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PATHOMORPHOSIS OF PERICICATRICIAL MYOMETRIUM: A NEW VIEW CONCERNING THE PROBLEM OF UTERINE SCAR

Abstract. *Objective of the study was assessment of morphological changes in the myometrium with uterine scar available. Reparative processes in the place of preliminary surgery on the uterine wall among middle-aged women are indicated to occur by means of incomplete regeneration and compensatory hyperplasia of the tissue structural elements. Three years after surgery loose connective tissue has practically transformed into scar tissue, but not completely. To prevent complications with uterine scar available the parity of no less than three years after surgery can be recommended. Pathomorphosis of the pericicatricial myometrium differs by imperfect angiogenesis in the scar margins, therefore scar tissues are in the condition of chronic persisting hypoxia, producing in its turn a negative effect on further regeneration.*
Key words: *uterine scar, pathomorphosis, pathomorphology, regeneration.*

Introduction. An increased number of surgeries on the uterus of women of a reproductive age contributed to cases when on the moment of pregnancy anatomical integrity of the myometrium is changed [1, 3, 9]. A scar available on the uterus increases the risk of complications during pregnancy and labor considerably [1, 3, 7, 9]. It makes special terms for out-patient observation of this group of pregnant women.

Uterine scar can be formed after Cesarean section (in the inferior uterine segment, corporal scar on the uterus), after conservative myomectomy before and after pregnancy (both without opening of the uterine cavity and with its opening). Uterine scar can result from uterine perforation in case of intrauterine surgery – abortions, hysteroscopy, and other traumatic complications. Uterine scars after ectopic pregnancy are known as well (in the interstitial portion of the uterine tube, in the point of junction of the rudiment uterine horn with the main uterine cavity, in the uterine cervix after extraction of the cervical pregnancy). Eventually, uterine scar can form after reconstructive-plastic surgery (Strassman's metroplastic surgery, removal of the uterine rudiment horn etc.). Irrespective of a type of surgery performed the formation of uterine scar is associated with the risk of its failure changing biomechanics of the endometrium and causing the risk of diastasis and uterine rupture [1, 2, 3, 7, 8].

In recent 20 years sonographic markers of partial or complete failure of the uterine scar have been formulated [1, 3, 11]. Though, till now there is no clear understanding how the myometrium is remodeled in the pericicatricial portion. The information concerning morphology of the uterine scar failure suggests the following criteria: 1) foci of connective tissue disorganization in the form of mucoid swelling, fibrinoid swelling and fibrinoid necrosis available; 2) necrosis of leiomyocytes advanced into the scar tissue and located on the border with a scar; 3) intramural hematomas and multiple petechial hemorrhages; 4) inflammatory infiltration of a lymphohisticytic character with a substantial content of polymorphic-nuclear leukocytes; 5) neoangiogenesis signs [4, 12]. Meanwhile, an accurate notion concerning morphological basis of pathomorphosis of the pericicatricial myometrium is still lacking.

After surgical injury reparation processes in the myometrium are considered to occur in the norm at the expense of regeneration of the smooth muscle cells (so-called morphological restitution).

In case of tissue reparation disturbance by the mechanism of substitution reparative processes are found both with disorganization of collagen fibrils and intercellular matrix, pronounced inflammatory reaction, and disturbed angiogenesis [4, 5].

Objective: to assess morphological changes in the myometrium with uterine scar available.

Materials and methods: the research was conducted on the base of the Regional Perinatal Center and Municipal Establishment «Maternity Home №5» in Odessa during 2017-2019. 426 women with uterine scar were registered during this period including 115 (27,0%) ones with two and more scars. An average age of the examined women was 33,4±1,1. Three cases of intranatal ruptures of the uterine wall along the "old" scar after Cesarean section were chosen for pathomorphological examination taken from middle-aged women with 33-40 weeks of gestation, without signs of metabolic syndrome, diabetes mellitus, systemic diseases of the connective tissue or other conditions able to disturb reparative processes in the tissues.

The samples of myometrium were preserved in 10 % neutral formalin solution on phosphate buffer (pH 7,2-7,4) during 24 hours. Preparation of histological specimens and their embedding in paraffin were conducted according to the common methods [6]. Microscopy and photography of the specimens were made on the photomicroscope Carl Zeiss (Germany). During histological examination micromorphological structure of the post-surgical scars and the myometrium perifocal tissue was determined. The amount of mitosis per 1000 cells was calculated, and an average distance between the nearest vessels and vascular square were measured.

Immunohistochemical examination was conducted additionally on the series paraffin sections of biopsy material using primary and secondary monoclonal antibodies of Dako sets (USA).

For the quantitative assessment of immunohistochemical examinations the number of cells with immune peroxidase mark (a positive staining) in 10 visual fields randomly selected was calculated under 400-fold microscope magnification (>200 cells) [10]. Proliferative activity index Ki67 (MiB1), collagens of 1 and 3 types, proteins of the muscular tissue intermediate filaments of desmine, and growth factor of the vascular endothelium and fon Willebrand (FW) factor were determined. The above indices were used to assess the level of reparative processes and the state of microscopic surrounding of the scar tissue.

The results obtained were statistically processed by means of nonparametric methods applying the software Statistica 10.0 (Dell StatSoft Inc., USA).

Results. Standard staining with hematoxylin and eosin enabled to find the following morphological manifestation: small pieces of the myometrium with pronounced parenchymal dystrophy of myocytes, their wave-like deformity and focal fragmentation (Fig. 1 Photo H&E 3,5,9). The connective tissue is spread among the muscular fibers in the form of eosinophilic linear and star-like mass located mainly around a great amount of thin-walled vessels of a sinusoid type. Single extra-vascular lymphocytes are located perifocally from the foci of sclerosis. Inflammation signs in the surrounding tissue and vascular walls are not found. The following lesions were found in the rupture area against the ground of the above picture: foci of muscular fibers delamination, microfocal necrotic changes of single myocytes, ruptures of the surrounding connective tissue (reparative foci) and fields of hemorrhagic infiltration. Perifocal irregular reactive inflammatory infiltration is found consisting of lymphocytes and macrophages mainly, with single basophils.

The level of proliferative activity index Ki67 in all the samples was less than 2%, which is indicative of the fact that reparative process in the tissue on the moment of intranatal rupture was practically completed.
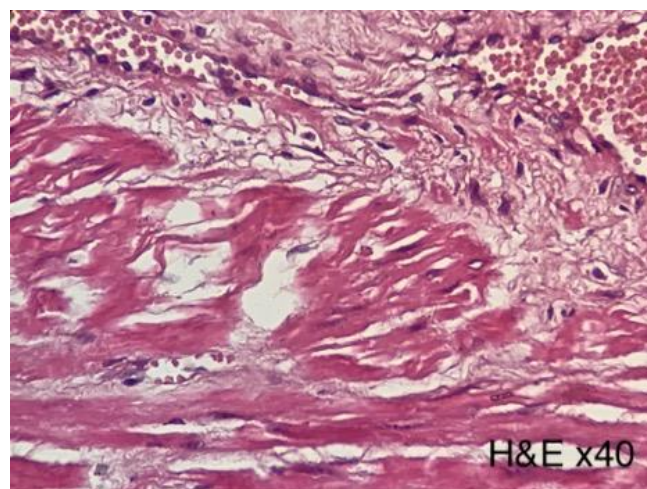

Fig. 1 Morphological picture of uterine scar. Hematoxylin, eosin. Magnification x40

Collagens of I and III types in the scar tissue were characterized by inhomogeneous content. Mostly collagens of I type are located in the form of fibril fractions in spaces between the bundles of the muscular fibers and in the basal membrane of the thin-walled vessels of a sinusoid type in the foci of connective tissue spread (scar tissue). Collagens of III type prevail in the membranes of myocytes, fibrocytes and fibroblasts. They are contained irregularly in the surrounding tissue of the scar margins (Fig. 2a).

Vascular endothelial growth factor (VEGF) is a signal protein produced by a cell under condition of hypoxia. Its function is initiation of neoangiogenesis in the tissue where active reparative process is taking place. It is contained in the intermediate connective tissue, get bounded with an appropriate receptor in the endothelium of a damaged vessel and provokes an active growth of new epithelium. In its turn, it results in the development of thin-walled microvessels as one of the most important human reparation chains. VEGF content in the samples submitted for examination was irregular (Fig. 2b). The immune peroxidase mark is more considerably evident in the tissues of a scar and perifocally in the myometrium, which is indicative of the fact that the tissue is under condition of chronic hypoxia. Irregular staining indicates that hypoxia is persisting.

In its turn, this index can be indirectly assessed as an unfavourable one concerning maturity of the scar tissue. In association with irregular distribution of collagens it is indicative of reduced elastic properties of the scar.

Fon Willebrand (FW) factor is a complex glycoprotein. Its function is provision of platelet attachment to the endothelium of a damaged vessel and thus ensuring hemostasis. FW is expressed by the mature vascular epithelium only. Therefore, it cannot be contained (or be presents in minimum amount) in the microvessels of a sinusoid type. It is this picture shown in the presented samples (Fig. 2c). It should be noted that vascular density on the given samples is rather high. The vessels are mature capillaries mainly, but immature thin-walled vessels are in sufficient amount as well. The distance between the vessels is not long which is indicative of the fact that reparative processes were very active.

Desmine is a protein of intermediate filaments located close to Z-line in the sarcomeres of myocytes. Its examination in the give samples
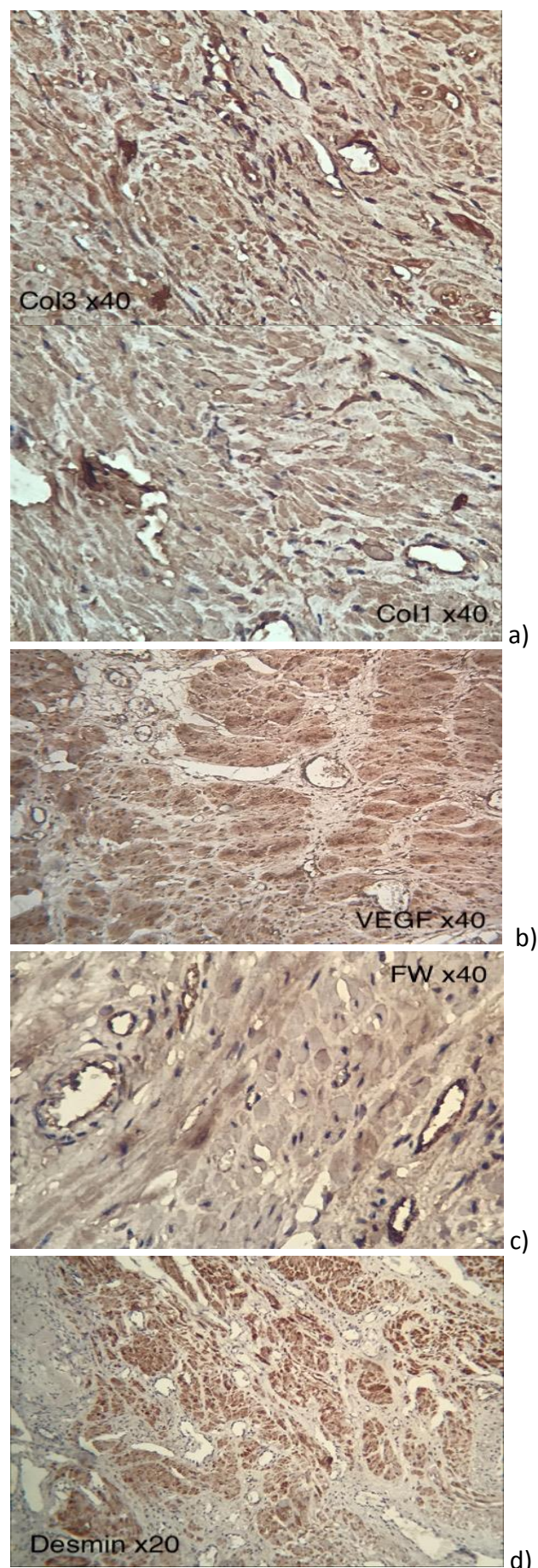

Fig. 2. Expression of the examined proteins by means of immunohistochemical method. Magnification x 400 (a – content of collagens 1 and 3, b –VEGF content, c – FW content, d –desmine content).

was made with the purpose to prove that healing in the postoperative wound occurred by means of incomplete regeneration (substitution), that is, at the expense of the connective tissue spread with compensatory hyperplasia of myocytes and muscular fibers. However, the muscular fibers in the connective tissue of a scar lose their one direction and are located rather chaotically (Fig. 2d). These changes also affect elasticity of the uterine wall in the place of previous surgery.

Conclusions:

1. In middle-aged women reparative processes in the place of preliminary surgery on the uterine wall take place by means of incomplete regeneration and compensatory hyperplasia of the tissue structural elements.

2. Three years after surgery loose connective tissue has practically transformed into scar tissue, but not completely. To prevent complications with uterine scar available the parity of no less than three years after surgery can be recommended.

3. Pathomorphosis of the pericicatricial myometrium differs by imperfect angiogenesis in the scar margins, therefore scar tissues are in the condition of chronic persisting hypoxia, producing in its turn a negative effect on further regeneration.

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