COMPARATIVE MORPHOLOGICAL CHARACTERISTICS OF THE UTEROPLACENTAL AREA IN ABNORMAL PLACENTATION

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ABSTRACT

The aim. *To carry out a comparative morphological characteristic of the uteroplacental area with abnormal placentation – pl. accreta, pl. increta, pl. percreta.*
Materials and methods. *The study included 47 patients with atypical placentation; the comparison group included 10 healthy pregnant women with uterine scar after a previous caesarean section. A histological study of uteroplacental area samples was performed with hematoxylin and eosin, methylene blue staining. An immunohistochemical study with primary antibodies to cytokeratin 7 (CK7), Hif2a, vascular endothelial growth factor, α-SMA was carried out. The differences between the compared values were considered to be statistically significant at $p < 0.05$.*
The results of the study. *Pl. accreta was determined in 12 (25.5 %), pl. increta – in 30 (63.9 %), pl. percreta – in 5 (10.6 %) patients. In all patients of the main group, the decidua was completely or partially absent in the area of abnormal placentation or was replaced by an uneven layer of fetal fibrinoid. Cases when placental villi unevenly penetrated into the thickness of myometrium in the form of "tongues" or "coves" bordered by fetal fibrinoid and often located intermuscularly were defined as pl. increta (n = 26). Cases with the placental villi ingrowth to the serous membrane were considered as pl. percreta (n = 5). In cases with deep variants of ingrowth (pl. increta and pl. percreta) (n = 31), the villi were visualized in the lumen of the vessels and the thinning of the lower uterine segment with the presence of stretched muscle bundles was revealed. Aseptic necrosis of the myometrium was found: in 2 (16.7 %) of 12 women with pl. accreta, in 26 (86.7 %) of 30 women with pl. increta and in 5 (100 %) women with pl. percreta. There were no areas of necrosis in the myometrium of the women of comparison group.*
Conclusion. *The appearance and increase of myometrial necrosis zones in response to an increase in the depth of placental villus ingrowth were detected. Myometrial necrosis zones could be the cause of activation of angiogenic factors and an important stimulus for the development of abnormal vascularization in placenta accreta spectrum.*

Key words: *angiogenesis, aseptic necrosis, placenta accreta spectrum, invasion in the myometrium, trophoblast, fetal fibrinoid*

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СРАВНИТЕЛЬНАЯ МОРФОЛОГИЧЕСКАЯ ХАРАКТЕРИСТИКА МАТОЧНО-ПЛАЦЕНТАРНОЙ ОБЛАСТИ ПРИ АНОМАЛЬНОМ ПРИКРЕПЛЕНИИ ПЛАЦЕНТЫ

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РЕЗЮМЕ

Цель исследования. *Провести сравнительную морфологическую характеристику маточно-плацентарной области при аномальном прикреплении плаценты – плотном прикреплении, врастании и прорастании плаценты.*
Материалы и методы. *В исследование включено 47 пациенток с атипичной плацентацией; группа сравнения – 10 здоровых беременных женщин с рубцом на матке после предыдущего кесарева сечения. Выполнено гистологическое исследование образцов маточно-плацентарной области с окрашиванием гематоксилином и эозином, метиленовым синим, а также проведено иммуногистохимическое исследование с первичными антителами к цитокератину-7, фактору роста эндотелия сосудов, гладкомышечному актину-альфа. Различия между сравниваемыми величинами признавались статистически значимыми при $p < 0,05$.*
Результаты исследования. *Плотное прикрепление плаценты (pl. accreta) было определено у 12 (25,5 %), врастание плаценты (pl. increta) – у 30 (63,9 %), прорастание плаценты (pl. percreta) – у 5 (10,6 %) пациенток. У всех пациенток основной группы децидуальная оболочка полностью или частично отсутствовала в зоне аномальной плацентации или была замещена неравномерным слоем плодного фибриноида. При pl. increta (n = 26) ворсины плаценты проникали в толщу миометрия неравномерно, в виде «языков» или «бухт», окаймлённых плодным фибриноидом, и часто располагались межмышечно. Случаи с прорастанием ворсин до серозной оболочки рассматривали как pl. percreta (n = 5). При глубоких вариантах врастания (pl. increta и pl. percreta) (n = 31) ворсины визуализировались в просвете сосудов, наблюдалось истончение нижнего маточного сегмента с присутствием растянутых мышечных пучков. Обнаружены асептические некрозы миометрия: у 2 (16,7 %) из 12 женщин с pl. accreta, у 26 (86,7 %) из 30 женщин с pl. increta и в 5 (100 %) случаях при pl. percreta. Участки некрозов в миометрии группы сравнения отсутствовали.*
Заключение. *Обнаружено появление и увеличение зон некроза миометрия в ответ на увеличение глубины врастания ворсин плаценты, которые могут являться причиной активизации ангиогенных факторов и важным стимулом развития аномальной васкуляризации.*

Ключевые слова: *ангиогенез, асептические некрозы, врастание плаценты, инвазия в миометрий, трофобласт, плодный фибриноид*

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INTRODUCTION

Placenta accreta spectrum (PAS) is a complication of pregnancy associated with its abnormal attachment to the uterine wall, in which the placenta does not separate spontaneously after childbirth, which can lead to perinatal complications, massive blood loss and maternal mortality. Worldwide, the incidence of placenta accreta varies from 1.7 to 900 per 100,000 births (an average of 189 per 100,000), which is associated with variability in the formulation of the diagnosis and its clinical confirmation [1], and in recent decades has been about 1 case per 500 births [2–5].

According to the FIGO (International Federation of Gynecology and Obstetrics) classification, which includes clinical and pathomorphological criteria, there are several degrees of placenta accreta: 1st degree (placenta accreta) – dense attachment or increment of the placenta to the muscle layer; 2nd degree (placenta increta) – villi germinate the muscle layer; 3rd degree (placenta percreta) – the placenta sprouts all layers of the uterus. Placenta percreta is divided into subtypes: 3a – invasion within the serous membrane of the uterus; 3b – invasion into the bladder; 3c – invasion into other organs/tissues of the pelvis [6].

In addition to the above FIGO classification, there is an equivalent Russian systematization of atypical placentation [7]. According to the Russian authors, the English-language terms correspond to the following Russian-language equivalents: pl. accreta – pathological growth of the placenta with complete or partial absence of the basal (main) part of the falling shell; pl. increta – placenta accreted to the myometrium and/or placenta penetrated into the myometrium; pl. percreta – placenta fused to the perimeter either with the uterus and organs lying next to it/the placenta penetrated into the perimetrium or with penetration into adjacent structures [7].

An increase in the frequency of placenta accretion in recent decades has been associated with an increase in indications for cesarean section (CS). However, placental overgrowth is also found in women without a scar on the uterus, but who have undergone other manipulations that lead to a violation of the integrity of the endometrium (surgical abortions, diagnostic or therapeutic curettage) [8–11]. Studying the morphofunctional features of the uteroplacental region during placenta accreta and identifying the mechanisms of formation of this complication will allow us to better understand its nature and further develop prevention and treatment tactics. Due to this, the aim of the study was to conduct a comparative morphological characterization of the uteroplacental region in abnormal placental attachment – dense attachment, ingrowth and germination of the placenta.

MATERIALS AND METHODS

The present study included 57 women, of whom 47 patients made up the main group (gestation period – 36.3 (35; 38) weeks) with histologically confirmed placental ingrowth. The comparison group consisted of 10 women at 38.5 (38; 39) gestation weeks with the presence of a scar on the uterus after a previous cesarean section, but without signs of placenta accretion. The work is based on the morphological analysis of samples of the myometrium and placenta. The study did not include patients with severe fetal pathology, multiple pregnancies, and fetus birth defects.

The study was performed in accordance with the ethical principles of the World Medical Association Declaration of Helsinki [12] and the Rules of Clinical Practice in the Russian Federation (Order of the Ministry of Health of the Russian Federation dated June 19, 2003 No. 266) [13]. The study was approved by the Bioethical Commission of the Avtsyn Research Institute of Human Morphology (Protocol No. 35 (11) dated March 23, 2022).

The FIGO classification was used to assess the depth of placental ingrowth [6, 14].

The material for the study was obtained during surgical delivery. Fragments of the myometrium with areas of dense attachment and ingrowth of placental villi were excised according to the operational tactics developed at Vidnovsky Perinatal Center [15].

For histological examination, the obtained pieces were fixed in a 10 % solution of neutral formalin, pH = 7.4 (Biovitrum, Russia) for 24 hours, then enclosed in paraffin, according to the standard procedure. Serial paraffin sections with a thickness of 4 microns were dewaxed and stained with hematoxylin and eosin. To prepare semifine sections with a thickness of 1 μm, samples of the uteroplacental region in the zone of dense attachment and ingrowth were fixed in a solution of 2.5 % glutaraldehyde and 1 % paraformaldehyde in a 0.1 M phosphate buffer (pH = 7.4); then additional fixation was carried out in a 1.5 % OsO_4 solution, dehydration and pouring to araldit. The average area of the semifine section was 0.97 ± 0.3 mm^2. The semifine sections were stained using the PAS method and finished with methylene blue.

Immunohistochemical staining of micropreparations was performed on a closed-type immunostainer (Ventana; Roche, UK) using primary antibodies to cytokeratin-7 (SK-7, cytokeratin-7; Thermo Fisher, USA; dilution 1:300; cat. No. PA5-82291) – for trophoblast visualization; to hypoxia-induced factor Hif2a (Abcam, UK; dilution 1:250, cat. No. ab109616) – to assess the severity of local hypoxia; to smooth muscle actin-alpha (α-SMA, α smooth-muscle actin; Cell Mark, Sweden; without dilution, cat. No. 202M) – to characterize the myometrium and vascular wall; to endothelial vascular growth factor (VEGF, vascular endothelial growth factor; Spring Bioscience, USA; without breeding, cat. No. E2611) – for visualization of vascular endothelium. The product of the immunohistochemical reaction was determined in the form of brown staining in the membrane and/or cytoplasm of cells. The negative and positive controls were set in accordance with the manufacturer's recommendations.

Statistical analysis of the research results was performed using MS Excel 2010 application software packages (Microsoft Corp., USA) and Statistica 10 software (StatSoft Inc.,

USA). The descriptive characteristics of quantitative indicators are presented in the form of median (Me), 25 % and 75 % percentiles (P25 and P75). The Mann – Whitney non-parametric test of the statistical significance of was used to assess the representative sampling of the compared groups. For indicators characterizing qualitative characteristics, the absolute value and the relative value were indicated as a percentage. The differences were considered statistically significant when the significance criterion was less than 0.05.

STUDY RESULTS

When analyzing the comparability of the comparison groups, there were no intergroup differences ($p \geq 0.05$) in age, patient body mass index, birth parity and the number of previous cesarean sections (CS) (Table 1).

Macro- and microscopic characteristics of the placenta and myometrium

The areas of ingrowth looked intraoperatively like a hernia with thinning of the uterine wall (Fig. 1a). In addition, in some cases (n = 33), areas of dense yellowish consistency with sizes from 0.5 to 3 cm^2 in diameter were visualized in the myometrium, which, during histological examination, represented areas of myometrial necrosis. Sometimes (n = 31) a network of large-diameter blood vessels was present in the myometrium in the uteroplacental region (Fig. 1b).

In the main group (n = 47), 22 (46.8 %) pregnant women had a medical history of one CS; 17 (36.2 %) had two CS; 4 (8.5 %) had three CS; 2 (4.25 %) had four CS, and 2 (4.25 %). In women, ingrowth was diagnosed in the absence of a scar on the uterus after cesarean section.

As a result of histological examination, it was revealed that 12 (25.5 %) patients showed dense attachment of the placenta (pl. accreta), 30 (63.9 %) – pl. increta, 5 (10.6 %) – pl. percreta, of which 2 patients had involvement of the bladder wall (3b), and in 3 patients the villi of the placenta germinated myometrium, located up to the serous layer of the uterus (3a).

In all patients of the main group, the decidual membrane was completely or partially absent in the zone of abnormal placentation or was replaced by an uneven layer of eosinophilic homogeneous substance visually corresponding to the deposits of fetal fibrinoid (FF). Cases when placental villi penetrated the thickness of the myometrium unevenly in the form of "tongues" or "bays" (Fig. 1c), bordered by fetal fibrinoid (Fig. 1d), and often located intermuscularly, were defined as pl. increta (n = 26). Cases with the placental villi ingrowth to the serous membrane were considered as pl. percreta (n = 5). In deep variants of ingrowth (pl. increta and pl. percreta) (n = 31), villi were visualized in the lumen of the vessels (Fig. 1e), and there was also thinning of the lower uterine segment with the presence of stretched muscle bundles (Fig. 1e), (Fig. 1b–f).

In 2 (16.7 %) in cases out of 12 with pl. accreta, in 26 (86.7 %) out of 30 with pl. increta and in all cases with pl. percreta, the presence of necrosis zones in the myometrium was noted (Table 2), representing varying degrees of eosinophilic, with an uneven mesh-granular structure, areas in the absence of nuclear basophilia (Fig. 1g).

In some women, there was a slight focal and diffuse inflammatory infiltration in the uteroplacental region (detected in 1–2 out of 10 visual fields at magnification ×400), represented mainly by macrophages and lymphocytes with an admixture of single neutrophils ($p > 0.05$). Due to the weak inflammatory infiltration, these areas of necrosis can be called aseptic. Along with this, FF deposits were present in the uteroplacental region. In the area of necrosis, villi embedded in FF with dystrophic changes, the so-called "shadow villi" (Fig. 1g), took place.

No necrosis zones were found in the myometrium of the comparison group. In the main group, areas of necrosis were observed in all forms of ingrowth, and the frequency of their occurrence in the group increased with the depth of ingrowth of villi into the uterine wall (Table 2).

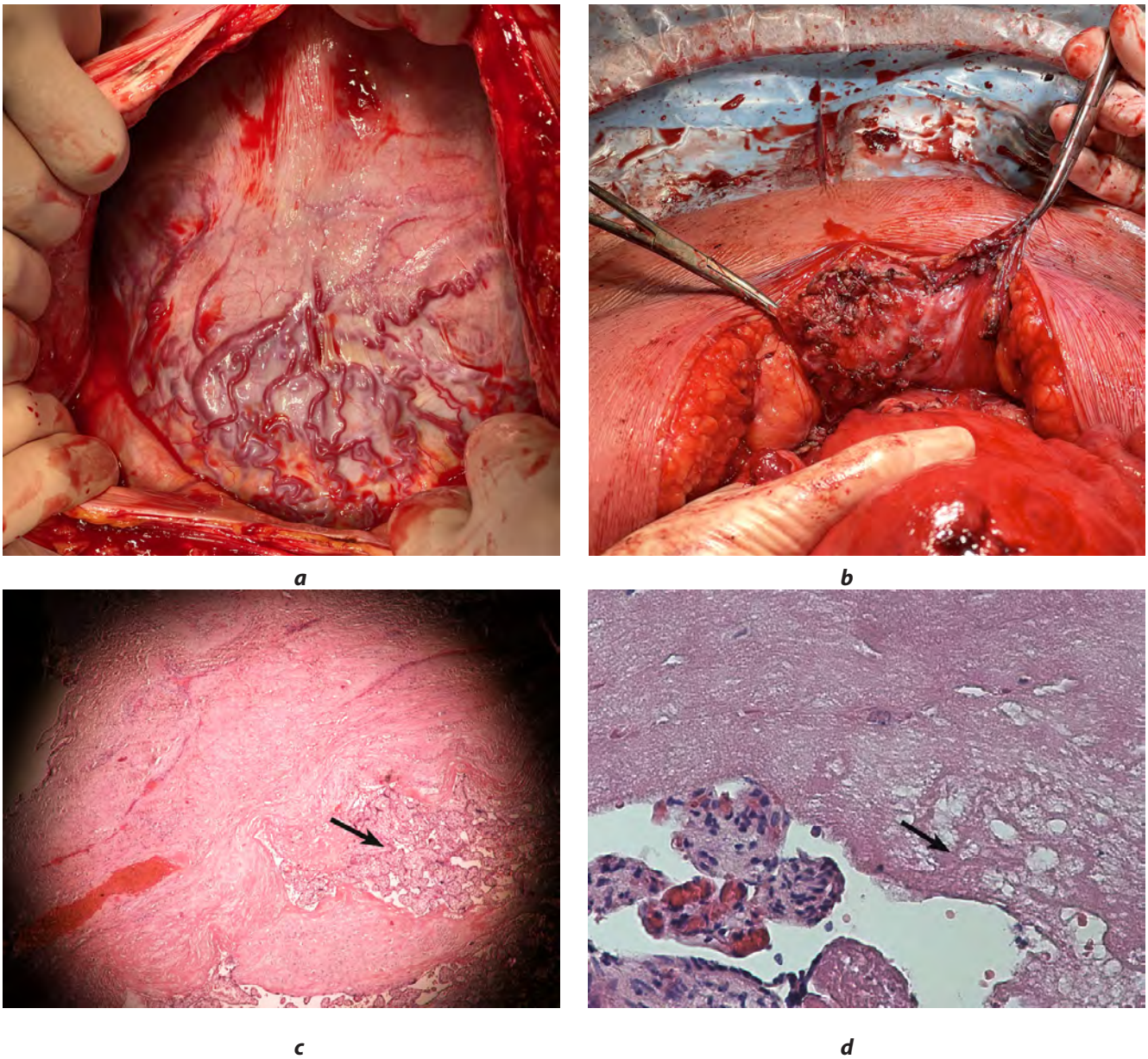
TABLE 1

COMPARABILITY OF COMPARISON GROUPS (MANN – WHITNEY U-TEST, $p < 0.05$)

The studied indicators, Me (P25; P75)	Patient groups		The level of statistical significance, Mann – Whitney U-test ($p < 0.05$)
	Main group (n = 47)	Comparison group (n = 10)	
Age, years	35 (32.5; 36.5)	34 (29; 36)	0.32
BMI, kg/m^2	27.7 (25.5; 30.7)	29.4 (26.8; 31.6)	0.33
Delivery parity, n	2 (1; 2)	1 (1; 2)	0.23
The number of cesarean sections in the anamnesis	2 (2; 3)	3 (2; 4)	0.1

When analyzing the maturity of the villous tree in the comparison group, the villi corresponded to the gestation period with a balance of mature intermediate (20–30 %) and terminal (up to 60–70 %) villi (Fig. 1h). In patients with placental ingrowth, the predominance of mature intermediate villi was noted; the proportion of fully capillarized terminal villi reached 10–20 %, single immature intermediate villi were found in small limited areas.

Trophoblast cells were poorly visualized when stained with hematoxylin and eosin (Fig. 1c–j), however, they were well detected when stained with methylene blue (Fig. 2a–c), including in the area of aseptic necrosis of the uterine wall (Fig. 2d). Trophoblast cells were also intensively stained during immunohistochemical examination with primary antibodies to cytokeratin-7 (Fig. 2f–h). The trophoblast in myometrium was represented both as single cells (Fig. 2h) and as groups of cells



a ***b*** ***c*** ***d***

FIG. 1.

Morphological features in placenta accreta spectrum. ***a*** *– uterine aneurysm with pronounced vascular collaterals on the anterior surface of the uterus (pl. increta).* ***b*** *– coagulated vessels between the posterior wall of the bladder and the anterior wall of the uterus (pl. percreta) (intraoperative picture).* ***c*** *– invasion in the form of "tongues" or "bays"; hematoxylin and eosin staining (marked by arrow), magnification ×20.* ***d*** *– an increased amount of fibrinoid against the background of the absence of decidual cells, contributed to the adhesion of the villus and does not prevent the penetration of invasive trophoblast into the myometrium thickness; hematoxylin and eosin staining, magnification ×100. e – thinning of the uterine wall to the serous membrane (marked by arrow), a lack of a decidual plate and accumulation of fibrinoid deposits; magnification ×20. f – visualization of placental villi in the lumen of blood vessels (marked by arrow); hematoxylin and eosin staining, magnification ×100.*

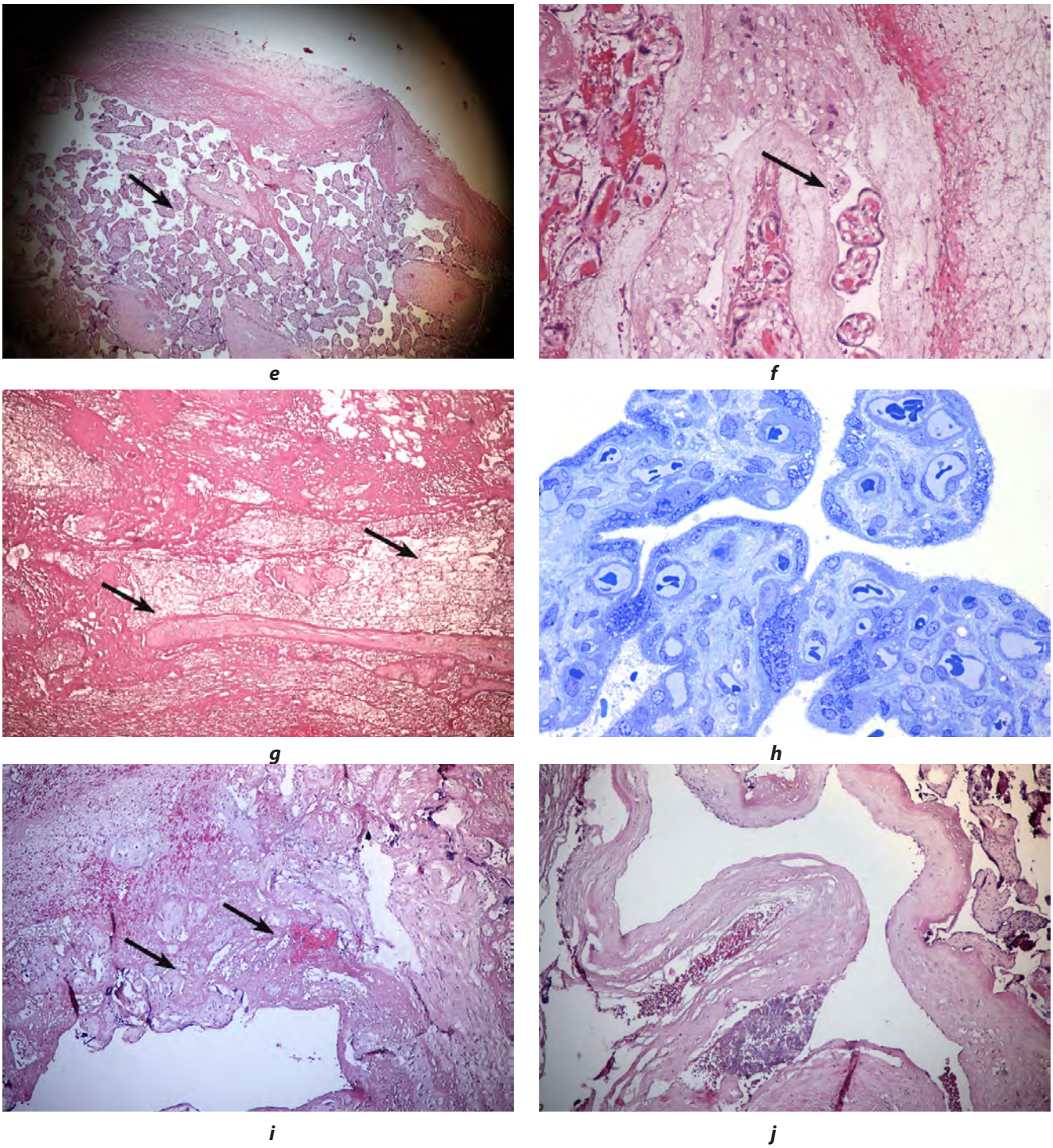


FIG. 1. (continued)

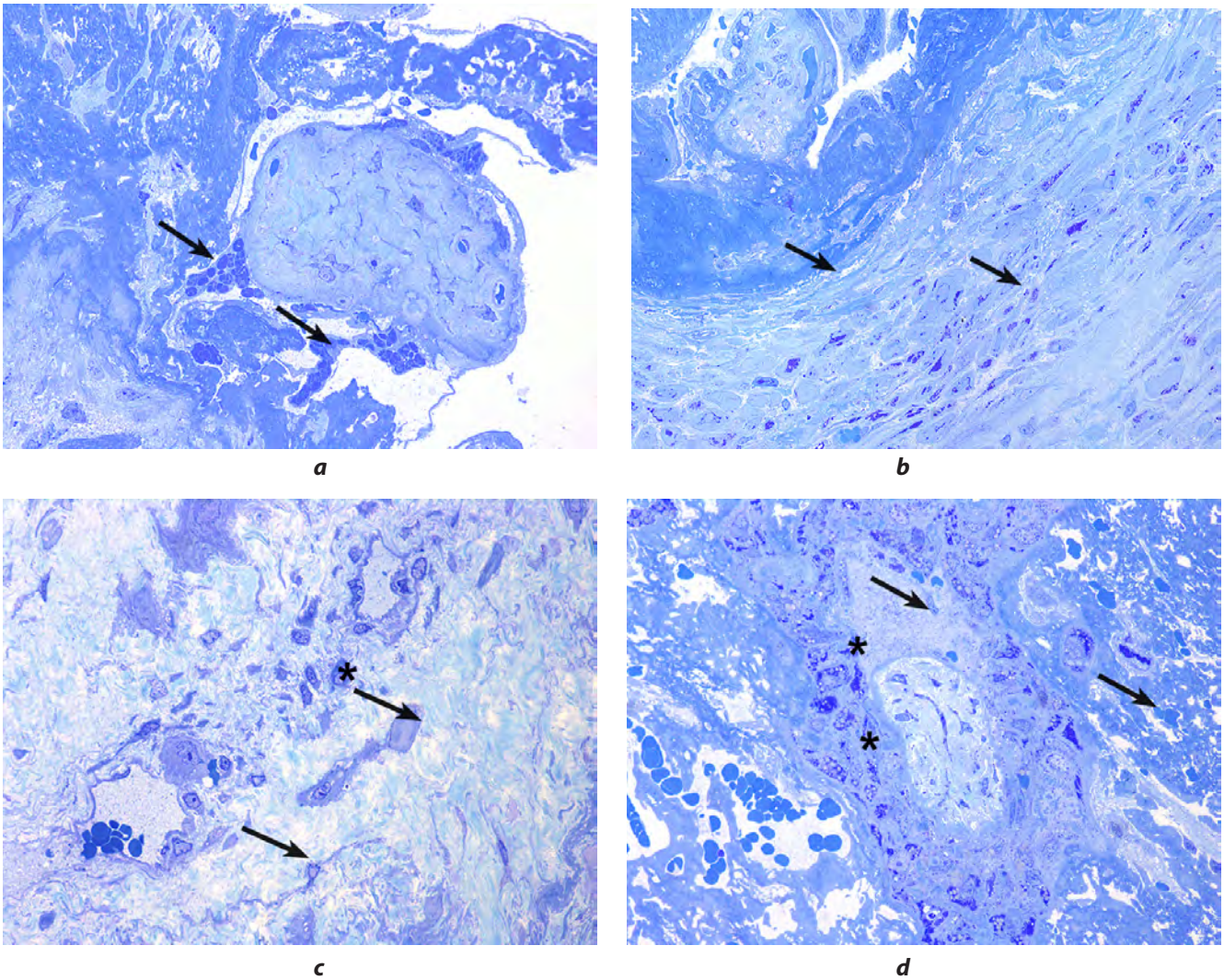
Morphological features in placenta accreta spectrum. ***e*** *– thinning of the uterine wall to the serous membrane (marked by arrow), a lack of a decidual plate and accumulation of fibrinoid deposits; magnification ×20.* ***f*** *– visualization of placental villi in the lumen of blood vessels (marked by arrow); hematoxylin and eosin staining, magnification ×100.* ***g*** *– aseptic necrosis of the myometrium is represented by monomorphic eosinophilic fields with local hemorrhages; there are "ghost villi" with the absence of nuclear basophilia and dystrophic changes; no inflammatory infiltration; aseptic necroses are associated with deep placenta accreta spectrum; hematoxylin and eosin staining, magnification ×100.* ***h*** *– villous tree in pl. increta (syncytiotrophoblast without any signs of damage) in its structure corresponds to the physiological course of pregnancy; methylene blue staining, magnification ×600.* ***i*** *– placental villi ingrowth into the lumen of the vessel; the vessel wall is replaced by fetal fibrinoid (marked by arrow); hematoxylin and eosin staining, magnification ×40.* ***j*** *– vessel in the ingrowth area with a thinned wall; hematoxylin and eosin staining, magnification ×100*

TABLE 2

REVEALING OF MYOMETRIUM ASEPTIC NECROSES DEPENDING ON THE DEPTH OF INVASION

The depth of invasion	The presence of necrosis zones in the myometrium	The proportion of women with necrosis zones in the myometrium of UPA
Healthy with CS	0/10	0 %
Placenta accreta	2/12	17 %
Placenta increta	26/30	87 %
Placenta percreta	5/5	100 %

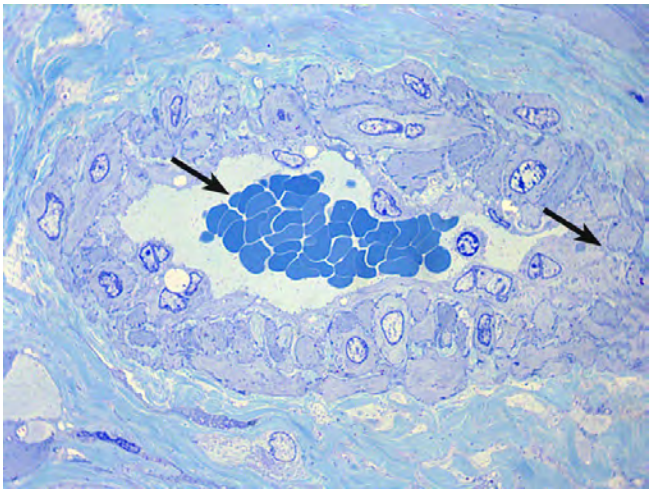
Note. CS – cesarean section; UPA – uteroplacental area.



a ***b*** ***c*** ***d***

FIG. 2.

Morphological features of the placenta and myometrium in placenta accreta spectrum. ***a*** *–invasive trophoblast cells are separated from the villus in the zones of the syncytial sprouts and penetrate into myometrium in the form of a beam (group with placenta accreta spectrum); fetal fibrinoid does not prevent trophoblast invasion (marked with arrows); methylene blue staining, magnification ×1200.* ***b*** *– increased deposits of fetal fibrinoid against the background of the destruction of the decidual plate; fetal fibrinoid does not limit trophoblast invasion (marked with arrows); in the myometrium, the dystrophic changes in the cells are visible, which is confirmed by the presence of pink granules (marked with asterisks); methylene blue staining, magnification ×600.* ***c*** *– abnormal invasion into the myometrium during placenta ingrowth; methylene blue staining (trophoblast cells are marked with arrows), magnification ×400.* ***d*** *– "ghost villus" in the zone of myometrial necrosis (homogeneous bluish masses), trophoblast is visualized around the villus (marked with arrows); magnification ×600.*



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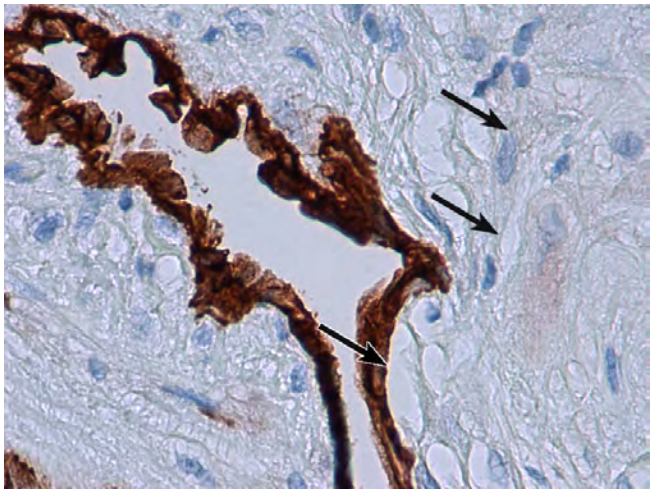

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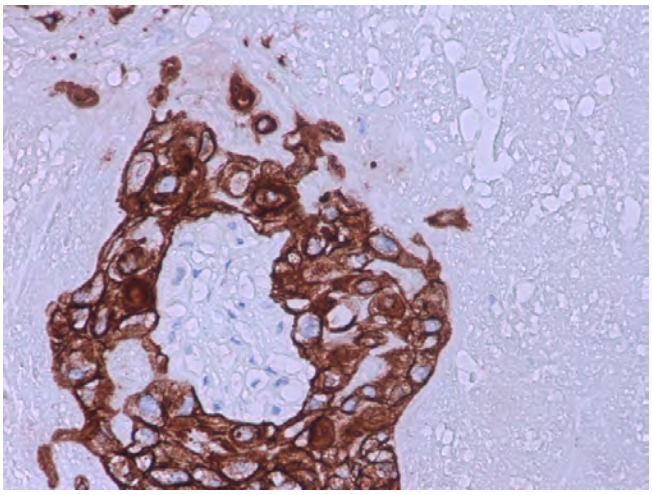

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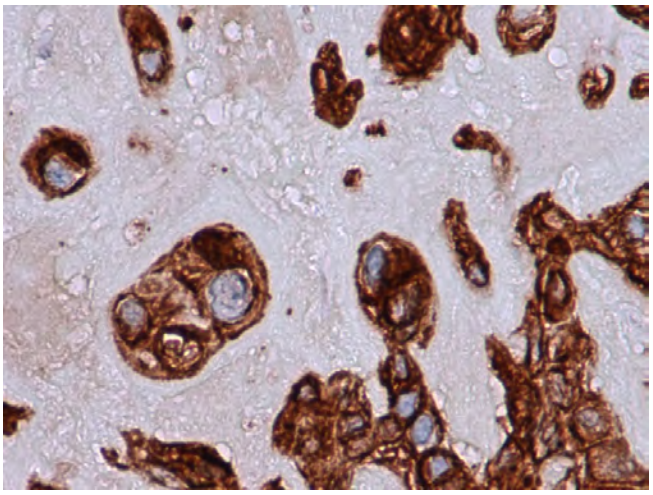

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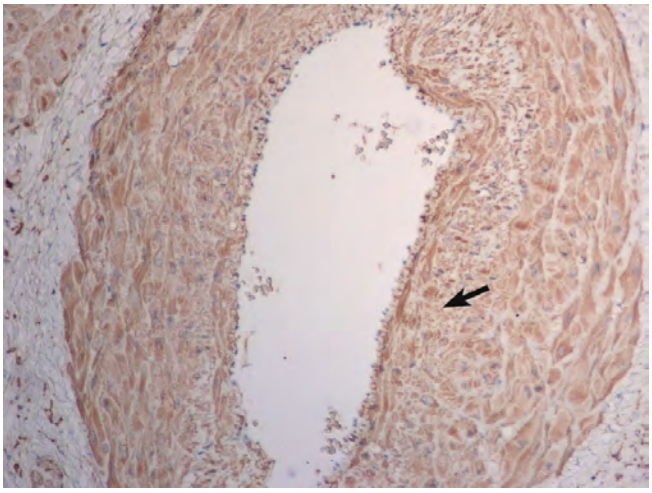

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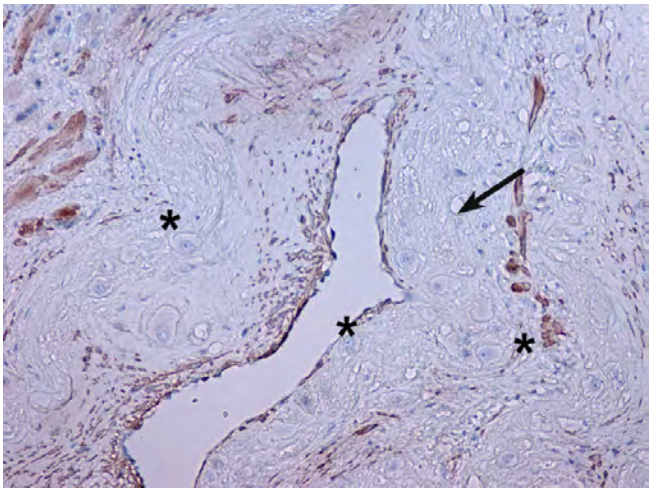

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FIG. 2. (continued)

Morphological features of the placenta and myometrium in placenta accreta spectrum. ***e*** *– replacement of the endothelium of myometrial vessel with trophoblast cells (marked by arrows) during physiological pregnancy; methylene blue staining, magnification ×1000.* ***f*** *– replacement of the vascular endothelium during uncomplicated pregnancy with trophoblast cells; trophoblast cells are stained brown with primary CK7 antibodies (marked by arrows), magnification ×400.* ***g***, ***h*** *– trophoblast cells in the area of myometrium aseptic necrosis are stained with primary CK7 antibodies; magnification ×200 (****g****), ×400 (****h****).* ***i***, ***j*** *– immunohistochemical study with primary α-SMA antibodies, positive staining of the vessel wall outside the area of ingrowth (marked by arrows) (****f****) and negative staining of the vessel wall in the area of the placental bed (****g****) (trophoblast cells are marked by asterisks); magnification ×200 (****i****), ×400 (****j****))*

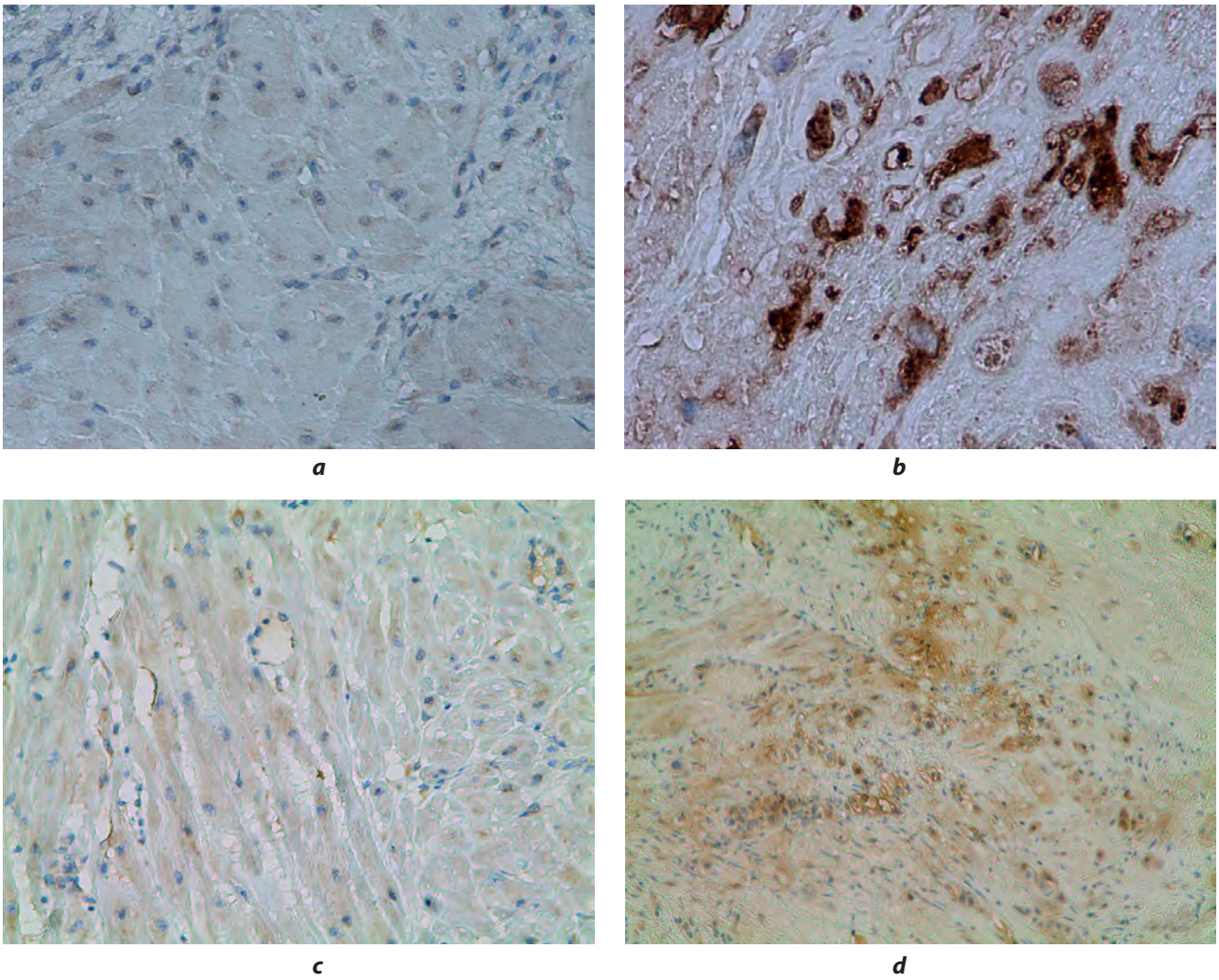

FIG. 3.

*Expression of hypoxia, and angiogenesis markers in placenta accreta spectrum: **a** –immunohistochemical study of myometrium with primary Hif2a antibodies during uncomplicated pregnancy, magnification ×200; **b** – aseptic myometrium necrosis with the presence of stained cells(Hif2a+) of invasive trophoblast, magnification ×400; **c**, **d** – immunohistochemical study with primary VEGF antibodies during uncomplicated pregnancy (a weak staining of the myometrium), moderately stained cells of invasive trophoblast (VEGF+) in the zone of aseptic myometrium necrosis in the area of ingrowth, magnification ×200 (**c**), ×100 (**d**)*

(Fig. 2f–h). If in the comparison group during physiological pregnancy, the transformation of uterine vessels occurred by replacing the endothelium and smooth muscle membrane of the vessel with an invasive trophoblast (Fig. 2e, f), then when the placenta grew, a violation of the topography of trophoblast invasion was observed and trophoblast cells were found not only in the vessels of the myometrium and among muscle fibers, but also in the scar tissue of the myometrium (Fig. 2b, c).

Smooth muscle cells were detected in the wall of non-modeled vessels (Fig. 3i) and were absent in the remodeled vessels of the placental bed area (Fig. 3j).

There were no villi in the myometrium of the uteroplacental region of the comparison group, and the hypoxia index Hif2a was practically not detected histochemically (Fig. 3a), as well as VEGF (Fig. 3c). In women with atypical placentation, there was a marked increase in Hif2a expression in trophoblast-like cells in areas near necrosis zones (Fig. 3b). In addition, an increase in VEGF expression was noted in these areas (Fig.3d)

DISCUSSION

The main factor contributing to abnormal attachment of placental villi and further invasion of the myometrium is considered to be previous uterine surgery, which leads to pathological decidualization in the scar area [6, 9, 10]. In our study, we conducted a comparative characterization of the uterine scar zone in women with normal pregnancy and women with placental villi ingrowth. As in the works of other authors, we have revealed the ingrowth of villi in the area of scar tissue. We found that damage to the uterine wall was accompanied by the formation of necrotic zones, which were absent in cases of scars without ingrowth. Moreover, the proportion of cases

with necrosis zones increased with the depth of ingrowth (Table 2), possibly reflecting the outcome of the process of myocyte damage as a result of abnormal trophoblast invasion with a violation of the architectonics of the uterine wall and vascular network (Fig. 2b, c), which most likely leads to impaired blood supply and ischemia of the adjacent myometrium.

Significantly, during physiological pregnancy, trophoblast invasion is strictly programmed and stops at the level of the spiral arteries, leading to an expansion of their diameter without affecting the radial and arcuate arteries located closer to the surface of the uterus [16–18]. When the placenta grows, trophoblast invasion becomes unregulated and often goes beyond the boundaries of scar tissue, affecting the adjacent layers of the myometrium [19] and the intravascular space, as shown in our study (Fig. 1c–g).

To confirm the hypothesis about the leading role of impaired blood supply to the uterine wall during the ingrowth of placental villi and subsequent ischemia in the appearance of necrotized areas of the myometrium, we studied the content of hypoxia factor Hif2a and vascular endothelial growth factor in the uteroplacental region. Previously, the important role of Hif2a in the first trimester in chorionic invasion was established [20], which is to some extent due to hypoxic conditions. All the women included in our study were in the third trimester of pregnancy, and we did not find data on the content of Hif2a in the uteroplacental region at this time in the literature. We found a more pronounced expression of Hif2a in trophoblast cells in the myometrial necrosis zones of the main group (Fig. 3b) compared with the myometrium of the comparison group (Fig. 3a). The content of VEGF in the myometrium in the main group during this gestation period was higher compared to the comparison group, which was consistent with the findings of other researchers [21, 22]. Surprisingly, a living trophoblast was found in the necrotized zones, actively expressing hypoxia factors, which could probably stimulate an increase in VEGF content in surrounding living tissues and promote enhanced angiogenesis directed to these zones; the presence of fetal fibrinoid in these zones may also contribute to its survival [23, 24] and be a manifestation of one of the programmed types of cell death – programmed necrosis – necroptosis [25].

As a result, necrosis zones with the expression factor of hypoxia Hif2a trophoblast may be one of the main causes of the abnormal vascular network observed in PAS (Fig. 1a, b).

The analysis of the maturity of the villous tree indicated that the maturation period of the villous tree was ahead of 2–3 weeks, given that the delivery period of patients with placenta accreta corresponded to 36–37 weeks [10].

CONCLUSION

Morphological examination of the uteroplacental region in PAS revealed the appearance and increase of myometrial necrosis zones in response to an increase in the depth of ingrowth of placental villi. During normal pregnancy, foci of uterine wall necrosis were absent. Necrosis zones may be the cause of activation of angiogenic factors and an important stimulus for the development of abnormal vascularization in PAS. In view of this, there is an increasing need for careful excision of areas of altered myometrium, especially areas of aseptic necrosis, to ensure the quality of subsequent metroplasty [15].

Conflict of interest

The authors of this article declare the absence of a conflict of interest.

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