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Immunohistochemical features of the uterus structure in case of fetuses with a gestational term of 29-36 weeks from mothers with the chronic infection of the lower genital tracts

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Abstract

In the following article we present results of the research on the uterus' wall structure in case of fetuses from mothers, whose pregnancy was complicated by the chronic infection of the lower genital tracts (HILGT), comparing to one in case of fetuses from healthy mothers. The main aim of our research was to disclose immunohistochemical features of the uterus' wall structure in case of fetuses with a gestational term of 29-36 weeks. The research methods: macroscopic, organometric, histological, immunohistochemical, morphometric, statistical. All fetuses have died intranatally as a result of an acute violation of utero-placental or placenta-fetal circulation.

The organometric research has revealed a fact of decrease of the following indexes: namely, the ones of weight, length and thickness of the uterus' wall in case of fetuses from mothers with a complicated pregnancy. Moreover, the decrease of the thickness' index is primarily connected with a fact of thinning of the endometrium as a structural component of the wall. Staining by picrofuxin according to Van-Gieson has revealed an increase growth of

the connective tissue both in endometrium and in myometrium of the uterus wall in case of fetuses from the main group. Moreover, in the muscular component, as a result of the aforementioned phenomenon, we can notice a violation or even in some places a complete lack of the structural organization of muscular fibers. The immunohistochemical research has revealed an increase of an apoptotic index in the endometrium of fetal organs of mothers with a complicated pregnancy comparing to indexes in case of fetuses from healthy mothers, which also contributes to the thinning of the layer as well as atrophic changes in it. In addition, in the structure of the connective tissue of the uterus of fetuses from the group of comparison the collagen of the I type prevails, while in case of fetuses from the main group the collagen of the III group prevails. Alongside with aforementioned features in case of fetuses from mothers with HILGT we can emphasize an increased glow of the endotheline-1 in vessels both of arterial and venous types.

All changes in the connective tissue structure in the uterus of fetuses from mothers with a complicated pregnancy, that were described above, could contribute to the violation of the organ's maturing as well as stabilization of its functional activity in the future life. The increased endotheline producing leads to the violation of the blood supply, as well as could enhance collagenogenesis. The prevalence of the collagen of the III type in a structure of the connective tissue is a manifestation of the chronic hypoxia, under the condition of which the organogenesis of fetuses takes place in case of this pathology as well as leads to the violation of the spatial organization of the uterus' main structural components. All features of the uterus wall structure in case of fetuses from mothers with HILGT, that have been established above, are prescribed by the chronic hypoxia and replication of the viral agents in the embryonic tissues as well as it could lead to make an implantation and pregnancy more difficult, likewise it could be a reason of development of pregnancy weakness in the following ontogenesis.

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

Імуногістохімічні особливості будови матки плодів зі строком гестації 29-36 тижнів від матерів із хронічною інфекцією нижніх статевих шляхів

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В статті наведено результати дослідження будови стінки матки плодів від матерів, вагітність у яких ускладнена хронічною інфекцією нижніх статевих шляхів (ХІНСШ) порівняно до такої у плодів від здорових матерів. Метою дослідження слугувало виявлення імуногістохімічних особливостей будови стінки матки плодів зі строком гестації 29-36 тижнів. Методи дослідження: макроскопічний, органометричний, гістологічний, імуногістохімічний, морфометричний, статичний. Всі плоди загинули інтранатально внаслідок гострого порушення матково-плацентарного та плацентарно-плодового кровообігу. Органометричне дослідження виявило зниження показників маси, довжини та товщини стінки матки плодів від матерів з ускладненою вагітністю відповідно до таких у плодів від здорових матерів. Причому зниження показника товщини стінки насамперед обумовлене потоншенням ендометрію як структурного компонента стінки. Фарбування пікрофуксином по ван-Гізон виявило посилене розростання сполучної тканини як в ендометрії, так і в міометрії стінки матки плодів основної групи. Причому у м'язовому компоненті внаслідок цього спостерігається порушення, а місцями – повна відсутність структурної організації м'язових волокон. Імуногістохімічним дослідженням встановлено підвищення апоптозного індексу в ендометрії органів плодів від матерів з ускладненою вагітністю відповідно до показників у плодів від здорових матерів, що також сприяє витонченню шару та атрофічним змінам в ньому. Причому в структурі сполучної тканини матки плодів групи порівняння превалює колаген I типу, натомість у плодів основної групи – колаген III типу. Поряд із вищенаведеними особливостями в матках плодів від матерів з ХІНСШ має місце підсилення світіння ендотеліну-1 в судинах як артеріального, так і венозного типу.

Описані зміни в структурі сполучної тканини матки плодів від матерів з ускладненням вагітності можуть сприяти порушенню дозрівання органу і становленню його функціональної активності у подальшому житті. Підсилення ендотеліну

продукуючої призводить до порушення кровопостачання органу, а також може підсилювати колагеногенез. Превалювання колагену III типу в структурі сполучної тканини є проявом хронічної гіпоксії, в умовах якої відбувається органогенез плоду при даній патології та призводить до порушення просторової організації основних структурних компонентів матки. Встановлені особливості будови стінки матки плодів від матерів з ХІНСШ обумовлені хронічною гіпоксією та реплікацією вірусних агентів в тканинах зародка і можуть сприяти утрудненню імплантації, виношуванню вагітності та бути причиною розвитку слабкості пологової діяльності у подальшому онтогенезі.

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

The relevance of the following topic: Despite of the modern diagnosis' methods as well as methods of the infectious treatment for pregnant, the relevance of the aforementioned topic becomes increasingly important. Thus, the intrauterine infections occupy a leading place in the structure of mortality in case both of pre-mature and full-term infants, as well as it contributes to the formation of the multiple malformations of the fetus on different stages of its formation [1]. According to the modern statistic data the complications of pregnancy because of the chronic infection of the lower genital tracts could be observed in between 50-70% of all pregnancies [2, 3], as well as in 40 % of all observations it becomes the main reason of death [3, 4]. However, the percentage of mortality in case of this complication reaches definitely higher indexes. The decrease of indexes is prescribed first of all by the insufficient examination of the pregnant (the examination for disclosing an existence of the chronic infectious pathology is not obligatory), as well as by the factor, that in most of cases the infectious process becomes a concomitant pathology on the basis of the chronic hypoxia, intranatal hypoxia, umbilical cord pathology likewise other conditions, which could lead to death [4, 5, 6]. Besides, we have to take into consideration the following fact: almost in 90 % of cases there is a so-called asymptomatic course of the infection, which leads to the late diagnosis and treatment of pregnant (in most of cases treatment begins, when changes in placenta or different malformations of fetuses are revealed) [5, 6, 7]. There are no doubts, that in the infectious pathology pathogenesis the head role is occupied by the term of pregnancy, when the infectioning took place, likewise by the type of pathogen and a route of infectioning the fetus [7, 8]. However, despite of all factors, that were mentioned above, there is a defeat of fetal internal organs of different stage of severity, which is developing and is manifesting as a violation of implementation and formation of its main structural components, as well as

could lead to the disorders in the subsequent ontogenesis [8, 9]. The organs of the female reproductive system, namely, the uterus, are the most favorable to the influence of the infectious pathology. According to the data provided by foreign and domestic authors, the number of 60% of women, who have a problem with the onset and delivery of pregnancy were born by women, whose pregnancy was complicated by the infectious pathology [9, 14]. However, despite of everything, what was disclosed above, the immunohistochemical features of uterus in case of mothers with a chronic infection of the lower genital tracts have not been studied yet.

The aim of the following research: to reveal immunohistochemical features of the uterus structure in case of fetuses with a gestational term of 29-36 weeks, from mothers with a chronic infection of the lower genital tracts.

The research material. The research material is presented by uterus of fetuses with a gestational term of 29-36 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, chlamydial infection, and a combination of cytomegalovirus and chlamydial infections; chlamydial infections and *Escherichia 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 lymphoedema and ascites.

Anthropometric 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 anthropometric 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, than 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 optical 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), (DAKOcloneEP1) and progesterone-receptor (PR), (DAKOclonePgR 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, 12]. For the correlation of the obtained digital data also correlation analysis and multidimensional regression analysis were used [8, 9].

The research results and its discussion

The macroscopic research revealed, that in all cases organs were pear-shaped. The cervix was 2,5 times larger than the body. The surface of organs is smooth, dark-red. The average organometric indexes of the fetal organs from the study groups are provided in the Table 1.

Table 1

The organometric indexes of the fetal uterus from the study groups with a gestational term of 29-36 weeks

Index	Group of comparison	Main group
The uterus weight, kg	4,77±0,17x10 ⁻³	4,31±0,15x10 ⁻³ *
The length of the uterus body, m	3,88±0,14x10 ⁻²	3,58±0,13x10 ⁻² *
The thickness of the uterus wall, m	7,91±0,27x10 ⁻³	7,47±0,26x10 ⁻³ *

Note p≤0,05

By analyzing the data from the Table 1 we can come up with the following conclusion: the organometric indexes of the fetal organs from mothers with HILGT are relatively decreased comparing to ones in case of fetuses from healthy mothers.

The observative histological reasrch of specimens allowed to reveal, that the structure of the fetal organs’ wall from the study groups is represented by endometrium, myometrium

and perimetrium. The indexes of thickness of the main structural components of the fetal uterus' wall is provided in the Table 1.

Table 2

The indexes of thickness of main structural components of the fetal uterus' wall in the study groups with a gestational term of 29-36 weeks(m)

Group	The thickness of endometrium	The thickness of myometrium	The thickness of perimetrium
Group of comparison	$2,77 \pm 0,09 \times 10^{-3}$	$3,43 \pm 0,12 \times 10^{-3}$	$1,71 \pm 0,05 \times 10^{-3}$
Main group	$2,36 \pm 0,08 \times 10^{-3} *$	$3,46 \pm 0,12 \times 10^{-3}$	$1,65 \pm 0,06 \times 10^{-3}$

Note $p \leq 0,05$

According to the morpho-metric data, which was provided in the Table 2, there is a relative decrease of the endometrium thickness, in case of the uterus wall of fetuses from mothers with HILGT comparing to the same index, in case of the uterus structure of fetuses from healthy mothers.

By summing up the data from the Tables 1 and 2 we can say, that the thinning of the uterus wall in case of fetuses from mothers with HILGT is primarily caused by the decrease of index of the endometrium thickness.

The histological research on specimens, stained by hematoxylin and eosin allowed us to declare, that the uterus wall in all cases was lined with endometrium, which was represented by a single layer of a prismatic epithelium and formed two layers - basal and functional with a clear boundary between them.

The basal layer in all researches is situated on the myometrium and is represented by grandular and stromal components. However, our attention is attracted by features of the functional activity of the endometrium glands.

Thus, there are a few glands in the uterus endometrium of fetuses from the group of comparison, in some fields of view those glands are single and unbranched, reach up tp 2/3 of the layer's thickness. The glandular epithelium is represented by the curved-shaped cells. In the epithelium cells there are no features of functional activity, while during the staining by a PAS-reaction there is a moderate intensity of staining the cells' strucutres. The cells of the epithelial surface of the organs outer layer has also no features of the secretory activity.

The inner lining of the uterus wall in case of fetuses from the main group are characterized by the presence of a large amount of glands, covered with high cylindrical

epithelium. The nuclei of epithelial cells are stained intensively by hematoxylin and eosin, and they also manifest features of a high functional activity in case of staining for RNP and DNP. Glands of the functional layer are numerous and possess features of the secretory activity. The cells' nuclei are located on different levels.

By applying the immunohistochemical method we have postulated an index of the apoptotic index in endometrium of the study groups. Thus, in case of organs of fetuses from the group of comparison it reaches $15,82 \pm 0,55$ %, in uterus of fetuses from the main group though – $26,47 \pm 0,93$ %. By comparing the data, which we have received, we can say, that in case of endometrium of fetuses from mothers with a complicated pregnancy an apoptotic index is relatively higher than one in cases of organs of fetuses from healthy mothers.

Staining by picrofuxin according to van Gieson has revealed a massive growth of the connective tissue in the inner and outer layers of endometrium in case of organs of fetuses from mothers with HILGT. By immunohistochemical method we have shown, that there is a prevalence of the collagen of the III type in the structure of connective tissue as well as there is a decrease of the glow intensity of the collagen of the I type. The massive growth of connective tissue could be observed also in the own plate of the mucous membrane.

The myometrium in fetal organs in the group of comparison consists of three layers, that are formed by smooth muscle cells. The connective tissue component of the layer is represented by small layers of the connective tissue, which are stained in red color by a picrofuxin according to van Gieson. The collagen of the I type prevails in the structure by being manifested as an intensive glow. The collagen of the III type is manifested as individual foci with a glow of moderate intensity.

The muscle fibers in organs of fetuses from healthy mothers in the same period of fetus development are acquiring a planar organization. Namely: they are located circularly in two layers of myometrium, as well as longitudinally - in the middle one.

The myometrium in organs of fetuses from the main group is represented by muscle fibers with the following direction: longitudinally - in the first layer, circularly - in the second layer, and obliquely - in the third layer. There is an intensive growth of the connective tissue between layers, that leads to violation in the structural connection between muscle fibers. We have also point our attention into a fact, that the intensive growth of the connective tissue could be observed both between layers of muscle fibers and around them, what deforms the layer's structure in a great way. Moreover, there is a clear perivascular and fabric hypostasis.

The indexes of the glow intensity of collagens in the structure of muscular layer of the fetal uterus in the study groups are provided in the Table 3.

Table 3

The indexes of the glow intensity of the collagens of the I and III type in the structure of myometrium in fetal uterus in study groups with a gestational term of 29-36 weeks (conv.un.opt.dens.)

Group	The intensity of glow of the collagen of the I type	The intensity of glow of the collagen of the III type
Group of comparison	0,248±0,009	0,206±0,001
Main group	0,331±0,012 *	0,218±0,009 *

Note $p \leq 0,05$

According to the data, which was presented in the Table 3 we can say, that in case of uterus of fetuses from the main group we can notice an increased synthesis of the collagens both of the I and III types comparing to the same indexes in the case of fetal organs in the group of comparison.

The vessels of the fetal organs are thinwalled and spasmodic in all cases. By applying the immunohistochemical method we have revealed indexes of the glow intensity of the endotheline -1 in vessels both arterial and venous types. These indexes are presented in the Table 4.

Table 4

The indexes of the glow intensity of endotheline-1 in the vessels' walls of fetal organs in the study group with a gestational term of 29-36 weeks (conv.un.opt.dens.)

Group	The intensity of glow in vessels of the arterial type	The intensity of glow in vessels of the venous type
Group of comparison	0,47±0,02	0,54±0,02
Main group	0,53±0,02 *	0,69±0,02 *

Note $p \leq 0,05$

The data from the Table 4 show a probable increase of the indexes of glow intensity of the endotheline-1 in vessels both of arterial and venous types in organs of fetuses from mothers with HILGT comparing to ones in case of fetuses from healthy mothers.

The perimetrium in all cases is represented by a loose fibrous connective tissue, the structure of which is dominated by the collagen of the III type.

Thus, the research, which has been provided, revealed the following features in the uterus of fetuses from mothers with HILGT comparing to ones in case of fetuses from healthy mothers. Namely, decrease of indexes of basic uterus sizes; thinning of the organ's wall, which is primarily caused by changes in endometrium; an enhanced growth of the connective tissue in myometrium and endometrium which contributes to violation of the spatial organization of the uterus' wall components; an increase of apoptotic index in endometrium; a violation of the collagen formation as a result of the collagen of the III type prevalence; an enhanced endothelium producing activity of the vascular component. According to the literature' data, a decrease of the indexes of weight, length and thickness of the organ's wall is caused by a violation of the organ's maturing under the conditions of the infectious process [14, 15]. An increase of the hormonal activity of glands is an indicator of premature maturation of the fetal organ [14, 15, 21]. The massive growth of the connective tissue in endometrium and myometrium is caused by a chronic hypoxia, which takes place in case of the chronic infection [16, 17, 18]. The replication of the pathogen as well as initiation of the pathological changes under the conditions of HILGT are stimulating apoptotic changes in the endometrium of fetal organs [19, 20, 22]. The chronic hypoxia leads also to the enhance of the endothelium producing activity of the vascular component, what consequently exacerbates sclerotic changes [23, 24]. All features of the uterus wall' structure in case of fetuses from mothers with HILGT, that were revealed, could lead subsequently to the disruption of pregnancy as well as could prevent pregnancies in general [25].

Conclusions

1. Weight, length and thickness of organ's wall in case of fetuses from mothers with HILGT are relatively decreased comparing to ones in case of fetuses from healthy mothers. Moreover, according to the data of the morphometric research, a thinning of the uterus wall in case of fetuses from the main group is caused by a decrease of the endometrium thickness' index.

2. Despite of the endometrium thinning in the endometrium of fetuses from the main group, there is a large number of glands in both components of the layer with features of the secretory activity in it, what could be confirmed by reactions on RNP and DNP. In addition, in both layer of endometrium of fetuses from both group we can notice a massive growth of the connective tissue with a prevalence of the collagen of the III type in its structure.

3. By applying the immunohistochemical method we have revealed an increase of the apoptosis index in the endometrium of fetuses from mothers with HILGT relatively to one in

case of fetal uterus from healthy mothers.

4. In the myometrium of fetal uterus in study groups we can reveal three main layers. However, if in case of fetuses from healthy mothers there is a clear structural organization of the muscle fibers layer; in case of fetuses from mothers with a complicated pregnancy though, in this component of the fetal uterus we can notice an enhanced growth of the connective tissue both between layers, as well as with growing into muscle structures, what contributes to the structural deorganization of this component in the uterus wall. By applying the immunohistochemical method we have revealed a prevalence of the collagen of the III type in the structure of connective tissue of myometrium of fetuses from mothers with a complicated pregnancy.

5. The endothelium producing activity in vessels both arterial and venous components are relatively decreased in case of fetuses from mothers with HILGT comparing to it in case of fetuses from healthy mothers.

6. All changes in the organs of fetuses from mothers with HILGT, that were revealed, are caused primarily by a chronic hypoxia as well as replication of pathogens, which take place in case of this pathology.

7. The structural changes in main layers of the uterus in case of fetuses from mothers with a complicated pregnancy could lead subsequently to a difficulty of an egg implementation, difficult pregnancy and development of the childbirth weakness.

Perspectives of the further research: to study immunohistochemical features of the ovaries and fallopian tubes structure in case of fetuses with a gestational term of 29-36 weeks, born from mothers with HILGT.

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