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## **Immunopathological changes in case of the diabetes of the first type. The impact of the mother's diabetes of the first type on the emryogenesis and fetogenesis of the fetus (Literature review, part II)**

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### **Abstract**

In the following article we have presented main risk factors of the development of the Diabetes Mellitus of the I type, as well as modern statistical data towards its correlation in a structure of the disease. We have revealed main markers of the disease, connected with the HLA system. We have also considered leading links in the pathogenesis of immunodeficiency development in case of patients with the Diabetes Mellitus of the I type relatively to the duration of the disease, presence of vascular complications as well as number of insulin units per day. We have provided clear criteria towards changes in the T-lymphocytes populations, what is prescribing changes in the helper-suppressor ratio. In addition, we have postulated that the autoimmune disorders, which are typical for the Diabetes Mellitus of the I type (DM of the I type) are leading to the increase in a number of apoptotically altered forms of T-lymphocytes, what is contributing to the deeping of changes in the immune system. Authors have studied main features of the interleukin-producing activity in case of patients with the

DM of the I type. Namely: increased number of pro-inflammatory interleukins on the background of decrease of anti-inflammatory ones. The precise analysis has revealed, that there are circulating immune complexes in the blood of patients with DM of the I type, which are leading microcirculation' disorders. The alterations, that were postulated and described relatively to the organism of patients with DM of the I type, are indicating deep disorders in the immune system and the morphological features of the thymus has to be studied, as far as the thymus as a central organ of the immunogenesis in case of fetuses from mothers, who are suffering from the DM of thr I type, in the aim of development of immunodeficiency in patients.

Alongside with the description of changes in the immune system in case of patients with the DM of the I type, in the following article we have provided a scientific views on changes in the embrion- and fetogenesis of the fetus under the influence of mother's DM of the I type. In addition, we have described morphological features of the placenta structure in case of this pathology, as well as pathomorphological changes in the strucutre of internal organs of fetus under the influence of this pathology in the mother's organism. It was postulated, that in case of children, who were born from mothers, who are suffering from the DM of the I type, there is a syndrome of diabetic feto- and embryopathy, which is developing and leading to the poliorganic failure in the subsequent ontogenesis.

**Key words: Diabetes Mellitus; pregnancy; embryogenesis; fetogenesis; fetus, thymus.**

**Імунопатологічні зміни при цукровому діабеті I типу. Вплив цукрового діабету I типу матері на ембріогенез та фетогенез плода (огляд літератури, частина II)**

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В статті наведено основні фактори ризику розвитку цукрового діабету I типу (ЦД), а також сучасні статистичні дані стосовно співвідношення їх у структурі захворюваності. Виявлено основні маркери хвороби, пов'язані із системою HLA.

Розглянуто ведучі ланки патогенезу розвитку імунодефіциту у хворих на цукровий діабет I типу відповідно до тривалості хвороби, наявності судинних ускладнень та кількості одиниць інсуліну за добу. Наведено чіткі критерії щодо змін в популяціях T – лімфоцитів, що обумовлюють зміни в хелперно – супресорном співвідношенні. Також показано, що аутоімунні порушення, характерні для ЦД I типу призводять до підвищення кількості апоптозно змінених форм T-лімфоцитів, що сприяє поглибленню змін в імунній системі. Авторами вивчено особливості інтерлейкін – продукувальної активності у хворих на ЦД I типу. А саме: підвищення кількості прозапальних інтерлейкінів на тлі зниження протизапальних. Глибокий аналіз виявив, що в крові хворих на ЦД I типу з'являються циркулюючі імунні комплекси, що призводять до розладів мікроциркуляції. Зміни, встановлені і описані в організмі хворих на ЦД I типу, свідчать про глибокі порушення в імунній системі і потребують вивчення морфологічних особливостей тимуса, як центрального органу імуногенезу, у плодів від матерів, хворих на ЦД I типу з метою розробки дієвих заходів лікування та профілактики розвитку імунодефіциту у хворих осіб.

Поряд із описом змін в імунній системі хворих на ЦД I типу в статті наведено науковий погляд на зміни ембріон- та фетогенезу плода під впливом ЦД I типу матері. Описані морфологічні особливості будови плаценти при даній патології, а також патоморфологічні зміни в структурі внутрішніх органах плодів під впливом даної патології матері. Встановлено, що у дітей, народжених від жінок, хворих на ЦД I типу, формується синдром діабетичної фето- або ембріопатії, що призводить до полі органної недостатності у подальшому онтогенезі.

**Ключові слова:** цукровий діабет; вагітність; ембріогенез; фетогенез; плід; тимус.

Diabetes of the first type - is a chronic autoimmune disease, in time of which occur progressive selective destruction of beta-cells, that are producing insulin in the islets of Langerhans of the pancreas [1, 2, 6]. It is well-known that the number of incidents of diabetes of the first type among children and adults increases steadily and, what is more, it engages a leader place among endocrine pathology in the world. Heredity plays without doubts a leading role in developing of the disease [3, 5]. Such factors like obesity, stress effects, viral infections, elderly and senile age, expressed atherosclerosis, toxicity, hypodynamy, pregnancy

- could be the first cause of the disease's development. But, in addition, it can also be trigger for disease's development for those people, who have a predisposition. [3, 6]. We should also pay attention on the fact, that the pathological influence of triggers factors is also predetermined by environment. Thus, the structure of children' morbidity in the Kharkiv region in the period of 2021 was dominated by children, who live in the city. Among the city population prevalence of the disease was 0,8 per 1000 people, when among the villagers around 0,4 per 1000 people [4]. Moreover, it is considered, that the frequency of registration of endocrine disease among children, who live in rural areas, higher, than among children, who live in urban ones [5, 6, 7]. It os also well-known, that women suffer from diabetes of the first type more often than men [8]. Increasing of the number of incidents of disease can be observed clearly from east to west and from north to south. Moreover, this feature is not related to social or environmental factors [9, 10]. The risk of incidence of the diabetes is increased in case of children, whose parents suffer from diabetes, and this risk can be counted like 60% - 100% [11]. The probability is decreased in such case, if just one of parents has this disease, and then it can be count like 30%-50%. All monozygotic twins are concordat as well. It means, that: if one of them is sick, this illness will be developed in the organism of the second, too [12]. The risk of disease's developing in the organism of siblings of patients with diabetes is significantly higher, than in the organism of children, who have sick parents. In addition, the higher level of incidence can be observed among children, whose parents have this disease. And, what is more, this rate will be higher, than in case with children, whose mothers have diabetes [13]. According to our observation of the age categories of patients we can say, that this disease is distributed in such way: 40% of cases is observed among children in the age till 15; 30% - in the age from 15 to 34; after 35 the level of the risk of disease's development is also 30% [14]. Modern statistics are defines the following major factors of disease's development and its relationship with the structure of morbidity in such way: social factors given 70%, 20% - is a genetic load, 10% - is the state of medical care [15].

As it was mentioned above, diabetes - is a multifactorial disease. And the significant role of its developing play mostly heredity inclinations. The priority genetic marker of the diabetes is system HLA, namely - such haplotypes as HLA-DR, HLA-DQ [16]. This is because of the fact, that the genes of this system and their products are not only markers of this disease, they are also a leading element of pathogenesis of the diabetes of the first type [17]. the set of genes of the HLA-system involved in the control of the immune response in

antigenic recognition and regulation of interaction of immunocompetent cells of the organism. Therefore, the slightest changes in the structure of haplotypes can lead to the development of the pathological conditions, including autoimmunization. The main role in triggering of the autoimmune process is given to HLA antigens - proteins, the expression of which can be observed on the surface of immune cells. Accurately these compounds can represent immunodominant peptides of the foreign protein to T-cells in the aim of detection and start the chain reaction of the immune response [18]. normally, the foreign' recognition is a background of an adequate immune response. If in the genotypes specific locuses of the HLA genes are presented, that encode HLA proteins, that contain identical plot with some pathogens, the immune attack against them is extends to the cells of its own body. Proteins, that are encoded by genes of loces HLA-DR and HLA-DQ, can participate in the process of autoimmunization independently of each other, and, what is more, they can complement each other with different effects. Among the all known genetic markers the most important in developing of diabetes are genes of the HLA area on the chromosome 6p21.3 (IDDM1) [19]. Numerous studies have shown that the tendency of development of the diabetes of the first type is defined by the presence of two variants of genes in the genotype form the DRB1 \*01, \*03, \*04, \*08, \*09, \*10, as well as allelic variants of DQA1\*0501\*0301, DQB1\*0201\*0302 [20]. The presence of just one gene in the genotype reduces the risk of the disease' development [21]. Children and close relatives of people, who suffer from diabetes of the first type are, at the same time carriers of the abnormal genes. In the number of research works was shown, that the homozygous states for HLA DRB1 \*3, DRB1 \*4 and heterozygous alleles of the same condition dramatically increase the likelihood of the disease's development. At the time, when the heterozygous state of this alleles with other markers, which are different from HLA DRB1 \*3, DRB1 \*4 reduce the risk of diabetes' of the first type development [22]. Near the data about the role of halotypes, there is a confirmation of the fact, that the association of the alleles in consist of DR and DQ (and of each gene over the 30), may also cause the protective action for disposition, development and severity of diabetes. We should definitely note also the presence of two major classes of HLA system: I and II. Molecules of each of them are represented in subclasses. Thus, the first class is represented by HLA - A, - B, - C, and the second one - by I - HLA-DR, -DQ i DP subclasses. Between HLA-I and HLA-II subclasses there is a fundamental difference, the background of which we can observe in the source of antigens [23]. HLA-I-dependent presentation is a

liberation from unnecessary, waste material of cells, which occurs in cells continuously and throughout of its life. HLA-II presentation includes the elimination of foreign proteins from the outside surroundings. HLA-dependent presentation has a clear focus. And this is because of the fact, that molecules of the first and the second classes provide an alternative supply of antigens: the first class - CD8, and the second one - CD4 lymphocytes [24]. We also know that the tissue's belonging to the organism, because of the antigen HLA-DR6, defines an adequate immune response. Whereas the class presentation of antigens HLA B8, DR3, DR4, which cause a relative hypofunction of T-suppressors and weakening of the elimination of immune complexes, is connected with developing of the primary immunodeficiencies as well as autoimmune systemic and autoimmune endocrine diseases [25]. Thus, we can say, that, the violation from the side of the second class of HLA system leads to disruption of the immune response to the bringing an antigen, which promotes development of the autoimmunization.

From all that we said above we can make a conclusion, that the violations of the second class of the HLA system provide an autoimmune response, which is mediated by T-cells' link of the lymphoid population. Therefore, it is advisable to verify and assess the role of the immune system in the development of the diabetes as a autoimmune disease. As a confirmation of the crucial role of the immune system in the pathogenesis of the diabetes could be experimental data about impossibility to induce diabetes in the organism of mice, which did not have thymus, as well as in the organism of mice, that were treated by immunosuppressants [26]. The role of the immune system can be confirmed also by the fact, that clinical manifestation of the disease is preceded by a long latent period without symptoms, the period of the hidden autoimmune aggression. And this period, as a continue, could be confirmed by the presence of autoimmunization markers [27]. To the group of this markers we can include antibodies to insulin, beta-cells of the pancreas, and insulin receptors [28] modern studies have shown, that the autoantibodies to islet pancreatic cells are specific markers of the autoimmunization in case of diabetes [29] it is proved that in the preclinical stage of diabetes we can see changes in the immune system, including production of the antibodies, that lead to destruction of the insulin-secreting cells of the pancreas. The action of the antibodies is realized in the autoimmune insula, which develops gradually; destruction of the endogenous insulin and desensibilisation of the receptors [30]. In the implementation of the autoimmune insula the most important role is played by macrophages, T-helpers, T-cytotoxic-suppressors and natural killer cells [31]. If on the surface of the beta-cells presents

an antigen, it can be recognized by T-helpers. And it will cause of trigger of the cascade of immune reactions as well as it will provide the direct cytotoxic effect on cells of the pancreas. Besides, clones of cells, we told above about, produce a large amount of cytokines, that stimulate beta-cells to express on the surface of the protein of the HLA-class, what will be incentive for the development of the new wave of the immune reaction, which will be directed on the damage of the beta-cells [32]. Producing of the antibodies to insulin receptors leads to their desensibilisation. And, as a result, receptors do not react on the presence of insulin. According to the data, that the insulin has a strong immunomodulate effect, the destruction of the insulin leads to the development of the secondary immunodeficiency state, the main features of which we should make out [33]. We can say, that the main feature of the immunodeficiency in case of the diabetes a imbalance of the subpopulations of the lymphocytes as well as changing of their functional activity [34]. Here we should say about: reducing of the number of mature forms of lymphocytes CD-3, CD-4, near the fact of increasing the number of immature Thy-lymphocytes, CD-8, CD-38 forms [35]. Quantitative changes of the staff of lymphoid population leads to decreasing of the immunoregulatory index (the helper-suppressor-ratio) [36]; as well as to inhibition of the reaction of the blasttransformation of the lymphocytes [37]. An autoimmune character of the disease leads to uneven nature of sensitivity to apoptosis CD4 and CD8 cells [38]. Thus, the most undergo to apoptosis are CD8, what will lead to increasing of the autoimmunization in case of such pathology. In T-cells population we can say, that the number of activated cells is increased. And we tell accurately about cells, which express receptors to CD30 on their surface. As it is well-known, the molecule of the CD30 is the marker of cells, which have to yield to apoptosis [39]. However, the number of apoptotically modified cells varies depending on the severity and duration of the disease [48]. Therefore, the number of CD95 lymphocytes can be uneditable, or it can be higher than normal as well. In the modern literature we can see data about reducing the number as well as about weakening of the cytotoxic and secretory function of natural killers in organism of people, who suffer from diabetes [46]. Along with the small increase of the number of CD8 cells in the lymphoid population, we can point also a defect of the antigen-specific and antigen-nonspecific function of suppressors-cells. Lack of the cell-suppressors function in this case plays a special role in the development of the autoimmunity and in the increasing of the cytotoxicity against  $\beta$ -cells of the pancreas [40].

Features of the interleukin-production activity are described. During the credible strengthening of the production of IL-1,2, the rates of IL-4,6,10 of the past did not change and, in some cases, they are reduced [41]. It is well-known, that the IL-1,2 are pro-inflammatory, on the one hand, and, on the other hand, they stimulate autoimmune processes. While the IL-4,6,10 have an opposite effect [47]. At the same time, in the organism of patients with diabetes we can note an increasing the level IL-8, what can tell about development of the microcirculatory disorders [42].

An important role in the patogenesis in case of diabetes of the first type as well as in the development of complications of the disease play circulating immune complexes (CIC). As you know a slight increasing of the number of CIC in blood leads to the formation of their deposits in tissues, to increased platelet aggregation and adhesion, These processes, from their side, lead to disruption of the blood microcirculation, to vascular occlusion as well as to damage or necrosis of tissues. Recent studies confirmed an increasing of CIC to 82% in the organism of patients with diabetes of the first type, in 1,5 times comparing to their number in blood of healthy person, and on the later stages of the disease as well. It means, that, as a result of the autoimmune disease, CIC plays a leading role in the development of the complications of the diabetes of the first type [43].

Thus, the literature's data indicates severe immune disorders in the organism of people, who suffer from diabetes of the first type. Due to that - the assessment of the state of the central body of the immunogenesis is reasonable, it means the assessment of the state of thymus of fetuses from mothers with diabetes of the first type.

Physiological stream of the pregnancy carries out as a result of the dynamic functioning of the immunoregulatory mechanisms in the organism of pregnant, that ensure the preservation of the fetus as a allograft in the organism of mother, and then his rejection in the process of birth [44]. In the accomplishment of the immunoregulation thymus plays a particularly important role. I.F. Labunets, Y.A. Grinevich, E. V. Kohanevich studied the activity of thymus during pregnancy, based on the content of the blood serum thymic factor (TSF) [45]. During this studies authors came to conclusion, that during the first trimester of pregnancy the level of the TSF is increased. During the second trimester this level is slightly elevated or normal one. In the third trimester this level is sharply increased and it reaches its maximum before the birth. In the literature there are different types of data about penetration of TSF through the placental barrier, about what could evident the law weight of the



hormones - 857D [46]. Thus, we can conclude, that during pregnancy is activated an an endocrine function of the thymus. As the fetus is developing, when appears a secretory activity of its thymus, the hormones of gland become a significant part of mother's TSF. Because of the fact, that the thymus is a central organ of immunogenesis, we can suggest a biological nature of increasing of the functional activity of thymus during pregnancy [47]: it means, supporting of the certain level of all subpopulations of T-lymphocytes, what ensures safety of the fetus in the organism of mother; as well as regulation of the suppressor and contrasuppressor cellular and humoral factors in the dynamic of pregnancy development [48]. The activation of thymus' functions depends on the increasing of the level of glucocorticoids and estrogen at the time of the first and the third trimesters of pregnancy (1<sup>st</sup> and 2<sup>nd</sup> half), which could be characterized as well because of the activation of the gland's function [49]. Thus, the thymus is an important link in providing physiological processes of pregnancy and birth. Various diseases of the mother lead to dysfunction of the thymus, causing at the same time a violation of the process of the gestation, increasing the level of immune complexes by improving the macrophages activation, changes the content and ration of different subpopulations of T-lymphocytes [50]. Considering the literature data about development of the diseases of the similar organs and systems of mother and fetus [51], we can establish, that the pathological states of thymus of mother could cause the violations in the immune system of the fetus and, it is possible, it can plays a role in the process of violation of the embryogenesis of fetus as well as violation in the thymus' function of the newborn [47, 51].

To the number of the diseases that have a negative influence on the course of pregnancy and childbirth we can include the diabetes mellitus of the first type (DM) [52]. The literature data indicates a cyclical course of the diabetes of the first type during pregnancy [53]. Because of it we can separate three stages of the pregnancy, during which we can observe changes in the status of mother. The first period of pregnancy (lasts approximately till 16<sup>th</sup> week) can be characterized by reducing of the demand of insulin, what can be a sign of the improvement of the disease process because of the hypohlickemic influence of the fetus [54]. it is known, that because of the enhanced diffusion, glucose passes through placental barrier and it is utilized by fetus many times faster, than in the body of adult. Therefore, this period can be characterized by the development of hypoglicemic states [55]. It is also due to the increasing of the glucose utilization, increasing of the fat reserves in the mother's organism under the influence of the chorionic gonadotropin, that activates glycolitic enzymes

[50]. Improvement of the mother's status can be also connected with loss of carbohydrates during toxicosis of the first half of pregnancy; as well as with the influence of chorionic gonadotropin on the activity of glycolitic ferments [43].

From the 16<sup>th</sup> to 28<sup>th</sup> week, on the 2<sup>nd</sup> stage of the pregnancy, we can say, that this time is characterized by deterioration of the disease and by the onset of decompensation of the carbohydrate metabolism, what can be explained by the contrinsular influence of placenta's hormones [44] as well as by increasing of the fats using in the conditions of the higher energy expend of the mother's organism [14]. All of this lead to the increasing of the glucose level as well as of the insulin resistance, what requires increasing of the insulin dose [28].

Third period of the pregnancy (after 28 weeks) can be characterized by more stable course of the diabetes. Due to the fetus' hyperinsulism we can note decreasing of the need of exogenous insulin [11]. Considering the literature data, which tells, that the insulin penetrate from the mother's organism to the fetus and vice versa in small amounts, the compensation of the mother's status at this period realizes due to the hypoglycemic effect of the fetus (free glucose diffusion from mother to fetus) [16].

As it is well-known, the endocrine status in the early neonatal period can be characterized by an adjustable balance of mother's hormones and by the own hormones of fetus and newborn [14]. Adaptive reserves of the fetus and newborn depend on the maturity of its endocrine system. Violation of the endocrine system formation in the antenatal period could become a basis of the development of endocrine diseases in future [13, 25, 32]. Severe cardiovascular and metabolic disorders in the organism of pregnant in case of diabetes of the first type could cause the violation of the formation and differentiation of fetus' vital organs and tissues, what, in the process of ontogeny, will be manifested by violation of their structure and function [36].

In the earliest stages of pregnancy vascular and metabolic disturbances, which are characteristic for diabetes of the first type, could be observed in the fetoplacental complex and, what is more, they can occur in future as a violation of the fetal development [29]. In the current publications different features of the fetoplacental complex in case of diabetes of the first type are described. Different changes of all structural elements of the fetoplacental complex attract an attention. And they can be caused by phenomenon of violation of the blood circulation, alteration, swelling and sclerosis [34]. Microscopic research of the placenta indicates the discrepancy of the placenta's weight and the term of gestation (increasing or

decreasing of the placenta's weight). Moreover, in this placentas we can observe more often paracentral attachment of the cord, multiple heart attacks, calcifications [19]. Violation of the placenta's maturation is the most characteristic feature for diabetes of the first type. There are two different types of the violation of maturation: the slow type, which can be observed more often and another one, early maturation [39]. In the slow type of violation, which can be note mostly in case of severe or middle stage of diabetes of the first type, with tendency to decompensation and severe vascular disorders, we can observe decreasing of the fetus' weight. Premature placental maturation, by which can be characterized diabetes of the first type of the mild stage, leads to macrosomia [34]. The correlation of changes in the bodyweight of fetus and severity of the diabetes of mother can be confirmed by literature data about the fact, that the diabetes of the first type in the severe stage with presence of serious vascular complications leads to changes in the fetoplacental complex from the 26<sup>th</sup> week of the fetal development; in case of the diabetes of the first type in mild stage all this changes are developing only since 30<sup>th</sup> week [19, 25]. Microscopically our attention can be attracted by the fact of the increasing of the area of the fibrinoid in inter villi spaces, dilatation of capillaries, large area of necrosis of the maternal area of placenta, as well as desquamation cytotrophoblaste with exposing of vessels [18]. In capillaries of villi as a manifestation of the microcirculation violation we can declaim a phenomenon of sludging of prolific erythrocytes in villous capillaries [46]. Dopplerometrical research of the blood circulation in arterial vessels FSP indicates the increasing of the vascular resistance in curved and spiral arteries, which increases the expression of vascular disorders in case of diabetes [35, 42]. Vascular changes lead to violation of placenta's hormones production [7, 8]. As it is known, fetuses and newborns with low maintenance of maternal and placental hormones are differed by decreasing of the level of adaptive possibilities in the postnatal period [7, 8]. To sum up, all features of the fetoplacental complex in case of diabetes of the first type, that were described above, we can say, that cardiovascular and metabolic disorders in case of diabetes of the first type favor the development of the fetoplacental insufficiency, which is impacted extremely adverse on the fetal development as well as the fact, that it is an unfavorable prognostic sign regarding to postnatal newborn's adaptation and, what is more, it leads to increasing of the perinatal losses [20, 23].

During the pregnancy, because of the diabetes of the first type, in the organism of fetus can be formed a syndrome, which includes a couple of malformations of development

and which is called “diabetic ebriopatia” (DE) [36]. As main factors, that could contribute DE we can name genetic factors, teratogenic effect of the insulin on the fetus and its antagonists, vitamin and hormonal violations in the organism of pregnant woman, who suffers from diabetes of the first type, vascular changes of the placenta in case of diabetes, chronic hypoxia of mother and fetus [16]. The main role in the pathogenesis of the DE is played by lack of the insulin and lability of the daily glucose rhythm in the organism of pregnant, who suffers from diabetes of the first type [12]. Changes in the glucose concentration lead to increasing of the level of contrinsular hormones and non-hormonal antagonists of the insulin in the organism of pregnant. This hormones and antagonists leads to diabetogenic effect, what consequently increases lack of the insulin, and what leads as well to the acute inhibition of the tissue respiration in the bud of one of the organs of fetus, that are, at those times, in the state of the most high mitotic activity and what, finally, leads to formation of the development’s malformation of one of the organs [11].

The fetus’ disease in the last fetal period, in the response on the activity of maternal diabetes is called “diabetic fetopatia” (DF) [41]. As the background of the DF we can name such factors as feto-placental insufficiency, hormonal placental dysfunction, lack of insulin, fluctuations in the glucose rhythm in the blood of pregnant [24, 50]. With labile course of the maternal diabetes could be connected mobilization and hyperfunction of the pituitary-adrenal system of the fetus, that are directed on the stabilization of the glucose maintenance in blood of mother and fetus [7, 19]. In the child’s organism from mother with satisfactory compensation of the DF develops a relative inter-pancreatic insulin insufficiency, which is caused by the inactivation and ruining of the insulin outside of fetus’ pancreas by his own as well as by maternal antagonists of the insulin. In the decompensative course of the diabetes of the first type in the mother’s organism develops a secondary pancreatic insufficiency of the insulin due to overexertion exhaustion of the insulin secretion from the side of fetus’  $\beta$ -cells (the relative pancreatic insufficiency in the organism of fetus is increasing because of the forced participation in the compensation of the mother’s diabetes [33, 48]. Fetuses and newborns with DF are very like to each other. Their resemblance can be described on the background of such phenotype features as puffiness, moon-similar fare, short neck, float eyes, common pastosity, expressive shoulder girdle, hypertrichosis, overhanging forehead, bright-red skin, long torso, short limbs [16]. Moreover, the more difficult is the state of children in the period birth and in following days, the more signs of the DF will be expressed [26, 31]. The

main and the most threatening for the children health and lives, who was born from mothers with diabetes of the first type, could be such features of the DF as: congenital malformations, fetal size changing (micro- and macrosomia), uneven growth of different organs and systems, respiratory distress-syndrome, hypoglycemia, polycythemia, hyperbilirubinemia, hypocalcemia, increased risk of developing of the diabetes of the first type [11]. The severity of symptoms, that were described above, is a directly proportional to the severity and duration of the disease, unstable compensation as well as to the age, when the mother fell ill in diabetes of the first type [17]. The most significant violations can be observed in the organism of newborns with severe stage of the disease and with duration of the diabetes in average of more than 5 years. The duration of the disease explains the frequency of vascular lesions in this group of women, what causes an intrauterine suffering of fetus (intrauterine hypoxia), complications of the pregnancy by polyhydramnios, infections, as well as the severe course of the childbirth because of the sustainable weakness of birth activity [22, 48]. Most of children, whose mothers have only early stages of the disease, born until the term. In the situation of such children with functional immaturity of different systems in the period of being a newborn, we can observe in a high frequency different “disadaptation syndrome”: edematous, icteric, hemorrhagic, violation of the brain blood circulation, respiratory distress syndrome, cardio-vascular disorders [53]. In case of women with diabetes of the first type on the latest stages there is a high rate of operational interventions in childbirth and childbirth by caesarean section [44]. Among infants, who was born as a result of caesarean section, the severe condition after birth can be observed in two times more likely, than in case of children, who was born naturally [23]. The main cause of the increased teratogenicity in case of the diabetes of the first type can be decompensation of the disease during pregnancy. It is known, that the organogenesis occurs the most actively in the first 8-10 weeks of pregnancy as well as, we can say, the the biggest number of congenital anomalies are formed in this period, too. Fetus produces his own insulin since the 9<sup>th</sup> week of the fetal development. The mother’s insulin does not across through the placental barrier and, because of it, in the first 8 weeks of pregnancy, fetus is not protected from hyperglycemia in case of decompensated diabetes of the first type in the organism of mother [22]. Teratogenic influence of the hyperglycemia is described by a lot of researchers, so it could not be doubts [39]. V. Olyjnik suggests such way of realization of the influence of hyperglycemia on fetus: in conditions of the glucose excess changes the structure of collagen, what consequently leads to violation of the process of

growth and division of cells. Mutagenic effect of products of the free radical lipid oxidation leads to the violation of metabolism of mioinositol and the arachnoid acid, what, finally, leads to shortage of prostaglandins in the embryo tissue during ontogeny. Author, by the referring to experiments, which were described in the literature, shows, that one of the primary agents, that trigger development of the congenital pathology, in case of the mother's diabetes of the first type, can be a tumornecrotical factor - cytokin, which is realised in a high quantity by epithelium of the uterine. To abuse of the emryogenesis can lead as well cetoacydosis of the first weeks of pregnancy as well as zinc deficiency, which can be observed in case of the diabetes of the first type [6, 8].

In case of diabetes of the first type of pregnant, one of the most frequent manifestation of the DF can be macrosomia (increasing of the fetus' weight) [50]. One of the main reasons of the macrosomia's developments is a hyperglycemia of mother, which is accompanied by hyperglycemia and hyperinsulinemia of fetus [22]. Increasing of the fetus' weight in case of the diabetes of the first type of mother is provided mainly due to the fat, but, at the same time, the amount of bones and muscles is not differ from this indicators of children from healthy mothers [7]. Insulin, because of having features of the anabolic hormone, influence increasing of the glycogen synthesis and, as a result, increasing amount of fat. Free fatty acids and ketone bodies, that, in case of presence of the ketoacidoosis, penetrating trough the placental barrier, intensify a lipogenesis [5]. Frequent hypoglycemia could stimulate a somatotropin secretion, what increases number of fat cells or, due to the activation of insulin-like growth factors - somatomedin. In the genesis of the fetus' macrosomia in case of the diabetes of the first type, the role of the excess of glucose corticoids is not excluded. This excess is provided by increased germinal zone of adrenal glands and by obese of mother as well.

The body weight of newborn can be as well excessive as insufficient. According to the literature data, in 50% cases of mothers with diabetes of the first type, children born with normal weight and, depending on severity of disease course and manifestations of vascular complications, the body weight of newborn decreases (as a result it would be less, than 3kg, because of the fetal hypoxia) [18].

Hyperinsulemia of fetus in the second half of pregnancy become a main reason of the uneven growth of fetus' organs and systems, tissues' sensitivity of which is not the same [17, 18]. Moreover, increasing of the weight of one group of organs (here we can tell about heart, liver, kidneys, adrenal, islet pancreas device) is accompanied by underdevelopment of another

ones (brains, thymus, bronchial-pulmonary system) [52]. This discrepancy is more expressed, if it is more heavy stage and severe of the diabetes of the first type. Hypertrophic cardiomyopathy in the organism of newborn is characterized by heart failure, which manifests in first hours of life already and, consequently characterizes by rapid growth of itself. Microscopically we can observe increasing the number of both cores as well as sarcoplasm of the cardial muscle fibers [24].

In the pancreas we can observe near the increasing of number and size of Langerhans islets, as a result of hyperplasia of  $\beta$ -cells, different dystrophic changes: vacuolization, degranulation of cytoplasm, nucleus pycnosis. This changes, consequently indicates depletion of this cells' secretion [10, 11]. According to the modern literature such changes in the pancreas are caused by the maternal diabetes of the first type, and could be observed in 80% of newborns, and, as a result, can be defined as "macropolinesia" of the pancreas [11, 19].

In the endocrine glands could be observed different hyperplasia and hypertrophy processes: hyperplasia of the acidophilus cells of the anterior pituitary, colloidal disquamous of the thyroid gland, as well as adrenal's adenoma [10, 46]. As a confirmation of negative effects on fetus from mother, who suffers from diabetes of the first type, could be large pockets of myeloid erythropoiesis in liver, kidneys, myocardium, pancreas and salivary glands, incomplete nephrogenesis (microcysts in the cortex of the kidney), absence of lymph follicles in the spleen and in the cortical substance of lymph nodes, underdevelopment of elastic tissue of lung [19, 38]. These features of fetus' immaturity, which is a violation of the tissue differentiation of organs, are a consequence of the damage effect on fetus of the diabetes of the first type as well as the fact, that it is a consequence of influence of chronic hypoxia because of the placenta's changes in the women's organism, who suffers from diabetes of the first type [42, 50].

As a result, despite of the hyperinsulinemia, in the fetus' organism could be observed a lack of insulin, what consequently leads to development of clinical and morphological features of the fetal diabetes. These features include diffuse fatty infiltration of liver, decreasing of the glycogen reserve in myocardium, liver and skeletal muscles of fetus, as well as middle infiltration of renal tubules by glycogen, what, as a result, could indicate hyperglycemia of fetus. As a feature of the fetus' diabetes of the first type could be generalized microangiopathy, which is shown by thickening of vessels' walls of micro-vascular course of

kidneys, skin, retina due to the proliferation of endothelium and peritelyum, as well as due to the significant wist and ectasy of vascular bed.

In the background of the distress-syndrome in organism of fetus from mothers, who suffer from diabetes of the first type, could be lagging of lung tissue maturation and pulmonary vascular system [27, 32]. Functional failure of the bronchial-lung system is more expressed in cases of newborns from mothers, who suffer from diabetes of the first type in severe stages and with predisposition to decompensation and, finally, it appears by delay of synthesis and destruction of sufractant [28]. For the newborn from mother, who suffers from diabetes of the first type, the most dangerous could be hypoglycemia, that may develop in first hours of life [47]. it could adversely affects on the state of central nervous system of fetus and, in addition, it could be a cause of the lag in mental development of child if future [13, 37]. The main role in the hypoglycemia development plays the hyperfunction of hyperplastic and hypertrophied insular apparatus as well as high capacity of the glucose uptake [41]. An important meaning is attached also to absence of compensatory possibilities in organism of newborns from mothers. Who suffer from diabetes of the first type: here we can tell about such facts, as, for example, hyperinsulinemia is not balanced by adequate activation of contrinsular hormones (glucose corticoids, catecholamines, glucagon). Thus, in the organism of newborns, that was born from mothers, who suffer from diabetes of the first type, level of the glucagon reaches to the normality till the end of the first day of life, while the same level in case of newborns from healthy mothers normalizes in first two hours of life. Therefore it is creating a situation, when in the organism of newborn there are reserves of glycogen, as a result of long hyperinsulinemia, but they cannot be used to fight with hypoglycemia because of the lack of glucagone and reducing the sensitivity to it because of the immaturity of fermental systems of of liver [35].

As a consequence of hyperinsulinemia could be as well a polycythemia due to the increased glucose consumption by the excess of red blood cells [26]. The leading factor of pathogenesis of polycythemia development is a stimulative effect of insulin, which increases the production of erythropoietin, as well as a chronic hypoxia of fetus as a stimulator of erythropoiesis.

In the organism of newborn from mothers, who suffer from diabetes of the first type, more often can be observed hyperbilirubinemia, than in organism of newborns, who was born from healthy mothers. Hyperbilirubinemia is clinically evident by jaundice and, it is a result of



hemolysis of erythrocytes in case of polycythemia and immaturity of fermentation systems of liver [11, 33].

Hypocalcemia, which is often combined with hypomagnemia, could be found not so rare in case of newborns, that was born from mothers, who suffer from diabetes of the first type. As manifestations of symptoms, that were described above, could be neurological disorders in organism of infants and children [37].

Hypocalcemia could be a reason of the fetal or newborn's death, because it leads to violation rhythm of cardiac arrhythmia or cardiac arrest.

The risk of diabetes development in the organism of fetus depends on the stage of diabetes in the organism of mother. In case of presence of diabetes of the first type in the organism of one of parents this risk reaches from 7% to 10% but this risk could dramatically increased in case of presence of the disease in the organism of both parents (30%). If mother is sick on the IDDM, the risk of the diabetes development in the organism of fetus reaches to 30%. Finally, in case of presence of IDDM in the organism of both parents, this risk reaches even to 60 % [5].

Thus, the diabetes of the first type of mother affects as well directly as indirectly on fetus, leading to the high rate of perinatal mortality, formation of the DF and DR, complicated course of the neonatal period and, additionally, it becomes a factor for increasing the risk of anomalies development in different organs and systems as well as of their disease in the period of postnatal ontogenesis [21, 29, 35, 42].

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