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Immunohistochemical features of the structure of fetuses' uterus with a gestational term of 21-28 weeks from mothers, whose pregnancy is complicated by chronic infection of the lower genital tract

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Abstract

The relevance of the following article is prescribed by the growing number of perinatal mortality and morbidity among newborns due to the mother's chronic infection of the lower genital tract (HILGT). It is commonly known, that HILGT contributes to the delay of the fetal development likewise is often manifested by the violation of internal organs and systems implementation. One of the most acute topic is the the fetus' reproductive system in ther early gestation terms. However, the immunohistochemical features of the fetuses' uterus structure with the gestational term of 21-28 weeks from mothers with HILGT on the current stage of the medical science development have not been described yet. The aim of the current research is to identify immunohistochemical features of the fetuses' uterus structure with the term of gestation of 21-28 weeks from mothers, whose pregnancy is complicated by HILGT. Material of the research: 25 fetuses from mothers, whose course of pregnancy was physiological (group of comparison) as well as 25 fetuses from mothers, whose pregnancy was complicated by HILGT (main group). All fetuses had died intranatally, as a result of

acute uterine placental and placental-fetal circulation. Research methods: organometric, histological, immunohistochemical, morphometric, statistical. The research results and their discussion: the organometric parameters of the fetuses' uterus from the main group were clearly decreased in comparison to such parameters in case of the group of comparison. The decrease of the parameter of the uterine wall thickness of fetuses from mothers with the complicated pregnancy prescribes thinning of the main structural components. Namely: endometrium, myometrium and perimetrium. In case of endometrium of fetuses' uterus a decrease of number of glands and the lack of their functional activity was noticed. It characterizes this layer as structurally immature.

At the same time, in case of fetal organs of fetuses from mothers with complicated pregnancies, we could notice an increase in the number of apoptotically altered cells. Comparing to the structure of layers of uterine walls in case of fetuses from mothers with physiological pregnancy, in the uterus of fetuses from mothers with complicated pregnancy our attention is attracted by a massive growth of the connective tissue. In the myometrium it contributes to the disruption of the muscle fibers structure likewise to its absence in some areas. By the immunohistochemical method it was possible to reveal a prevalence of the collagen of the III type in the structure of connective tissue likewise in the walls of blood vessels. It is connected primarily with disruption of the collagen' maturation. The vascular component of the uterine wall in case of fetuses from mothers with HILGT differs from ones in case of fetuses from mothers with physiological pregnancy. This difference is grounded on the increase of endothelin-producing activity by vessels of both arterial and venous types. By processing preparations by monoclonal antibodies to estrogen, it has been postulated, that the intensity of the reaction as well as number of cells in the fetuses' organs of the main group are clearly decreased comparing to ones in cases of fetuses from the group of comparison. The disorders of the fetuses' uterus in case of fetuses from mothers with HILGT, that were provided in the current article, are prescribed by chronic hypoxia, endocrine disorders as well as influences of the infectious agents, that are taking place in case of such pathology. The characteristic features of the fetuses' uterus structure in case of fetuses from mothers, whose pregnancy is complicated by HILGT, indicate gross violation in the organ's implementation on the early stages of the fetal organogenesis, likewise they could be a leading link of pathogenesis of primary infertility' development in the future ontogenesis.

Key words: fetus; pregnancy; uterus; chronic infection; lower genital tract.

Імуногістохімічні особливості будови матки плодів зі строком гестації 21-28 тижнів від матерів, вагітність яких ускладнена хронічною інфекцією нижніх статевих шляхів

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Актуальність статті обумовлена зростаючою кількістю перинатальної смертності та захворюваності серед новонароджених, що обумовлені хронічною інфекцією нижніх статевих шляхів (ХІНСШ) у матері. Відомо, що ХІНСШ сприяє затримці розвитку плоду і проявляється частіше у порушенні закладки внутрішніх органів і систем. Однією з вразливих є статева система плода у ранні терміни гестації. Але на даному етапі розвитку медичної науки імуногістохімічні особливості будови матки плодів з терміном гестації 21-28 тижнів від матерів з ХІНСШ не було описано. Метою дослідження послужило виявлення імуногістохімічних особливостей будови матки плодів зі строком гестації 21-28 тижнів від матерів, вагітність у яких ускладнена ХІНСШ. Матеріал дослідження: 25 плодів від матерів, перебіг вагітності у яких був фізіологічним (група порівняння) та 25 плодів від матерів, вагітність у яких була ускладнена ХІНСШ (основна група). Всі плоди загинули інтранатально внаслідок гострого порушення матково-плацентарного та плацентарно-плодового кровообігу. Методи дослідження: органометричний, гістологічний, імуногістохімічний, морфометричний, статистичний. Результати дослідження та їх обговорення: органометричні показники матки плодів основної групи були вірогідно знижені відповідно до таких в групі порівняння. Зниження показника товщини стінки матки плодів від матерів з ускладненою вагітністю обумовлює стоншення основних структурних компонентів. А саме: ендометрію, міометрію та периметрію. В ендометрії матки плодів основної групи встановлено зниження кількості залоз та відсутність їх функціональної активності, що характеризує даний шар як структурно незрілий. Поряд із тим в фетальних органах плодів від матерів з ускладненою вагітністю спостерігається підвищення показника кількості апоптозно змінених клітин. Порівняно зі структурою шарів стінки матки плодів від матерів з фізіологічною вагітністю в матках плодів від матерів з ускладненою вагітністю звертає на себе увагу масивне розростання сполучної тканини. В міометрії це сприяє порушенню структури м'язових

волокон та відсутності її на окремих ділянках. Імуногістохімічним методом виявлено превалювання колагену III типу в структурі сполучної тканини та в стінках судин. Це пов'язано, насамперед, із порушенням дозрівання колагену. Судинний компонент стінки матки подів від матерів з ХІНСШ відрізняється від такого у плодів від матерів з фізіологічною вагітністю підвищенням ендотелін – продукуючої активності судинами як артеріального, так і венозного типів. При обробці препаратів МКАт до естрогену встановлено, що інтенсивність реакції та кількість клітин в органах плодів основної групи вірогідно знижені порівняно з такими у плодів групи порівняння. Наведені в статті порушення будови матки плодів від матерів з ХІНСШ обумовлені хронічною гіпоксією, ендокринними розладами та впливом інфекційних агентів, що мають місце при даній патології. Описані особливості будови матки плодів від матерів, вагітність у яких ускладнена ХІНСШ, свідчать про грубі порушення закладки органу на вранішніх етапах органогенезу плода і можуть бути ведучою ланкою патогенезу розвитку первинного безпліддя у подальшому онтогенезі.

Ключові слова: плід; вагітність; матка; хронічна інфекція; нижні статеві шляхи.

The relevance of the research topic is prescribed by ever-increasing percentage of the intrauterine infections in the structure of perinatal mortality and morbidity [1, 2]. According to the modern literature, the infection causes the death of newborns in 40% of cases' while in 50-60% of cases the same is manifested among hospitalized full-term newborns, and in 70% of cases - it is manifested among premature newborns [3, 4]. Infectioning, first of all, leads to delay of fetal development likewise to formation of numerous malformations [4, 5]. The action of infectious agents contributes to the violation of implementation and formation of internal organs and systems of the fetus [5, 6], which further causes their structural and functional immaturity [3, 6, 7]. The influence of infectious pathology on embryogenesis of the fetus is certainly being studied. However, unfortunately, there is no mandatory screening on presence of infectious pathology or any possible mandatory virological or bacteriological examination on pacentas and internal organs for the presence of infection in any country, even there is a data postulating, that in some cases there are incompatible pathologies or those, that indicate an extreme degree of fetal immaturity [4, 7]. Moreover, we have to pay our attention to the fact, that there is always a possibility of existence of latent or subclinical course of the infectious process, which generally makes it impossible to predict the violation of embryo- and fetogenesis [2, 5]. One of the systems, which implementation and formation occurs

throughout the whole pregnancy is the female reproductive system [7]. However, on the current stage of the medical science development there is no clear description of the immunohistochemical features of the fetuses' uterus structure from mothers with a chronic infection of lower genital tract at different stages of pregnancy.

The main aim of the current research is to identify immunohistochemical features of the fetuses' uterus structure with a gestational term of 21-28 weeks from mothers, whose pregnancy is complicated by the chronic infection of lower genital tract.

The research material. The research material is presented by uterus of fetuses with a gestational term of 21-28 weeks. The group of comparison consists of 25 fetuses from mothers with the physiological pregnancy (according to the medical documentation: exchanging cards of the maternity hospital, histories of pregnancies and childbirth, individual cards of pregnant women and mothers). The main group consists of 25 fetuses from mothers, whose pregnancy was complicated by the chronic infection of the lower genital tract (HILGT). According to the results of clinic and laboratory research of the lobes of the internal organs of fetuses and placenta (bacteriological and biochemical examination, polymerase chain reaction), the most common infections were caused by herpes virus, cytomegalovirus infection, enterococcus, chlamidial infection, and a combination of cytomegalovirus and chlamidial infections; chlamidial infections and excherichia coli; herpes virus and cytomegalovirus infection.

All fetuses had died intranatally and antenatally as a result of acute uterine-placental circulatory disorders (premature detachment of the normally located placenta), as well as placental-fetal blood circulation (umbilical cord pathology).

Examinations of the fetuses from the main group revealed signs of the photometric disproportion, subcutaneous lymphadema and ascites.

Antropometric indicators of the fetuses from the group of comparison reached the following values: body weight $0,538\pm 0,019$ kg, body length $0,26\pm 0,04$ m, the coefficient of harmony $19,84\pm 3,61$ kg/m³. In the main group the body weight of fetuses reached the following data: $0,548\pm 0,195$ kg, body length – $0,24\pm 0,02$ m, the coefficient of harmony – $18,07\pm 0,63$ kg/m³.

By analyzing antropometric indicators of fetuses from the studied groups, we can come up with the following conclusion: the body weight of fetuses from mothers with a complicated pregnancy is clearly bigger, while the body length and the coefficient of harmony are clearly lower, that the same indicators in case of fetuses from healthy mothers. Moreover, the increase of the body weight as well as the decrease of the body length are

confirmations of the photometric disproportion in the main group.

The research methods: macroscopic, organometric, histological, immunohistochemical, morphometric, statistical.

After removal all organs were examined and the main dimensions were measured. There were three pieces cut from different parts of every organ. After that those pieces from examined organs were fixed in alcohols of increasing concentration and filled with paraffin. From the blocks, that were made in a such way, the sections with a thickness of 3-5 μm were made. The specimens were stained by histological methods: by the hematoxylin and eosin, picrofuxin by the van Gieson method [8, 9].

The study on specimens, that were stained by histological methods, likewise the morphometric research was leaded on the Olympus BX-41 microscope with use of the programm: Olympus Db-soft (Version 3:1) [8, 9, 10].

The immunohistochemical study was leaded by the direct method of Koons in the modification of M. Brosman (1979) by using MCAT for collagen types I, III and IV, endotheline -1, and CD 95 (Chemicon International Inc., Temecula California) and peroxidase method [9]. The specimens, that were treated by MCAT with the use of the direct method of Koons were studied on the fluorescence microscope "Axioskor 40" (Carl Zeiss, Germany). The oprical density of immunofluorescence of collagens of the I, III and IV types, endotheline-1, as well as the number of apoptotically altered eggs were studied by the method of G.I. Gubina-Vakulik and co-authors (G.I. Gubina-Vakulik, I.V. Sorokina, V.D. Markovskii, L.S. Kupriianova, R.V. Sydorenko. The method of quantitative determination of antigen content in biological tissues. Patent for the utility model: № 46489; CO 1 № 33/00 from 25.12.2009, Bulletin № 4). The research was leaded by using "Axioskor 40" microscope with the use of Biostat.exe. software.

The degree of the staining intensity was described as follows: (-) - for negative reaction (no stained cells); (+) - weak (positively stained individual scattered cells); (++) - moderate (more intensively stained cells) and (+++) - excessive (almost all cells are intensively stained) [9].

The evaluation of the immunohistochemical reaction with treatment of specimens by MCAT to estrogen and progesterone were leaded by taking into account the intensity of staining, likewise with establishing the percentage of the immunopositive cells according to the general number of cells [9]. As a MCAT the estrogen-receptor alfa (ER), (DAKO clone EP1) and progesterone-receptor (PR), (DAKO clone PgR 636) were used.

Statistically the obtained data was processed on the personal computer by using

statistical packages „Excell for Windows”, „Statistica 7.0. for Windows”, „SigmaStat 3.1. for Windows” 1 [10, 11]. The distribution for compliance to the Gaussian law was checked by using Shapiro-Wilk or χ^2 Pearson criteria. For the parameters, that did not have a Gaussian distribution as well as for small samples, non-parametric methods of statistics were used: median (Me) and a quartile distribution with upper (Uq) and lower quartile (Lq, and/or maximum [max] and minimum [min] values.

For the role of the group characteristics for traits with distribution, corresponding to the Gaussian's law, the arithmetic mean (M) was determined, and its standard deviation (SD) [10, 11]. For the correlation of the obtained digital data also correlation analysis and multidimensional regression analysis were used [10, 11].

Results and discussion: the location of uterus in all cases was typical one. Namely: slightly to the right of the middle sagittal plane of the body; the bottom and the body were on the right in the pelvic cavity, the cervix was in the pelvic cavity.

The uterus was pear-shaped in all observations. The surface of the organ is smooth, grayish-bluish. In the organ the body and the cervix could be identified. The indicators of ration of the uterus' body length to the uterus' cervix length were: in the group of comparison - 1:2,7; while in the main group they were - 1:2,5. By analyzing the ration of the uterus' body length to the uterus' cervix length, we could say, that in the main group this index is decreased according to the ones from the group of comparison.

The average organometric parameters of the fetuses' uterus from the study groups are presented in the Table 1.

Table 1 - Organometric indexes of the fetuses' uterus from the study groups

Group	Uterus weight, kg	Uterus body length, m	Density of uterus' wall, m
Group of comparison	$3,24 \pm 0,11 \times 10^{-3}$	$3,80 \pm 0,13 \times 10^{-2}$	$7,25 \pm 0,18 \times 10^{-3}$
Main group	$2,64 \pm 0,09 \times 10^{-3*}$	$3,62 \pm 0,13 \times 10^{-2*}$	$6,83 \pm 0,24 \times 10^{-3*}$

Note. ($p \leq 0,05$)

The data of the Table 1 shows a significant decrease of the indexes of weigth, body length and the thickness of uterus' wall in case of fetuses from mothers with HILGT comparing to the same indexes in case of fetuses from mothers with physiological pregnancy.

The observative microscopic research of preparations, that had been stained by

histological methods, disclosed, that the organs' wall of each fetus was presented by three components: by endometrium, myometrium and perimetium with the clear border between each of three. The indexes of the thickness of layers in uterus' wall are presented in the Table 2.

Table 2 - The indexes of the thickness of layers in the uterus' wall in case of fetuses from the study groups, m

Group	Thickness of endometrium	Thickness of myometrium	Thickness of perimetrium
Group of comparison	$2,57 \pm 0,09 \times 10^{-3}$	$3,14 \pm 0,11 \times 10^{-3}$	$1,54 \pm 0,04 \times 10^{-3}$
Main group	$2,37 \pm 0,08 \times 10^{-3*}$	$2,97 \pm 0,10 \times 10^{-3*}$	$1,49 \pm 0,05 \times 10^{-3*}$

Note. ($p \leq 0,05$)

By analyzing the data from the Table 2 we could definitely say, that in all cases in the fetal organs' structure prevails myometrium, while the perimetrium reaches its lowest indexes. By comparing indexes in groups, we could come up with a conclusion, that the thickness of the wall's layers in the fetal organs in case of fetuses from the main group is clearly decreased relatively to the same index in the group of comparison.

The morphological examination revealed superficial and deep layers in the structure of the uterine mucosa in all observations, what corresponds to the organs' structure on the current stage of the fetal development.

In the superficial layer of uterus in case of fetuses with the physiological pregnancy, the numerous tubular glands with the features of proliferative activity take place; in the deep layer there are no features of the functional activity of glandular component, even though the gland spread for the 1/3 of the entire endometrium thickness. The glandular component of the superficial as well as of the deep layers of the uterus in case of fetuses from mothers with the complicated pregnancy have no signs of the proliferative activity. The glands are solitary, in the deep layer they spread at least for 1/3 of the entire depth of the endometrium thickness.

In the structure of endometrium we could define apoptotically changed cells, the general number of which reaches $14,72 \pm 0,52$ % in the group of comparison; and $21,16 \pm 0,44$ % - in the main group. These indexes are disclosing a clear increase of number of the apoptotically changes cells in endometrium of fetuses from mothers with HILGT.

By using histological and histochemical methods it was postulated, that there was a growth of the connective tissue likewise in the superficial, as in the deep endometrium layers

in the uterus wall of fetuses from mothers with complicated pregnancy comparing to the structure of the organ's wall in case of mothers with physiological pregnancy. Moreover, if in the fetus' endometrium in case of the group of comparison we could notice mostly the collagen of the I type as small areas; so, in the fetus' endometrium in case of the main group the collagen of the III type prevailed.

In all cases myometrium was manifested as two layers: outer and inner ones.

In the myometrium of fetuses from mothers with the physiological pregnancy a vascular zone prevails, which obtains 40-50%, while the subserous zone obtains up to 5-10%. The cell composition is presented by elongated cells with an oval nucleus and condensed chromatine. The size of the cells is different, what determines their functional load in the subsequent ontogenesis. The cells are forming thin chaotically arranged muscle fibers. Between cells there is a focal growth of connective tissue, which is stained red by picrofuxin by the method of van Gieson. By using the immunohistochemical method by applying MCAT to collagens of the I and III types it was postulated, that the collagen of the I type discloses as an intensive glow, while the collagne of the III type, oppositely, discloses as small foci of moderate intensity.

The myometrium of fetuses from mothers, whose pregnancy was complicated by the HILGT differs from one, from mothers with the physiological pregnancy by postulating a lack of a clare structural organization in muscle fibers due to the growth of the connective tissue in this layer. We have to point out, that the fibers of connective tissue are growing as around of the muscle bundles, likewise they grow in them, what makes impossible to determine the direction of the musles' fibers as well as to determine their purpose towards the outer or inner myometrium layers. The massive growth of the connective tissue is dislosed by staining it with picrofuxin by applying the van Gieson method as well as by treating the specimens with MCAT to the main collagen types. Thus, by applying the immunohistochemical method the intensive glow of the collagen of the III type as large foci was shown.

The indexes of the glow intensity of collagens of the I and the III type in the connective tissue component in case of fetuses from the study group are presented in the Table 3.

Table 3 - The indexes of glow intensity of collagens of the I and the III types in uterus of fetuses from the study groups (conventional unit of optical density)

Group	The intensity of glow of collagen of the I type	The intensity of glow of collagen of the III type
Group of comparison	0,177±0,006	0,115±0,008
Main group	0,212±0,007*	0,311±0,011*

Note. ($p \leq 0,05$)

The data, which is presented in the Table 3 reveals the following: in case of organs of fetuses from the group of comparison indexes of the glow intensity of collagen of the I type prevail towards these indexes in case of collagen of the III type. In the fetuses' uterus from the main group, oppositely, the glow intensity of collagen of the III type prevails towards this index in case of collagen of the I type. If we are comparing the indexes of intensity of the main collagen types in groups we could come up with the conclusion, that in fetal organs of fetuses from mothers with the complicated pregnancy we could recognize an increased collagen production relatively to organs of fetuses from mothers with physiological pregnancy. It could be confirmed by the clear increase of glow intensity indexes of collagen of the I type, likewise of the III type as well.

The vessels of fetuses' organs from the group of comparison are presented by arteries, arterioles and venules with a moderate blood supply. The cells of the vascular zone are characterized by proliferative activity. In the structure of connective tissue of a vascular wall the collagen of the IV type is manifested by an intensive glow. At the same time a vascular component of the uterus in case of fetuses from the main group differs by thickening the walls as well as phenomena of hyalinosis. The proliferative activity of the vascular component is moderate, some part of vessels is obliterated. The Collagen of the IV type is manifested as a glow with a decreased intensity in separate areas.

By the immunohistochemical method an endotheline-producing activity of the vascular component in organs of fetuses from the study group was manifested. The average glow intensity indexes of collagen of the IV type as well as of the endotheline-1 in vessels of fetal uterus are presented in the Table 4.

Table 4 - The indexes of the glow intensity of collagen of the IV type and the endotheline-1 in the vascular component of the fetuses' uterus in study groups, (conventional unit of optical density)

Group	The glow intensity of collagen of the IV type	The glow intensity of the endotheline-1 in arterial component	The glow intensity of the endotheline-1 in the venous component
Group of comparison	0,134±0,005	0,41±0,01	0,52±0,02
Main group	0,115±0,004*	0,48±0,02*	0,47±0,02*

Note. ($p \leq 0,05$)

Thus, the data in the Table 4 reveals a clear decrease of the glow intensity in case of the collagen of the IV type in vascular component of fetuses' organs from the main group relatively to ones from the group of comparison. The indexes of glow intensity of the endotheline-1 in fetuses' organs from mothers with complicated pregnancy in the vessels of the arterial component are clearly increased, while in the venous component are clearly decreased comparing to ones in the fetal uterus of fetuses from mothers with physiological pregnancy.

The perimetrium in all cases is presented by the connective tissue, in the structure of which prevails the collagen of the I type in organs of fetuses from the group of comparison, while, in the fetuses' uterus from the main group prevails the collagen of the III type.

The treatment of specimens by MCAT to estrogen and progesterone disclosed the following features in uterus of fetuses from the study groups. Namely: in the organs of the group of comparison: (++, 75 % stained cells) in specimens, that were treated by MCAT to estrogen as well as a negative reaction in case of specimens, that were treated by MCAT to progesterone (--, no stained cell). In fetal uterus of fetuses from the main group: a moderate positive reaction (++, 40 %) in specimens, that were treated by MCAT to estrogen as well as a negative reaction in case of specimens, that were treated by MCAT to progesterone.

Thus, the decrease of cells' number takes places, that proceeds with a positive reaction to estrogen, in case of fetuses' organs from mothers with complicated pregnancy relatively to those in case of fetuses' organs from mothers, whose course of pregnancy was physiological one. The negative reaction to progesterone in all observations is physiological on this stage of embryogenesis.

Thus, in the current article we had provided main features of the fetuses' uterus

structure with a term of gestation 21-28 weeks from mothers, whose pregnancy was complicated by the chronic infection of the lower genital tract relatively to ones in case of fetuses from mothers with the physiological pregnancy. The organometric indexes of the fetuses' organs from mother with HILGT are clearly decreased in comparison with ones in case of fetuses from healthy mothers, which is determined, first of all, by changes in the placenta vessels as well as its impaired maturation, that are characteristic for this pregnancy' complication [12, 13]. The mismatch of placental development towards the term of pregnancy leads to the disorder in the fetus' internal organs formation [13, 15]. The organ's wall in all cases is presented by three main components, among of which the myometrium prevails. The indexes of thickness of uterus' wall layers in case of fetuses from the main group are clearly decreased relatively to those in the group of comparison. There is no doubts, that the decrease of a general index of the uterus wall thickness determines thinning of its main structures. Moreover, in the endometrium of fetuses from mothers with HILGT the decrease of number of glands facilitates it, likewise it is also facilitated by disruption of its distribution as well as a lack of its functional activity [14, 18].

In the endometrium of fetuses from mothers with complicated pregnancy relatively to ones in case of fetuses from healthy mothers a number of apoptotically changed cells is clearly increased. From one side, it is determined by vascular disorders in placenta as well as by lack of its endocrine function [17, 18], from another side, though, it is caused by an action of viral agents, which stimulate the cell death by apoptosis [19, 21].

By the immunohistochemical methods a massive growth of the connective tissue in all layers of the uterus wall is presented in case of fetuses from the main group. It is determined preliminary by the chronic hypoxia in the system mother-placenta-fetus, which is forming and is a leading syndrome in condition of the chronic infection [20]. The growth of the connective tissue leads to the disruption of the structural myometrium organization.

In the structure of the connective tissue in case of fetuses from mothers with HILGT the collagen of the III type prevails, an appearance of which informs about a disorder in the collagens maturing in condition of chronic hypoxia, which is stimulated by the chronic infection [16].

The level of endotheline-producing activity of the vascular component in organs of fetuses from the main group is clearly increased relatively to ones in the organs of fetuses from the group of comparison. Moreover, we have to pay attention to the fact of increasing the level of glowing an arterial component relatively to venous one. To the changes, that were described above, could lead as chronic hypoxia, likewise directly pathogens of the infectious

pathology [19].

By treating specimens by MCAT to estrogen there is a clear decrease of the cells number in the fetuses' uterus disclosed in case of fetuses from mothers with complicated pregnancy relatively to ones, whose in the fetuses' organs from mothers, whose pregnancy was physiological. The aforementioned changes could be stimulated by apoptotic changes, likewise by hormonal dysfunction of the placental component [17, 20].

The aforementioned changes in the structure of the fetuses' uterus from mothers with HILGT determine a disruption in implementation as well as in formation of the fetal organs on the current stage of intrauterine development, which could lead to disruption of the functional activity in the subsequent ontogenesis. Thus, a decrease of number and functional activity of the glandular component of the endometrium will complicate the onset of the uterine pregnancy; the disorder of the muscular component structure could be manifested by insufficient hypertrophic changes during pregnancy or during contractile activity while the childbirth; an increase of the endothelin-producing activity of the vascular component will facilitate a deepening of hypoxia as well as developing deeper violations of organogenesis during the latest terms of gestation; the violation of the hormonal activity will be manifested by endocrine disorders of the reproductive system in adolescent age as well as in the life of woman in the future.

Conclusions: The organometric indexes of the fetuses' uterus from the main group are clearly decreased in comparison with those in the group of comparison. These changes are influencing a thinning of the main organs' structural components.

2. The number of apoptotically changed cells in the endometrium of fetuses from mothers with complicated pregnancy is increased ($21,16 \pm 0,44$ %) comparing to those in case of fetuses from mothers with physiological pregnancy ($14,72 \pm 0,52$ %).

3. Staining by the van Gieson method had disclosed a massive growth of the connective tissue in all layers of the uterine wall in case of fetuses from the main group relatively to organs of fetuses from the group of comparison. It stimulates a disorder of the development of glandular component as well as forming of the muscular component. By the immunohistochemical method it was revealed a prevalence of the collagen of the III type in the structure of connective tissue, what indicates changes in the collagens maturation.

4. In vessels both arterial and venous types in the fetuses' uterine from mothers with HILGT we could indicate an increased endothelin-producing activity relatively to the vascular component of the fetuses' uterine from mothers, whose course of pregnancy was physiological.

5. The hormone-producing activity of the fetal organs (40% of stained cells) in case of fetuses from mothers with complicated pregnancy is decreased relatively to one in case of fetuses from healthy mothers (75% of stained cells).

6. The revealed immunohistochemical features of the uterine structure in case of fetuses from mothers with HILGT are caused by chronic hypoxia, endocrine disorders as well as vascular changes in the mother-placenta-fetus system, which is forming under the condition of infectioning.

7. The immunohistochemical features of the fetuses' uterine structure in case of fetuses from mothers, whose pregnancy was complicated by HILGT, that were revealed, are indicating deep disorder in implementation, formation as well as stabilization of the organs functional activity as well as it will facilitate a development of the primary infertility in the subsequent ontogenesis.

The perspectives of the future research: to disclose immunohistochemical features of the fetuses' uterine structure with the gestational term of 29-26 as well as 27-40 weeks from mothers, whose pregnancy is complicated by chronic infection of the lower genital tract.

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