured during the first part of pregnancy negatively affected the child’s attention/concentration index measured at the age of six. The adverse health effects of stress may also include an increased risk of certain birth defects (cleft palate, cleft lip with or without cleft palate, transposition of the great arteries and tetralogy of Fallot). Chronic high glucocorticoid exposure in utero is associated with adult hypertension and according to some data with coronary disease. Impaired glucose tolerance has also been noticed. We can conclude that some of the most common diseases of the modern society may have their origins in prenatal life.

CONCLUSION

Fetal developmental potential is determined at the moment of conception by genetic inheritance. However, this development is modulated by environmental factors. Basic and clinical researches into fetal life present us with ever deeper understandings of important role that the environment plays in prenatal and postnatal life. It is important to recognize that both, the mother and the fetus, actively participate in the maintenance of the physiological intrauterine environment. Unfortunately, the fetus is not entirely protected from harmful influences of the external factors. By altering the intrauterine environment, these factors can have a long-term effect on fetal health. Finally, physiological fetal growth and development is the precondition for optimal child development.

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