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Structural Changes in the Fallopian Tubes in Patients with Ectopic Pregnancy

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RELEVANCE Ectopic (extrauterine) pregnancy (EP) occupies a leading place in the structure of urgent gynecological morbidity. This pathology poses a threat to the health and life of a woman, being one of the leading causes of maternal mortality during pregnancy in the first trimester. Among emergency gynecological operations, surgical interventions for EP make up about 50%, and in recent years, most operations are performing by the laparoscopic method. However, up to now, the pathomorphological changes in the fallopian tubes in patients with EP remain poorly understood.

AIM OF THE STUDY. To investigate the features of pathomorphological changes in the fallopian tubes in women with tubal pregnancy, operated on by the laparoscopic method, to substantiate the volume of surgery in patients with this pathology.

MATERIAL AND METHODS. Morphological examination was carried out in 100 women operated on for tubal pregnancy using the laparoscopic method. A comprehensive morphological study of the removed fallopian tubes was performed.

RESULTS AND DISCUSSION. The implantation of the ovum in the fallopian tube led to significant changes in its macro- and microstructure, that changes were caused by the invasion of chorionic villi and involved all layers of the tube wall, differing only in the depth of penetration and prevalence. The anatomical features of the structure of the fallopian tubes contributed to the deep invasion of the ovum into the myosalpinx and subserous parts of the tube, creating the possibility of wall rupture in this area.

CONCLUSIONS. 1. In all cases of ectopic pregnancy, implantation of the ovum was accompanied by invasion of cytotrophoblast and syncytiotrophoblast, and this invasion involved all layers of the tube wall, differing only in depth and prevalence. The invasive properties of the cytotrophoblast lead to the development of pronounced degenerative changes in the tube wall, which leads to functional inferiority of the tube after the onset of tubal pregnancy in it.

2. The chronic productive endo- and myosalpingitis diagnosed in most patients with ectopic pregnancy with deformation of the tube lumen against the background of changes in the tube wall caused by cytotrophoblastic invasion is an indication for tubectomy. Performing organ-preserving operations on an anatomically and functionally altered fallopian tube is impractical, since there is a high risk factor for recurrent tubal pregnancy in this tube.

KEYWORDS: ectopic (extrauterine) pregnancy, laparoscopy, morphological examination

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CTI – cytotrophoblastic invasion
EB – ectopic pregnancy

INTRODUCTION

Ectopic (tubal) pregnancy (EB) occupies a leading place in the structure of urgent gynecological morbidity [1–7]. Despite all the achievements of modern science, until now this pathology poses a threat to the health and life of women, being one of the leading causes of maternal mortality during

pregnancy in the first trimester [8–11]. Among urgent gynecological operations, the frequency of surgical interventions for EB varies in different gynecological hospitals from 8.8 to 55.0%, and in recent years, most operations have been carried out by the laparoscopic method [12–14].

In the structure of EB, the dominant position is taken by tubal pregnancy, which accounts for 96.5–98.5% of cases [15–18]. This circumstance demonstrates the special significance of this localization of EB and explains the greatest interest in the diagnosis and treatment of patients with this pathology.

The incidence of EB (in relation to the total number of pregnancies) is 1.2–2.0% and maintains a steady upward trend, especially in the group of young nulliparous women and women aged 30–40 years [8, 19–21]. Of particular relevance is the problem of the "first" EB, since more than 50% of patients after surgical treatment have impaired reproductive function, and the frequency of repeated ectopic nidations is 7–17% [1, 16, 20, 22]. Optimization of management tactics for patients with EB is widely discussed in the literature; nevertheless, a number of its aspects require clarification and addition.

The question of the volume of surgical intervention, as well as the possibility of conservative treatment of EB [1, 8, 16, 23], remains debatable. The results of the effectiveness of the performed organ-preserving operations on the fallopian tubes (tubotomy, squeezing of the ovum), as well as conservative treatment by introducing methotrexate, are very contradictory [1, 8, 23].

It should be noted that the pathomorphological changes in the fallopian tubes in patients with EB remain poorly understood. The results of these studies can not only make it possible to understand the insufficiently studied issues of the morphogenesis of this disease, but also solve the issue of justifying the rational volume of surgical interventions in patients with this pathology.

THE AIM of the study was to investigate the features of pathomorphological changes in the fallopian tubes in women with tubal pregnancy, operated on by the laparoscopic method, to substantiate the volume of surgery in patients with this pathology.

MATERIAL AND METHODS

Morphological examination was carried out in 100 patients who underwent surgical treatment for tubal pregnancy using the laparoscopic method.

Laparoscopy was performed under endotracheal anesthesia, allowing complete relaxation of the muscles of the abdominal wall. To carry out laparoscopy, we used an endosurgical stand with equipment from Karl Storz (Germany). Nitrous oxide was used to create pneumoperitoneum. When performing laparoscopy, the localization of EB in various parts of the fallopian tube was diagnosed. It was noted that in 82 patients (82.0%) the ovum was located in the ampullar section of the tube, while in other parts of the tube it was determined much less frequently: in the isthmic section – in 15 (15.0%) and in the interstitial section – in 3 patients (3.0%). Interstitial localization of tubal pregnancy presented certain difficulties for performing laparoscopic surgery. Patients with this localization of EB underwent laparoscopic removal of the tube with excision of the uterine angle using a bipolar instrument and / or a ligating and transverse endoscopic instrument with a Liga Sure knife (5 mm in diameter) with obligatory suturing of the excised area with 2–3 Vicryl sutures.

A detailed morphological study of the fallopian tubes removed during the operation was carried out. Morphological studies of structural changes in the fallopian tubes were carried out in accordance with generally accepted criteria [24–26].

The first stage of the macroscopic examination was an external examination, – the size and shape of the tube were determined, the serous cover, its integrity, and the presence of hemorrhages were assessed. After that, along the entire length of the fallopian tube, cross-sections were made through the full thickness with an interval of 0.4–0.5 cm. The morphological conclusion included an indication of the section of the tube in which the implantation occurred, the stage of development and the form of pregnancy disorders. A histological examination of all sections of the fallopian tube was performed, both in the zone of implantation of the ovum and its other anatomical parts (funnel, ampulla, isthmus). Pieces of tissue were fixed with neutral formalin, embedded in paraffin, and the obtained sections were stained with hematoxylin and eosin according to Van Gieson and studied using the MSB reaction for fibrin [26]. On the basis of the results of clinical, ultrasound and laparoscopic examination, as well as data of macro- and microscopic analysis of the removed fallopian tube, the pathogenetic variant of tubal pregnancy was determined: progressive tubal pregnancy, incomplete tubal abortion; complete tubal abortion; tubal pregnancy resulting in rupture [22].

RESULTS AND DISCUSSION

The histological picture of tubal pregnancy was characterized by the presence of elements of the ovum, trophoblast tissues, and blood clots in the dilated tube. In some cases, the chorionic villi were associated with the folds of the mucous membrane, growing into the wall of the tube, or were located freely in fresh or hemolyzed blood. The length of the fallopian tubes ranged from 6.5 to 10.4 cm, averaging 8.9 ± 0.25 cm. In most cases (89 cases), a diffuse or local increase in the thickness of the fallopian tube was diagnosed, the diameter of the tubes was from 0.7 to 3.5 cm. The fallopian tubes had the largest diameter in ampullar localization of EB, which was due to the greater ability of this anatomical area to stretch.

The spread of pathological changes in the fallopian tubes during tubal pregnancy (chorionic villi, decidual tissue, destructive changes in the endo- and myosalpinx, focal and diffuse hemorrhages, focal and diffuse leukocyte infiltration) increased correspondingly to an increase in the length of the fetus.

In comparison with uterine pregnancy, the number of chorionic villi in the ectopic trophoblast was significantly reduced, and most villi were with symptoms of hyalinosis. The chorionic tissue was immature; there were dense cords of syncytio- and cytotrophoblasts with lacunar spaces.

Histological examination of serial sections of the fallopian tube outside the zone of implantation of the ovum revealed changes in the endosalpinx, myosalpinx, serous layer and mesosalpinx. The totality of morphological changes in different layers of the tube determined the picture of chronic nonspecific productive salpingitis.

The greatest changes in various parts of the tube were found on the side of the endosalpinx. As a rule, these were deformations and sclerosis of the endosalpinx folds of varying severity, narrowing of the tube lumen. With the progression of atrophic processes in the endosalpinx, the mucous membrane of the ampullar region acquired the appearance of short, rough folds with sclerosis of their stroma, hyalinosis of the walls of arterial vessels, or underwent complete restructuring in the form of pillow-like thickenings with the presence of glands of different shapes in the thickness of the mucosa. This led to a pronounced narrowing of the tube lumen. The diagnosed changes in the lumen of the tube prevented the passage of the fertilized egg, as a result of which implantation occurred distal to the deformation areas of the lumen of the tube.

The sclerotic-deforming processes of the endosalpinx were combined with changes in the myosalpinx of different nature and severity. In all cases, the muscle layer was diagnosed with signs of chronic inflammation in the form of diffuse or perivascular lymphoplasma cell infiltration extending to the outer sections of the tube wall or combined with inflammation in the stroma of the endosalpinx folds.

In the serous layer of the tube and fibro-adipose tissue of the mesosalpinx, inflammatory changes in the form of diffuse and large-focal perivascular infiltration were diagnosed. The fimbrial part of the tube from the side of the mucous membrane is normally characterized by

pronounced folding. In the removed tubes, deforming changes in the folds of the endosalpinx were revealed while maintaining a sufficiently wide lumen of the fallopian tubes. Morphologically, the disorganization of the endosalpinx manifested itself in the form of coarsening, shortening, flattening of folds, sclerosis of their stroma, with or without signs of chronic inflammation in the connective tissue stroma. In some sections of the tubes, tree-like branching folds were diagnosed with their complete or partial atrophy in other sections (Fig. 1 A – C).

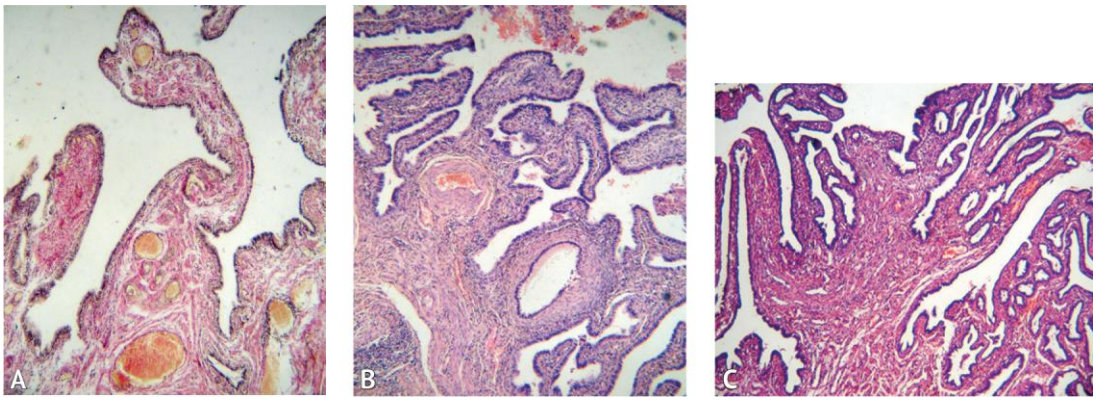

Fig. 1. Morphological changes in the folds of the endosalpinx in the fimbrial section of the tube: A, B — short, rough, deformed folds of the endosalpinx with sclerosis of the stroma and walls of blood vessels, x100 magnification; C — treelike branching fold of the endosalpinx, x34 magnification; A — Van Gieson staining; B, C — staining with hematoxylin and eosin

Signs of chronic perisalpingitis, varying in severity and prevalence, were identified. In some cases, they were combined with changes in all layers of the tube wall, in others – with changes in the endosalpinx, and in others signs of chronic perisalpingitis were isolated. As a result of the adhesions along the serous-muscular layer of individual sections of the tube, non-straightening bends at 90–180º appeared, which looked like a "double-barreled gun" in the transverse sections. Histologically, there was no mesothelium layer in the fusion zone, and the muscle layers were separated by a layers of loose connective tissue of different thickness (Fig. 2 A, B). Along with serous-serous adhesions of the tubes, other morphological changes in the serous layer were determined, such as, for example, reactive hyperplasia of the mesothelium or its squamous cell metaplasia, invagination of the mesothelium into the serous layer with the formation of inclusive microcysts, as well as the presence of short or wide fibrous adhesions (Fig. 2 C, D). It should be noted that in all cases, certain manifestations of perisalpingitis were combined with signs of chronic inflammation in the serous layer of the tube, sometimes they spread to the mesentery of the tube. In all cases, signs of perivascular inflammation prevailed in the form of loose or dense lymphatic-plasma cell infiltrates (Fig. 3 A, B). Morphological signs of chronic sclerotic-deforming salpingitis of the fallopian tubes in EB were found in 80% of cases.

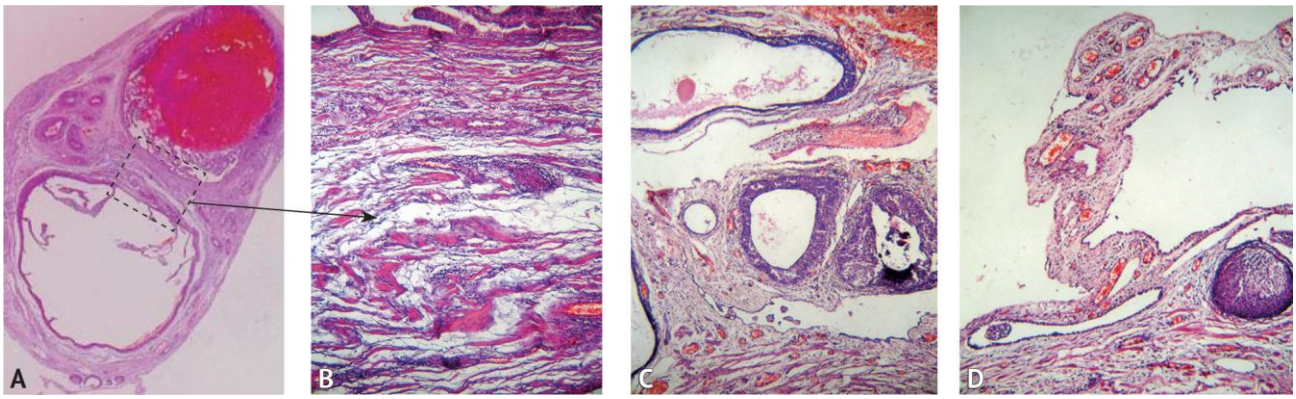

Fig. 2. Morphological manifestations of chronic perisalpingitis: A — scanning the transverse section of the tube, fusion along the serous layer with the formation of a "double-barrel"; B — zone of fusion along the serous layer; C — numerous mesothelial cysts; D — fibrous adhesion of the serous layer of the tube, staining with hematoxylin and eosin, x100 magnification

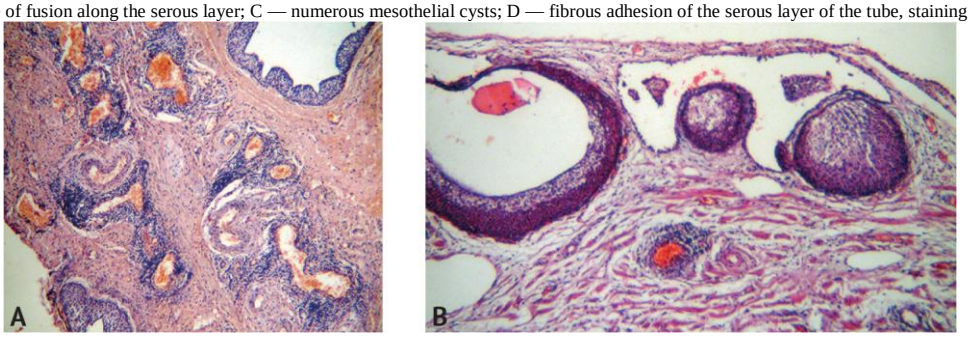

Fig. 3. Morphological manifestations of chronic perisalpingitis: A — perivascular inflammatory infiltrates in the serous layer; B — serous mesothelial cysts with pseudosquamous metaplasia; staining with hematoxylin and eosin, x100 magnification

In 15% of cases, the development of repeated EB was observed in the contralateral tube. The morphological changes in these tubes did not differ from those in the primary tubal pregnancy. The most interesting was the morphological study of the fallopian tubes in 3 patients, in whom a true recurrent EB developed in the tube after a previously performed organ-preserving operation. The diagnosed pregnancy developed in the ampullary part of a tube and ended with an incomplete tubal abortion. In morphological examination in the isthmic part of the tube, the endosalpinx was characterized by flattening, shortening and thickening of the folds. At the border of the ampullar part and the isthmus, the deformation of the tube consisted in the presence of two gaps. The muscle layers were completely traced in one lumen and 2/3 in the other. In this case, the muscle fibers had the wrong orientation, in places they were hypertrophied, and in parts they were replaced by connective tissue. In the intermuscular layers, lymphatic-plasma-cell inflammatory infiltration was determined diffusely and perivascularly. The endosalpinx of both the main lumen and the additional lumen was distinguished by a pronounced deformation of the folds: from complete atrophy to the preservation of single short folds with stromal sclerosis fused at their apexes and forming cribrous and cystic structures (Fig. 4 A – D).

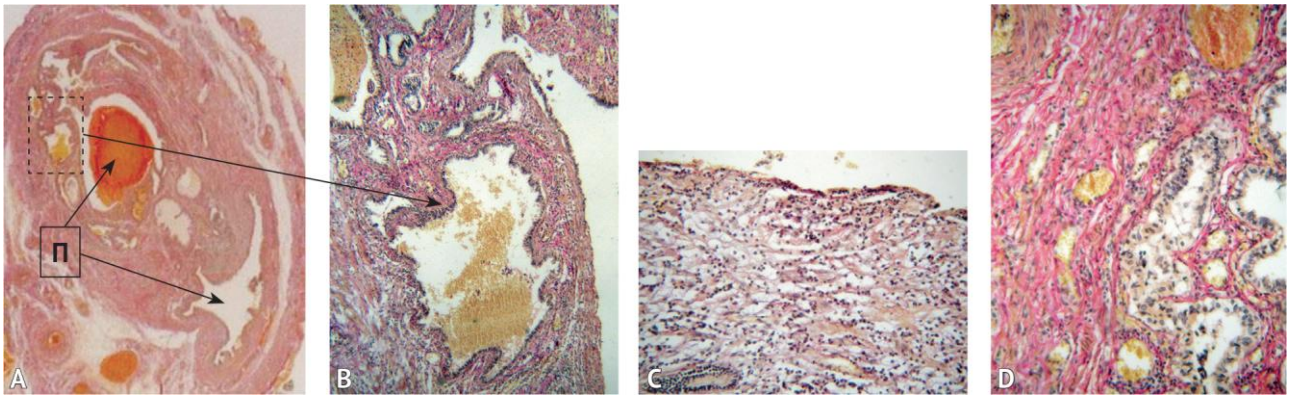

Fig. 4. Morphological changes in the fallopian tube during repeated ectopic pregnancy: A — scanning a cross-section of the isthmic section of the tube with two lumens (П); B — atrophy of endosalpinx folds with cystic enlargement of glands in the mucous membrane, x100 magnification; C — mucosal atrophy with inflammation of the false lumen wall, x200 magnification; D — fibrous replacement of the false lumen wall, x100 magnification; Van Gieson stain

The greatest signs of deformation of the lumen of the tube were found in its ampullar section outside the zone of implantation of the ovum. They consisted in the presence of several lumens of the tube, and two of them retained the structure of the myosalpinx throughout or partially along the perimeter, while differing in the circular arrangement of muscle fibers, up to their complete replacement with connective tissue.

Surgical interventions in the form of a previously performed tubotomy with the removal of the ovum and placental tissue in conditions of incomplete tubal abortion with deep chorionic invasion of the tube wall, dissecting hemorrhages and reactive inflammation in response to placental abruption cause a long process of secondary healing with deformation of the tube lumen, questioning the further implementation reproductive function.

Thus, the pronounced deformation of the fallopian tube in the form of the presence of false lumens and sclerotic-atrophic changes in the endosalpinx, which developed after organ-preserving surgery during tubal pregnancy, indicates that the wound healing process was accompanied by prolonged inflammation and did not lead to a complete restoration of the anatomical structure of the tube. The presence of deformation of all layers of the wall of the fallopian tube and ongoing inflammation after organ-preserving operations disrupt the functional ability of the tube and create conditions for the development of repeated EB in it.

The data obtained by other researchers, along with the morphological changes diagnosed by us, are extremely important for the choice of the optimal tactics for managing patients with tubal pregnancy. Thus, the results of bacteriological examination of the fallopian tubes and the cervical canal showed a high frequency of microbial contamination of the fallopian tubes (69%) and the presence of signs of acute inflammation in them (72%), while in the cervical canal the frequency of infection was only 41% [23, 27]. It should be noted that the most common infectious agents were ureaplasma, mycoplasma, herpes simplex virus [23, 27]. A significant frequency of microbial seeding of the fallopian tubes, as well as prolonged persistence of infection, can lead to obliteration of the operated tube after organ-preserving operations.

We carried out studies to determine the features of the development of cytotrophoblast migration during tubal pregnancy. Changes in the fallopian tubes in the zone of implantation of the ovum were quite polymorphic in terms of the depth of prevalence of cytotrophoblastic invasion (CTI), the degree of hemorrhagic impregnation, gestational rearrangement of the walls of arteries and veins, developing against the background of sclerotic, deforming and inflammatory changes in all layers of the tube wall.

The depth of the CTI was different in different pathogenetic variants of tubal pregnancy. In the majority of observations, the CTI had an unevenly aggressive character from the beginning of gestation. This aggressive character of the CTI was accompanied by active migration of the cytotrophoblast into the tube wall, reaching in most cases the muscle layer, less often the serous layer. The invasive properties of the cytotrophoblast lead to the development of pronounced degenerative changes in the tube wall with damage to the receptor apparatus, which is one of the reasons for the functional inferiority of the tube after the onset of tubal pregnancy.

In all cases of tubal pregnancy, the CTI initially invaded the endosalpinx, leading to focal, complete or circular destruction of the mucosal folds along the entire perimeter of the tube (Fig. 5 A). The same pattern of invasion was observed in the myosalpinx. In most of the observations, the myosalpinx CTI spread throughout the entire thickness of the wall, unraveling the muscle fibers or completely lyzing them (Fig. 5 B, C). In such cases, only the intact serous layer, often with massive hemorrhagic permeation, maintained the integrity of the tube. As a rule, the rupture of the tube occurred in the areas of replacement of the muscle layer by cytotrophoblastic elements. However, this pattern was not observed everywhere. Often, the CTI, involving the endosalpinx and the inner layers of the myosalpinx, was accompanied by gestational restructuring of the blood vessel walls with the CTI into the lumen of the vessels. This led to the destruction of blood vessels and the development of intramural hemorrhages of different scale and prevalence.

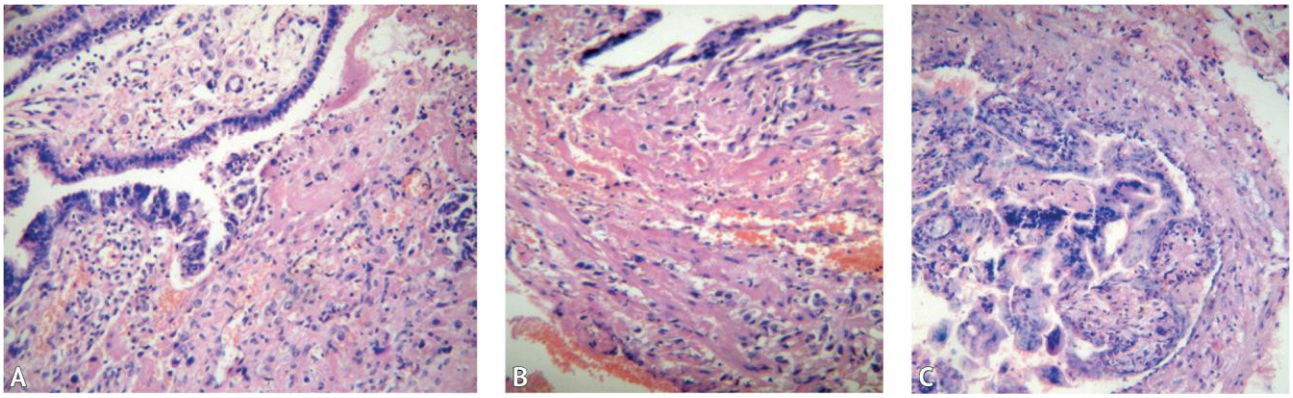

Fig. 5. Features of morphological changes in the fallopian tube in the zone of implantation of the ovum: A — destruction of the endosalpinx fold by cytotrophoblast cells; B — cytotrophoblastic invasion of the myosalpinx with complete replacement of muscle fibers; C — giant cytotrophoblast cells in the lumen of the vein; staining with hematoxylin and eosin, x100 magnification

In several cases, during isthmic implantation of the ovum, a local CTI arose throughout the entire thickness of the muscular layer of the tube, leading to a complete through defect with the spread of cytotrophoblastic elements to the peritoneal cover of the tube. In some cases, EB implantation of the ovum in the mucous membrane led to local cytotrophoblastic lysis of the muscle layer with the invasion of chorionic elements into the connective tissue of the mesosalpinx, with a violation of the integrity of the fetus. In this case, the main lumen of the tube remained intact from pregnancy, and the rapid regeneration of the mucous membrane did not allow to accurately determine the site of primary implantation. Reactive inflammatory changes in the myosalpinx were found only in cases of abnormal pregnancy of the type of incomplete tubal abortion, when detachment of the ovum occurred with morphologically confirmed signs of dystrophic and necrotic changes in the chorionic villi structures. In these cases, signs of exudative inflammation with dissociation of muscle fibers and cytotrophoblastic structures were observed in the myosalpinx. Similar data were obtained by other scientists, who also analyzed the features of the CCI in different variants of the course of tubal pregnancy [25, 27].

In the presence of clinically confirmed progressive EB, a macroscopic examination of the tube showed its local bulbous thickening, and the preservation of the ovum was diagnosed on the section. Histologically, in these cases, in the implantation zone, a diffuse CCI along the entire perimeter of the tube with complete destruction of the endosalpinx folds and shallow invasion of the myosalpinx was determined. At the same time, vascular plethora in the absence of necrobiotic changes was determined in the cellular structures of the chorionic syncytium, cytotrophoblast, chorionic villi, membrane of the ovum.

The study of the fallopian tube in cases of complete tubal abortion, as a rule, did not reveal areas of primary implantation or decidual rearrangement of the endosalpinx. Confirmation of complete tubal abortion was the detection of elements of placental tissue in the blood clots removed from the abdominal cavity. The absence of direct and indirect signs of pregnancy in the fallopian tube could be explained by the initial implantation within the endosalpinx and the regeneration of the mucous membrane after the release of the ovum into the abdominal cavity. Histologically, a certain age of complete abortion could be judged only by the degree of necrotic changes in the placental tissue in blood clots.

CONCLUSIONS

1. In all cases of ectopic pregnancy, implantation of the ovum was accompanied by invasion of cytotrophoblast and syncytiotrophoblast, and it touched all layers of the tube wall, differing only in depth and prevalence. The invasive properties of the cytotrophoblast lead to the development of pronounced degenerative changes in the tube wall, which lead to functional inferiority of the tube after the onset of tubal pregnancy in it.

2. Chronic productive endomyosalpingitis diagnosed in most patients with ectopic pregnancy with deformation of the tube lumen against the background of changes in the tube wall caused by cytotrophoblastic invasion is an indication for tubectomy. Performing organ-preserving operations on an anatomically and functionally altered fallopian tube is impractical, since it is a high risk factor for repeated pregnancy in this tube.

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