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Pathomorphological features of the uterus' wall structure in case of fetuses with a gestational term of 37-40 weeks from mothers with a chronic infection of the lower genital tracts

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Abstract

In the following article we have provided a data towards a comprehensive research of the pathomorphological features of the uterus' wall structure in case of fetuses from mothers with HILGT comparing to ones in case of fetuses from healthy mothers.

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

On the basis of the organometric research we have revealed a probable decrease of the weight, length and thickness indexes likewise one of the main components of the uterus wall in case of fetuses from mothers with a complicated pregnancy comparing to ones in case of fetuses from healthy mothers.

By applying histological method we have revealed an increased growth of the connective tissue both in the endometrium and myometrium in case of fetuses from mothers with HILGT relatively to one in case of fetuses from mothers with a physiological pregnancy. Moreover, the massive growth of the collagen fibers leads to the disorder in the strucutral organization of the muscle component. The uterus' endometrium in case of fetuses from the

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main group could be characterized by a few glands without features of the functional activity comparing to one in case of fetuses from the group of comparison. In the structure of the connective tissue in case of uterus of fetuses from mothers with a complicated pregnancy we have revealed mainly the collagen of the III type, while the collagen of the I type could be revealed in the form of small loci of reduced intensity of glow.

By applying the immunohistochemical method we have revealed an increase of the apoptotic index in the endometrium of fetuses from mothers with a chronic infection of the lower genital tracts comparing to one in case of fetuses from healthy mothers. By applying MCAT to endotheline-1 we have revealed an increased glow of the endtheliocytes in the vessels both of arterial and venous types, in case of fetuses from the main group comparing to one in case of fetuses from the group of comparison. In the uterus of fetuses from mothers with HILGT we could observe a decreased hormon producing activity comparing to one in case of fetuses from mothers with a physiological pregnancy. All changes, that were revealed in the uterus of fetuses from mothers with an infectious pathlogy declare an existance of the severe disorder in the implementation and formation of main organ's components, as well as are caused mainly by a chronic hypoxia as well as influence of the infectious agent. All pathomorphological features of the uterus wall structure in case of fetuses from mothers with HILGT, that were revealed, could contribute subsequently to the complications in the pregnancy's onset as well as could lead to the disruption of one.

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

Патоморфологічні особливості будови стінки матки плодів зі строком гестації 37-40 тижнів від матерів із хронічною інфекцією нижніх статевих шляхів

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В статті наведено дані щодо комплексного дослідження патоморфологічних особливостей будови стінки матки плодів від матерів з ХІНСШ порівняно з такими у плодів від здорових матерів.

Методи дослідження: макроскопічний, органометричний, гістологічний, імуногістохімічний, морфометричний, статистичний.

Органометричним дослідженням було виявлено вірогідне зниження показників маси, довжини, товщини та основних компонентів стінки матки у плодів від матерів з ускладненою вагітністю відповідно до таких у плодів від здорових матерів.

Гістологічним методом встановлено посилене розростання сполучної тканини як в ендометрії, так і в міометрії плодів від матерів з ХІНСШ відповідно до такої у плодів від матерів з фізіологічною вагітністю. При чому, масивне розростання колагенових волокон призводить до порушення структурної організації м'язового компоненту. Ендометрій матки плодів основної групи характеризується нечисельними залозами без ознак функціональної активності відповідно до такого у плодів групи порівняння. В структурі сполучної тканини в матках плодів від матерів з ускладненою вагітністю виявляється переважно колаген ІІІ типу, в той час як колаген І типу виявляється у вигляді невеликих осередків зниженої інтенсивності світіння.

Імуногістохімічним методом показано підвищення апоптозного індексу в ендометрії плодів від матерів з хронічною інфекцією нижніх статевих шляхів відповідно до такої у плодів від здорових матерів. Використання МКАт до ендотеліну-1 виявило підвищення світіння ендотеліоцитів в судинах як артеріального, так і венозного типів у плодів основної групи відповідно до такої у плодів групи порівняння. В матках плодів від матерів в ХІНСШ спостерігається зниження гормон продукуючої активності відповідно до такої у плодів від матерів з фізіологічною вагітністю. Виявлені зміни в матках плодів від матерів з інфекційною патологією свідчать про грубі порушення закладки і формування основних компонентів органу та обумовлені хронічною гіпоксією та дією інфекційного агенту. насамперед патоморфологічні особливості будови стінки матки плодів від матерів з ХІНСШ можуть сприяти у подальшому утрудненню настання та порушенню розвитку вагітності.

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

Introduction

As one of the major problems of the modern obsterics and gynecology, that we are supposed to name here, are complications of pregnancy caused by the infectious pathology [1, 7]. On one hand, this is because of its prevalance among pregnant women, on the other hand

though, this is because of a high amount of stillbirth and disorders of the fetal formation in utero [2, 3]. Despite of this fact, on the aforementioned stage of development of the care for pregnant women there is no mandatory screening of this pathology, likewise in most of cases it is comordbidity and is not conseidered as a main reason of death of fetus and newborn. In addition, we have to emphasize, that in 30-50% of cases an infectious process is hidden [4, 5]. However, the percentage of formation of the development' disorders, which are incompatible with life is constantly growing [6, 7]. It is well-known, that the infectioning during pregnancy lead to the disorder of organogenesis of the cardio-vascular, nervous, endocrine, urinary and reproductive systems of fetus. The stage of severity of this disorder depends on the type of pathogen, stage of the infectious process during pregnancy, as well as existance of comorbidities of mother [8, 9]. It is known, that severe disorders are observed mainly in case of systems, the formation of which is completed till the childbirth, what makes a restoration of cell composition in the subsequent ontogenesis impossible. As one of those systems we can name a female reproductive one [10, 11, 12]. However, on the following stage of the science development the pathomorphological features of the uterus wall structure in case of fetuses from mothers with a chronic infection of the genital tracts have not been described yet.

The aim of the research is to disclose pathomorphological features of the uterus wall structure in case of fetuses 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 37-40 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 cytumegalovirus 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.

Antropometric indicators of the fetuses from the group of comparison reached the following values: body weight 0.538 ± 0.019 kg, body length 0.26 ± 0.04 m, the coefficient of harmony 19.84 ± 3.61 kg/m³. In the main group the body weight of fetuses reached the following data: 0.548 ± 0.195 kg, body length -0.24 ± 0.02 m, the coefficient of harmony -18.07 ± 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, 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 μ m 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 led 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) [13].

The evaluation of the immunohistochemical reaction with treatment of speciments by MCAT to estrogen and progesterone were led 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 $\chi 2$ 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/ormaximum [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 [14].

The research results and its discussion. The organs of fetuses were located in the following way: the bottom and the body were in the plane of the pelvis, and the cervix was located in the pelvic cavity. The uterus in all cases was pear-shaped. The ratio of cervix to body reached 2:1. The main organometric indexes of the fetal organs are provided in the Table 1.

By analyzing data from the Table 1, we can come up with the following solution: main organometric indexes of the fetal uterus from mothers with a complicated pregnancy are clearly decreased comparing to ones in case of fetuses from healthy mothers.

The observative histological research of specimens, that were stained by hematoxylin and eosin allowed to reveal, that the uterus wall in all observations are represented by three

components: endometrium, myometrium, perimetrium. The average indexes of thickness of the uterus layers of fetuses from study groups are provided in the Table 2.

Table 1

The organometric indexes of fetal organs from the study group with a gestational term of 37-40 weeks

Index	Group of comparison	Main group
Weight of uterus, kg	$4,87\pm0,17x10^{-3}$	4,19±0,15x10 ⁻³ *
Length of the uterus body, m	$3,98\pm0,14x10^{-2}$	3,27±0,11x10 ⁻² *
Thickness of the uterus wall,	$7,95\pm0,27x10^{-3}$	7,51±0,26x10 ⁻³ *
m		

Note $p \le 0.05$

Table 2

The indexes of thickness of main structural components of the fetal uterus from the study groups with a gestational term of 37-40 weeks, (m)

Group		Thickness of	Thickness of	Thickness of
		endometrium	myometrium	perimetrium
Group	of	$2,87\pm0,09x10^{-3}$	$3,45\pm0,12x10^{-3}$	$1,74\pm0,05$ x 10^{-3}
comparison				
Main group		$2,44\pm0,09x10^{-3}$ *	$3,46\pm0,12x10^{-3}$	$1,61\pm0,06x10^{-3}$ *

Note $p \le 0.05$

The data from the Table 2 reveals a probable decrease of the thickness index of endometrium and perimetrium in case of fetuses from mothers, whose pregnancy was complicated by HILGT comparing to one in case of fetuses from healthy mothers.

The endometrium of fetal organs from study groups is represented by basal (deep) and functional surface layers. Basal layers is represented by stroma and glands.

In organs of fetuses from healthy mothers there are few glands, the bottom of which are located at the base of basal layer, as well as they are covered with cylindrical single-row epithelium. In the functional layer glands are represented by glandular tubes, that begin at the base of the basal layer. The number of glands of basal and functional layers is the same.

In the uterus of fetuses from mothers with HILGT glands of basal layer are spreading only for 1/3 of the endometrium thickness and do not have features of the functional activity. Glands are covered by cylindrical epithelium with hypochromic nuclei. The number of glands in the functional layer does not exceed one in the basal layer.

The staining of specimens according to Brache and Felgin-Rossenbeck methods has revealed an intensive reaction in the epithelium cells in uterus of fetuses from healthy mothers

as well as a fact of its decrease in case of uterus of fetuses from mothers with a complicated pregnancy.

The endometirum stroma is represented by connecitve tissue. By applying the immunohistochemical method we have revealed, that in the composition of connective tissue in the fetal organs from the group of comparison the collagen of the I type prevails as a diffusive intensive glow; while, the collagen of the III type is manifested as single foci of glow of a reduced intesity. In fetal organs from the main group the collagen of the I type is manifested as small foci of glow of reduced intensity, while the collagen of the III type though is represented as numerous large foci with an intensive glow.

The average apoptotic index in the endometrium of uterus of fetuses from healthy mothers reaches 17,36 0,61%, while in the uterus of fetuses from mothers with a complicated pregnancy $-27,68 \pm 0,76\%$. By analyzing these indexes we can come up with the following solution: the number of apoptotically altered cells in endometrium of fetuses from main group is clearly increased comparing to one in case of fetuses from the group of comparison.

In the myometrium of fetuses from healthy mothers there is a clear spatial organization of muscle fibers: in the middle layer fibers are located longitudinally, while in the other ones - circularly. In the myometirum of fetuses from mothers with a complicated pregnancy there is a disorder in the spatial organization of muscle fibers as a result of excessive growth of the connective tissue; muscle fibers are delicate, they have chaotic direction, some of them are replaced by connective tissue. The indexes of the glow intensity of the main types of collagens in the fetal myometrium from study groups are provided in the Table 3.

Table 3

The indexes of glow intensity of collagens in the myometrium of fetuses from study groups with a gestational term of 37-40 weeks (conv.un.opt.dens.)

Group	The intensity of glow of the	The intensity of glow of the
	collagen of the I type	collagen of the III type
Group of comparison	0,273±0,011	$0,188\pm0,007$
Main group	0,234±0,008 *	0,355±0,012 *

Note p \leq 0,05

By analyzing data from the Table 3 we can come up with the following solution: in the myometirum of fetuses from mothers with a complicated pregnancy there is an increased collagen formation due to the collagen of the III type.

The vessels of myometrium in all cases are thin-walled with a moderate blood supply. The data, which was collected as a result of the immunohistochemical method towards the level of endotheline producing activity of the vascular component of uterus from study groups are provided in the Table 4.

Table 4

The indexes of the endotheline producing activity of the vascular component of fetal organs from study groups with a gestational term of 37-40 weeks (conv.un.opt.dens.)

Group	Vessels of the arterial type	Vessels of the venous type
Group of comparison	$0,68\pm0,02$	$0,82\pm0,03$
Main group	0,95±0,03 *	1,08±0,04 *

Note $p \le 0.05$

The data from the Table 4 declares a probable increase of glow of the endotheline-1 in the walls of blood vessels both of arterial and venous types in organs of fetuses from mothers with a complicated pregnancy relatively to one in case of fetuses from healthy mothers.

The serous membrane of the uterus wall in all observations was represented by loose fibrous connective tissue, which is being stained in red by picrofuxin according van Gieson.

In all observations in the main group we have declared an inflammatory infiltration of endometrium and perimetrium. The cellular composition of this infiltration is represented by lymphocytes, plasma cells, fibroblasts and single leukocytes.

By applying the immunohistochemical method with MCAT to hormones we have revealed a positive reaction to estrogen (90% of cells) as well as negative one to progesterone in organs of fetuses from healthy mothers. In the uterus of fetuses from mothers with a complicated pregnancy there is a weak positive reaction (30% of cells) to estrogen and a negative one to progesterone.

Thus, all aforementioned organometric indexes in organs of fetuses with HILGT are caused by a chronic hypoxia, which is being formed in placenta in case of this pathology [15, 16]. The immunohistochemical features of the collagens' formation in uterus wall of fetuses from the main group are prescribed by an action of the infectious agent and could lead to the subsequent disorder in the onset and delivering of pregnancy [17, 18, 19]. The increase of apoptosis indexes on endoemtrium of fetuses from mothers with a complicated pregnancy will lead to a decrease of the functional activity of cellular component as well as could stimulate menstrual irregularities in the subsequent ontogenesis [20, 21]. In organs of fetuses from the main group we can notice a decrease of the functional activity, which is caused by persistent disorders in the placental complex in case of this pathology [22, 23]. All postulated changes

cumulated together declare severe disorders in implementation and organogenesis of the fetal uterus under the condition of infectioning as well as could lead to the subsequent disorder of the onset and delivering of pregnancy [24, 25].

Conclusions.

- 1. The organometric indexes of organs of fetuses from mothers with HILGT are clearly decreased comparing to ones in case of fetuses from healthy mothers.
- 2. The uterus wall of fetuses from study groups is represented by three components. In organs of fetuses from the main group there is a clear thinning of endometrium and perimetrium comparing to the group of comparison.
- 3. In organs of fetuses from mothers with HILGT there is a probable decrease of number and functional activity of glands both of basal and functional endometrium layers relatively to one in case of organs of fetuses from healthy mothers.
- 4. In the frame of the immunohistochemical research we have revealed, that in case of organs of fetuses from mothers with a comlicated pregnancy there is a disorder in the collagen formation, as well as an increased number of apoptotically altered cells in endometrium relatively to ones in case of fetuses from mothers with a physiological pregnancy.
- 5. In vessels both of arterial and venous types in organs of fetuses from the main group there is an increased endotheline producing activity comparing to one in case of fetuses from the group of comparison.
- 6. The hormonal activity of organs of fetuses from mothers with HILGT is clearly decreased (30% of cells) comparing to one in case of fetuses from healthy mothers (90% of cells).
- 7. The pathomorohological features of the uterus wall structure in case of fetuses from mothers with a physiological pregnancy are fully corresponding with a gestational term of fetus. However, in the uterus wall structure in case of fetuses from mothers with HILGT there are severe disorders both of structural organization and functional activity of fetal organs.
- 8. All pathomorphological features in the uterus wall of fetuses from the main group, that are mentioned above, are a manifestation of a chronic hypoxia, which is caused by an influence of the infectious agent as well as could lead to the subsequent formation of primary infertility of women, who were born from mothers with this pathoogy.
- 9. Perspectives of the future research: to study pathomorphological changes of the structure of ovaries and fallopian tubes in case of fetuses from mothers with a chronic infection of the lower genital tracts.

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