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Review Article

Pathophysiology of Intrauterine Development

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Abstract

The process of early ontogenesis consists of a number of regular, qualitatively different stages of morphophysiological transformations, hereditarily determined and occurring under conditions of continuous interaction with the external environment, which acts as a more general system in relation to the developing organism. The mother's and fetus's organisms are closely interconnected. For the embryo, fetus, the mother's organism is the external environment, therefore, the pathology of intrauterine development of the fetus is considered in connection with pathological changes in the mother's organism. The absence of a set of conditions that must be created by the mother's body (restructuring of its functions) to ensure optimal conditions for the development of the embryo or fetus is the most important reason for the cessation of its development or even the formation of anomalies in the body.

Keywords: ontogenesis; morphophysiological transformations; developing organism

Introduction

The process of early ontogenesis consists of a number of regular, qualitatively different stages of morphophysiological transformations, hereditarily determined and occurring under conditions of continuous interaction with the external environment, which acts as a more general system in relation to the developing organism. The mother's and fetus's organisms are closely interconnected. For the embryo, fetus, the mother's organism is the external environment, therefore, the pathology of intrauterine development of the fetus is considered in connection with pathological changes in the mother's organism. The absence of a set of conditions that must be created by the mother's body (restructuring of its functions) to ensure optimal conditions for the development of the embryo or fetus is the most important reason for the cessation of its development or even the formation of anomalies in the body. [1] It is known that of the 50% of blastocysts that die in the first week, they die from the accumulation of lethal genes and from the absence of conditions necessary for their development. Gametes, blastocysts, embryos, fetuses, and newborns can be exposed to pathogenic effects.Anomalies that arise from the moment of differentiation of embryoblasts until the end of organ formation (up to 12 weeks) are referred to as embryopathies; anomalies that develop after the 12th week are referred to as fetopathies. The experimental data show that the embryo's susceptibility to damage is highest in the initial period of development. Then it gradually decreases, but at certain intervals it increases again. These periods of high sensitivity are called critical or sensitive.At this time, the cells of the embryo acquire high receptivity to impulses that determine its development in the desired direction, and the embryo enters a new stage of morphogenesis. [2] Studies of early ontogenesis and histogenesis in animals provide an idea of the periodicity of the functioning of the genetic apparatus, the activation at certain time intervals of the synthesis of RNA and specific proteins associated with cell determination and differentiation. [3] Critical periods are the most dangerous for the life of the embryo, since at this time its cells exhibit a particularly high sensitivity not only to physiological, but also to damaging factors affecting it. There are two critical periods. The first in humans occurs during the first week of pregnancy - this is the preimplantation or tubal period of embryogenesis. The second critical period is that of major organogenesis, including the formation of the placenta, and lasts from 3 to 8 weeks. Most embryopathies owe their origin to the action of damaging factors during critical periods of development. However, it should be borne in mind that intoxication, diseases of the pregnant woman and other factors can damage the brain, endocrine and reproductive systems of the fetus at any stage of development, since their critical periods exceed 8 weeks. The importance of critical periods in embryo development is manifested in the fact that pathogenic factors of different nature cause the same pathological changes, the occurrence of which is determined by the time of their action. On the other hand, the same type of influences affecting the embryo at different times do not cause the same effect [4]. For example, irradiation of pregnant female rats with the same dose of X-rays on the 10th day of pregnancy causes anencephaly, on the 11th day - micro- and anophthalmia, on the 14th day - limb anomalies. [5] The action of pathogenic factors during the first critical period leads to delayed implantation of the blastocyst and to death or to the occurrence of general anomalies - delayed development, decreased viability of the fetus. Damage caused during the

second critical period manifests itself as morphological changes in one or another organ, and these local damages can be combined with developmental anomalies of a general nature. The consequences of adverse effects also depend on the site of action. Thus, the introduction of a pathogenic agent into the yolk sac does not cause structural changes, visible disturbances of organogenesis and its timing. Application of the same substance to the surface or introduction into the chorioallantois cavity entails a change in organogenesis The earlier the pathogenic factor manifests itself, the more extensive the damage will be. [6] A study of amniotic fluid, performed from the 14th to the 16th week of pregnancy by means of amniocentesis, allows determining the maturity of the fetus, and performing prenatal diagnostics of many hereditary diseases associated with metabolic disorders. Timely diagnosis provides indications for termination of pregnancy. Studying the cells contained in the amniotic fluid makes it possible to determine the sex of the fetus chromosomal aberrations. Organic and inorganic substances, enzyme activity, hormones, etc. are determined in the liquid part [7] A relationship has been established between the content of creatinine and urea in the amniotic fluid and the growth and weight of the fetus[8]. The content of total protein in the amniotic fluid is lower than in the serum of the fetus and the mother's body, and the ratio of albumins and globulins in it is different; in terms of their composition, the proteins of the amniotic fluid are closer to the proteins of the serum of the fetus than to the maternal body. The amniotic fluid also contains amino acids.[8] In case of fetal hypotrophy, amino acids are administered intra-amniotically, which are absorbed and digested by the fetus. Apparently, some of them are used for the synthesis of fetal protein. Amniotic fluid is swallowed by the fetus and provides it with the necessary amount of fluid in the first hours after birth. The mechanism of formation of amniotic fluid is not clear. The wall of the amnion has formations such as endocrine glands and the lymphatic system. Its cells are rich in dehydrogenases. The amniotic fluid contains a significant amount of chorionic gonadotropin.

The fetal membranes are very permeable to water and electrolytes. [9]

Pathophysiology Of the Cell (To the Mechanisms of Embryopathies)

The cell is the basic unit of life, the basic unit of biological activity, the basis of function. It is endowed with all the properties of life: irritability, metabolism, the ability to reproduce, mutate. The mechanism of action of a number of factors causing fetal malformations and diseases is cell damage and disruption of its normal functioning. Cell damage is characterized by disruption of its internal movement (locomotiveness), internal and external deformations, disruption of the formation and release of pseudopodia. At each stage of development, the cell has its own characteristic of internal movement. When a cell is damaged, the coordination of movement is lost. The cells of the body are integral integrated systems in which all elements (nucleus, organelles, cytoplasm) interact.[10] Damage caused by toxins, drugs, and anesthetics stops both the internal movement (locomotority) and external movement of embryonic cells (locomotority), thereby inhibiting the formation and release of pseudopodia.[11] Anomalies in the development of the embryo and fetus can be caused by substances that concentrate in the membranes of the lysosomes of cells. By increasing their permeability or destroying the membranes of lysosomes, these substances promote the release of an excess amount of hydrolases, resulting in the formation of an excess amount of decay products of substances, an increase in ionic and molecular concentration, an increase in the amount of water in the cell, a decrease in pH below 6 (primary cell acidosis). Hydrolases are involved in the processes of cell development and death. The release of such an enzyme as deoxyribonuclease, which differs from all other hydrolases by the presence of two active centers, can cause mutation due to damage to both DNA chains, leading to the formation of developmental abnormalities in the embryo and fetus. Large doses of vitamin A, trypan blue, which reduce the stability of lysosome membranes, can lead to similar changes in development. [12] In embryo pathology, the state of the cell membranes and its organelles is important, being an obligatory mediator and participant in all processes occurring in the cell. With the help of membranes, cells interact with each other, implementing contact, adhesion, fusion and, in addition, interaction with the environment.The importance of membranes is confirmed by the fact that ribosomes are placed on membranes, mitochondria are entirely represented by membranes. Damage to membranes is expressed in a decrease in the activity of their enzyme systems and is manifested in an increase in sorption, a violation of nonequilibrium (penetration of substances against the concentration gradient). This state of reversible cell damage was defined as paranecrosis, and its physiological expression is parabiosis by N. E. Vvedensky. When a cell dies, the processes occurring in the membrane are subject to physicochemical laws, losing the properties of active transfer of substances. Of great importance in the pathology of embryonic development is damage to mitochondria - highly dynamic structures in which the most important processes of life - energy-reproducing and genetic - intersect. In eukaryotes (organisms with a true nucleus), unlike prokaryotes (organisms that do not have a true nucleus, such as bacteria, viruses, blue-green algae) the mitochondria of somatic cells are considered to have some genetic autonomy due to the presence of their own DNA in the form of a double-stranded loop without protein and the protein synthesis apparatus. Mitochondrial DNA encodes up to 70 nucleotides that are part of membrane proteins. [13] Damage to mitochondria is expressed in swelling, increase in size, fragmentation of the inner membrane, decrease in the number of cristae, lightening of the matrix, which will be expressed in disruption of the processes of oxidation, phosphorylation, and deamination of amino acids. Increased permeability of the mitochondrial membrane, which occurs when it is damaged, leads to the release of part of the Krebs cycle substrate into the hyaloplasm with subsequent oxidation by hyaloplasmic enzymes. When mitochondria are damaged, their energy-reproducing and genetic functions are disrupted. In the early period of embryogenesis, before the functioning of the nervous system, all influences on the embryo are carried out humorally by acting directly on its structural elements. Damage to embryonic tissues under the influence of pathogenic factors is formed in a shorter time. Disruption of embryogenesis can occur at the earliest stages when the blastomere cytoplasm is damaged, since the regulation of gene activity at this stage of development is determined by the cytoplasm and is carried out at the transcription level (derepression and inactivation of genes).During organogenesis, developmental disturbances are determined by changes in selective adhesion; at later stages of development, gene activity may be influenced by altered intercellular influences and hormonal factors. At the end of organogenesis, regulation of gene activity is carried out at the translational level, since most genes are stably inactivated during this period. [14] At this time, the possibility of any pathological deviations increases. Violation of the natural course of development processes entails a distortion of the formation of the fetus. During embryogenesis, along with proliferation, processes of cell destruction occur, probably carried out under the influence of hormones. At the same time, the influence of genetic factors cannot be ruled out Cells incapable of differentiation are destroyed, for example, partial resorption of the Müllerian and Wolffian ducts occurs. Cells disintegrate in the absence of conditions for their free movement, then the loss of some cells creates the possibility of invagination, separation of layers, etc. Provisional organs are subject to destruction. In mammals, organogenesis requires the death of some cells. It is believed that cell disintegration is predetermined by their inability to adapt to form-forming stimuli. During intensive cell division, irregular mitoses appear (approximately 10%). A. P. Dyban (1959) suggested that it is precisely the

destruction of cells with abnormal mitoses that is important in the process of regulating morphogenesis, and the fact that during normal embryogenesis, cell disintegration occurs in the same places, at the same stage of development, speaks of the genetic determination of this process. Some authors believe that cell destruction during embryogenesis is part of normal development, programmed by the genome, and is carried out by the same mechanisms that control growth and morphogenesis. As a result of such destruction, the organ receives its final form. [15] Irradiation during embryogenesis either deprives cells of the ability to divide or leads to the appearance of abnormal daughter cells. If the chromosomal abnormality is not pronounced, the cell survives until a stimulus for differentiation appears, to which it is unable to respond. Then two outcomes are possible: the cell dies or gives rise to an embryonic tumor. The concept explains the mechanism of a number of embryopathies. Thus, its cause may be insufficient destruction, physiological destruction of tissues, and, finally, it is possible that it is during cell death that a phenotype mutation occurs.

Chromosomal Aberrations

The properties of each person are strictly individual, not repeatable and are created by heredity, environment and chance, interfering with the implementation of a complex program of individual development. The maternal organism interferes with the basic, established genotype plan of development of the organism, changing it to one degree or another. Many genes have low penetrance and expressivity, due not only to the genotype, but also to the strong influence of the mother's organism on the development of the fetus. The law of the formative interaction of heredity and environment concerns all the characteristics of the organism. Its influence also extends to the formation of such integrative characteristics as instincts, temperament, intelligence, inclinations, etc. Impaired fetal development may be a consequence of the impact of exogenous and endogenous pathogenic factors on the gametes of the parents, capable of causing mutations and aberrant changes. The number of children with hereditary diseases is half that of those with congenital diseases or chromosomal abnormalities. A significant number of cases of intrauterine fetal death are apparently due to chromosomal aberrations. Non-disjunction of chromosomes in meiosis, resulting in the formation of gametes with an increased or decreased number of chromosomes compared to the norm, and their subsequent fusion with a gamete having a normal chromosome complex, leads to the formation of a zygote containing 47 or 45 chromosomes. Such anomalies of the chromosome complex due to sex chromosomes include: Klinefelter syndrome (XXV - 47 chromosomes), trisomy A (XXX - 47 chromosomes), trisomy Y (XYY - 47 chromosomes), and Shereshevsky-Turner syndrome (XO - 45 chromosomes). With trisomy, cell differentiation is delayed, sensitivity to regulatory influences decreases, the cell becomes unstable to mutagenic influences, as a result of which it mutates more easily. There are known cases of chromosomal abnormalities—XXXX, XXXXY, XXYY, XXXXY—that can be explained only by admitting non-disjunction of chromosomes during both the first and second divisions of meiosis, or the first divisions of the zygote, or by assuming that two cells with an abnormal number of chromosomes merged during fertilization. The average frequency of non-disjunction of sex chromosomes in gametogenesis is 0.25%, and out of 100 born, one child carries some kind of chromosomal aberration (deletion, inversion, translocation, chromosome break). Nondisjunction of autosomes produces various anomalies depending on which pair the nondisjunction occurred in. Thus, trisomy of the 21st autosome causes Down syndrome. According to the World Health Organization (WHO, 1965), this is the most common anomaly of the chromosomal complex (1 in 500 births). A frequent manifestation of chromosomal aberrations is mental retardation, and later infertility. This is typical for boys with Klinefelter syndrome (chromosomal complex XXY), girls with trisomy X (karyotype XXX), and girls with Shereshevsky-Turner syndrome (karyotype XO). The reasons for non-disjunction of chromosomes have not been fully elucidated. Of great importance is the disruption of endocrine homeostasis in the pregnant woman. B. N. Klosovsky (1962) subjected the parents of a number of children with chromosomal abnormalities to a thorough study and found that almost all the mothers of these children had ovarian dysfunction, and some of the fathers also suffered from diseases that could affect the usefulness of the gametes. It is known that children with Down syndrome are more often born to older primiparous women. The tendency for chromosome non-disjunction during meiosis and the first divisions of the zygote increases with the age of the primiparous woman. This can be facilitated by a violation of the functional structure of the ovaries, the inferiority of the follicular epithelium and gametes, the slow passage of the gamete through the genital tract, and delayed fertilization. weakness and late development of the decidual reaction of the uterus, delayed implantation, insufficiently active blood circulation in the endometrium. An illustration of such pathogenesis of fetal developmental disorders is the Veatch experiment - delayed fertilization of the "aging" amphibian egg, which leads to the appearance of two-headed axolotls with additional tails and atypical tissue growths. Hormonal homeostasis is highly likely to be disrupted in an elderly woman's body, and this may be what causes non-disjunction of chromosomes during meiosis. Children born to women over 40 giving birth for the first time make up 3.5% of all children, but they account for 39.5% of all cases of Down syndrome. They also have other developmental defects caused by chromosomal aberrations. It has been established that Down's syndrome is not uniform both clinically and cytologically; this can obviously explain why children with Down's syndrome are also born to young primiparous mothers. The cytological difference is that in some cases trisomy of the 21st autosome is found, while in others trisomy with translocation of the extra 21st chromosome onto the 15th is found. [16] 17, 18th pair of chromosomes. Down syndrome of translocation origin is usually not related to the age of the mother's body, and children with such a karyotype are born to young mothers. The probability of a repeated birth of a child with Down syndrome in the case of trisomy of the 21st autosome is 1:1000, while with translocation of the extra 21st chromosome the probability is much higher - 1:3. There are data in the literature on the birth of children by women suffering from Down syndrome, and some of the children born inherit trisomy on chromosome 21. Non-disjunction of chromosomes, which is the cause of Down syndrome, can also occur in the initial stages of zygote division. As a result, some of the embryo's cells will have an abnormal set of chromosomes, while the remaining cells will retain a normal karyotype. This phenomenon is called mosaicism, which also occurs when the sex chromosomes do not separate. In case of mosaicism of the chromosome set on the 21st pair of chromosomes, it is possible to have children with all the external signs of Down syndrome, but with normal mental activity, allowing them to study in a normal school. Their karyotype is characterized by the ratio of the number of cells with a normal number of chromosomes to the number of cells with trisomy on the 21st autosome as 10:3. There is tissue incompatibility between the mother and the fetus, since half of the genetic set is received from the father. There are several hypotheses to explain the reason for its non-rejection, but the mechanism of this phenomenon remains unclear at present. [17] There are certain reasons to believe that habitual spontaneous abortions in women may be associated with sensitization of them to fetal antigens received from the father.

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