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## IMMUNOHISTOCHEMICAL STUDY OF TROPHOBLASTS CELLULAR REGULATION PROCESSES IN CHORIOAMNIONITIS AND BASAL DECIDUITIS COMBINED WITH IRON-DEFICIENCY ANEMIA IN GRAVIDAS

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*The purpose of the study* is to establish quantitative parameters of cell proliferation and apoptosis in the trophoblast of the chorionic villi in chorioamnionitis and basal deciduitis combined with iron-deficiency anemia in gravidas by means of immunohistochemical method.

*Materials and methods.* 198 placentas were examined. The immunohistochemical procedure was performed using primary antibodies against Ki-67 and Bax antigen with imaging by a polymer system with diaminobenzidine dye. The number of Ki-67-positive nuclei of the chorionic villi trophoblast was counted, and for the Bax antigen, the optical density of the immunohistochemical staining was measured by means of microdensitometric method. Comparison of differences in mean trends was performed using the odd Student's two-sided t-test ( $p \leq 0.05$ ).

*Results and discussion.* The number of Ki-67-positive trophoblast nuclei in acute chorioamnionitis with iron-deficiency anemia in gravidas was  $56 \pm 3.8$  ‰, and the relative units of optical density of immunohistochemical staining for protein Bax –  $0.234 \pm 0.0012$ , in chronic –  $59 \pm 3.6$  ‰ and 0.2, respectively.

The number of Ki-67-positive nuclei of the chorionic villi trophoblast was counted. Placentas with acute as well as chronic chorioamnionitis and basal deciduitis showed even higher averages ( $p < 0.001$ ).

In acute basal deciduitis in anemia, the number of Ki-67-positive trophoblast nuclei was  $56 \pm 3.2$  ‰, the average optical density of immunohistochemical staining for protein Bax –  $0.236 \pm 0.0016$ , in chronic –  $57 \pm 3.7$  and  $0.249 \pm 0.0015$ , respectively.

It should be noted that in chronic chorioamnionitis and basal deciduitis, these rates were higher than in acute. With the same regularity the average indicators of optical density of immunohistochemical staining on protein Bax in a trophoblast of chorionic villi at comorbid iron-deficiency anemia concerning an inflammation without anemia increase.

We have shown that proliferative activity in iron-deficiency anemia varies with gestational age and placental prematurity, but iron-deficiency anemia in gravidas and chorionic tree maturation both individually and in combination lead to the intensification of these processes.

We obtained a justification for the arithmetic mean thickness and volume of the placenta relative to observations of placenta with inflammation without anemia in this comorbid pathology.

*Conclusion.* Iron-deficiency anemia in gravidas leads to the intensification of proliferative processes and Bax-dependent apoptosis in the trophoblast of the chorionic villi of the placenta relative to the placenta from physiological pregnancy. In acute as well as in chronic chorioamnionitis and basal deciduitis, the proliferative activity and apoptotic processes in the trophoblast of the chorionic villi of the placenta increase, while comorbid iron-deficiency anemia in gravidas intensifies only the processes of Bax-dependent apoptosis.

**Keywords:** inflammation of the placenta, trophoblast of the chorionic villi, anemia.

**Research relation to the plans, programs and department themes.** The work was performed at the Department of Pathological Anatomy of Bukovinian State Medical University (Chernivtsi, Ukraine) as a part of research work "Improvement of pathological diagnosis of various forms of placental insufficiency", state registration number 0119U101347.

**Introduction.** The placenta is a biological monitoring organ, a pregnancy reflector, a prognosticator of health. The processes of cell number regulation play an important role in the growth of organs in the process of their development. In the absence of risky effects, the regulation of cell number is carried out mainly by regulating the intensity of cell proliferation and apoptosis (death) processes, which are normally in a certain balance [1]. Destruction of these mechanisms in the trophoblast, stromal and endothelial cells of the villous chorion, decidual and amniotic membranes lead to changes in the placental-fetal interrelationships, and afterward – to the formation of placental insufficiency [2]. The processes of proliferation and apoptosis in the chorionic villi under the influence of various factors on the placenta are of great interest for scientists [2-5]. For example, at the Department of Pathological Anatomy of Bukovinian State Medical University in the context of the research work: "Improvement of pathological diagnosis of various forms of placental insufficiency" the determination of the lev-

el of proliferative processes and processes of death in conditions of iron-deficiency anemia in gravidas (IDA) with impaired maturation of the chorionic tree in women who gave birth at 29-32 and 33-36 weeks of gestation is investigated<sup>1</sup>.

Morphological manifestations of inflammation of the placenta have been and remain the subject of many studies [6-8]. Though, in Ukrainian and foreign scientific literature there are insufficient data on the processes of proliferation and apoptosis in the chorionic villi in chorioamnionitis and basal deciduitis. The influence of iron-deficiency anemia on the course of these processes in inflammation of the placenta in gravidas is not sufficiently studied. Even if scientific sources mention that moderate hypoxia in placental tissues caused by IDA leads to stimulation of proliferative processes in the trophoblast of the chorionic villi of the placenta, and strongly inhibits proliferation processes [9]. Through the evaluation of immunohistochemical method of expression of antigens Ki-67 and Bax the mechanisms of regulation of placental cell count in the combination of acute and chronic chorioamnionitis, as well as basal deciduitis with IDA can be better clarified.

**The purpose of the study** was to establish quantitative parameters of cell proliferation and apoptosis in the trophoblast of the chorionic villi of the placenta in acute and chronic chorioamnionitis and basal deciduitis in iron-deficiency anemia in gravidas by means of the immunohistochemical method.

**Materials and methods.** 198 placentas were studied in 37-40 weeks of gestation period. The number of observations in specific study groups is given in the **table**. In particular, in order to compare and interpret the data, placentas in physiological pregnancy (n = 20) and observation of iron-deficiency anemia in gravidas without inflammation of the placenta (n = 21) were studied. The investigation was done at the Department of Pathological Anatomy of Bukovinian State Medical University. The material for the study was carried out and collected on the basis of the children's department of the Regional Municipal non-profit Enterprise "Chernivtsi Regional Pathological Bureau" from 2014 to 2018 and material harvesting and research design were approved by the Biomedical Ethics Committee of Bukovinian State Medical University (protocols No. 2 dated April 10, 2014 and No. 4 dated December 19, 2019). The material was fixed for 20-22 hours in a 10% neutral-buffered formalin solution, followed by dehydration in an ethanol ascending battery and poured into paraffin at 560C. Serial sections (5 μm thick) were cut using a standard microtome. After histological sections have been dewaxed, an immunohistochemical procedure was performed using primary antibodies against Ki-67 antigen and Bax protein with visualization of primary antibodies by the

polymer system (DAKO) with diaminobenzidine dye. The nuclei were incubated in Mayer's hematoxylin. Digital copies of the image were obtained using a Delta Optical Evolution 100 microscope (Plano chromatic lenses) and an Olympus SP-550UZ digital camera.

To quantify the results of immunohistochemical determination of Ki-67 antigen one counted the number of Ki-67-positive nuclei of the trophoblast of the chorionic villi of the placenta. To quantify the Bax antigen, the optical density of histochemical discoloration in relative units of optical density (in the range from "0") was measured by computer micro densitometry in the environment of the computer program ImageJ (1.48, W. Rasband, National Institutes of Health, USA) "10" to "1", on the basis of logarithmic transformations of brightness in gradations from "0" to "255"). The arithmetic means and their errors (for optical density) were calculated using the computer program PAST 3.16 (free license, O. Hammer, 2018)[11].

The comparisons of discrepancies in the mean trends were performed using an odd Student's two-sided t-test with a preliminary check of the normality of the distribution in the statistical samples. Differences at  $p \leq 0.05$  were considered statistically significant.

**Results.** We have obtained data on a significant increase in the number of Ki-67-positive nuclei in the trophoblast of the chorionic villi at IDA ( $48 \pm 2.9 \%$ ) relative to the placentas of physiological pregnancy ( $3 \pm 0.9 \%$ ,  $p < 0.001$ ), which were localized exclusively in the cytotrophoblast in individual mononuclear or dinuclear cells. Placentas with acute as well as chronic chorioamnionitis and basal deciduitis showed even higher averages ( $p < 0.001$ ) (**Table**).

More interesting is the fact that comorbid IDA does not cause any form of inflammation of the chorionic and basal plates of the placenta to increase the proliferation of trophoblast of the chorionic villi of the placenta, which is confirmed by the average number of Ki-67-positive trophoblast nuclei ( $p \leq 0.05$ ). The visual assessment of Ki-67-positive trophoblast nuclei in observations of chorioamnionitis in IDA can be performed in the **Figure 1**. The immunohistochemical study of the proapoptotic protein Bax in the trophoblast of the chorionic villi showed an equally clear expression of this antigen even during physiological pregnancy ( $0.123 \pm 0.0014$ ), the level of which varied greatly within the same villi and from villi to villi. The character of the color was combined and diffuse-granular. In agreement with the quantitative indicators of the optical density of immunohistochemical staining in women with IDA placentas, there was an increase in the processes of apoptosis relative to the placenta from physiological pregnancy ( $0.204 \pm 0.0014$ ,  $p < 0.001$ ). According to the data in the **Table**, it is visible that the optical density of immunohistochemical staining for Bax protein in inflammation of the chorion-

**Table** – Quantitative indicators of immunohistochemical determination of proliferative antigen Ki-67 in the trophoblast of the chorionic villi of the placenta in combination with different forms of chorioamnionitis and basal deciduitis with iron deficiency anemia in gravidas ( $M \pm m$ )

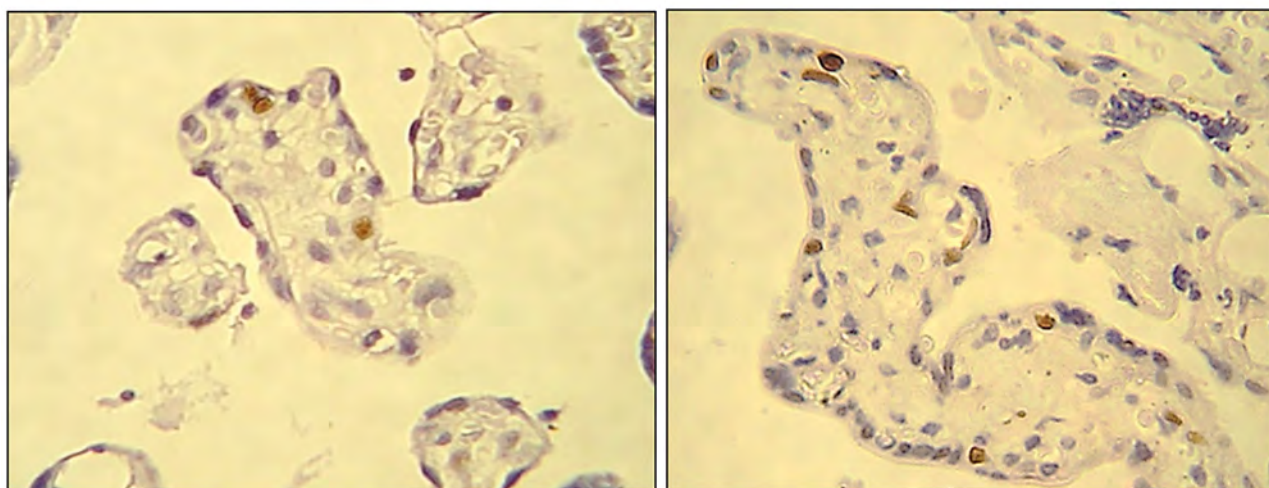
Research groups	Ki-67 – positive nuclei in trophoblasts of chorionic villi (%)		Optical density of immunohistochemical staining for Bax protein in the trophoblast of the chorionic villi (relative unit optical density)	
	Observation of inflammation of the manure during pregnancy without anemia	Observation of inflammation of the manure in iron deficiency anemia in gravidas	Observation of inflammation of the manure during pregnancy without anemia	Observation of inflammation of the manure in iron deficiency anemia in gravidas
<b>Acute chorioamnionitis</b>	(n=23) 54±2.3 p <sub>1</sub> <0.001 p <sub>2</sub> >0.05	(n=21) 56±3.8 p <sub>3</sub> >0.05 p <sub>4</sub> =0.03	(n=23) 0.206±0.0013 p <sub>1</sub> <0.001 p <sub>2</sub> >0.05	(n=21) 0.234±0.0012 p <sub>3</sub> <0.001 p <sub>4</sub> <0.001
<b>Chronic chorioamnionitis</b>	(n=20) 57±3.5 p <sub>1</sub> <0.001 p <sub>2</sub> >0.05	(n=21) 59±3.6 p <sub>3</sub> >0.05 p <sub>4</sub> =0.02	(n=20) 0.218±0.0015 p <sub>1</sub> <0.001 p <sub>2</sub> <0.001	(n=21) 0.230±0.0014 p <sub>3</sub> <0.001 p <sub>4</sub> <0.001
<b>Acute basal deciduitis</b>	(n=16) 53±3.1 p <sub>1</sub> <0.001 p <sub>2</sub> >0.05	(n=15) 56±3.2 p <sub>3</sub> >0.05 p <sub>4</sub> >0.05	(n=16) 0.212±0.0014 p <sub>1</sub> <0.001 p <sub>2</sub> <0.001	(n=15) 0.236±0.0016 p <sub>3</sub> <0.001 p <sub>4</sub> <0.001
<b>Chronic basal deciduitis</b>	(n=21) 55±2.8 p <sub>1</sub> <0.001 p <sub>2</sub> >0.05	(n=20) 57±3.7 p <sub>3</sub> >0.05 p <sub>4</sub> >0.05	(n=21) 0.224±0.0016 p <sub>1</sub> <0.001 p <sub>2</sub> <0.001	(n=20) 0.249±0.0015 p <sub>3</sub> <0.001 p <sub>4</sub> <0.001

**Notes:** p<sub>1</sub> – the probability of the difference between the physiological pregnancy and the study group; p<sub>2</sub> – the probability of the difference between the group of placentas with IDA and the study group; p<sub>3</sub> – the probability of the difference between the inflammation and comorbid inflammation in IDA; p<sub>4</sub> – the probability of the difference between the inflammation in combination with IDA and without inflammation in IDA.

ic and basal plates of the placenta on average, with a high statistical probability, is higher relative to observations of physiological pregnancy. It should be noted that in chronic chorioamnionitis and basal deciduitis, these rates were higher than in acute (**Figure 2**). With the same regularity the average indicators of optical

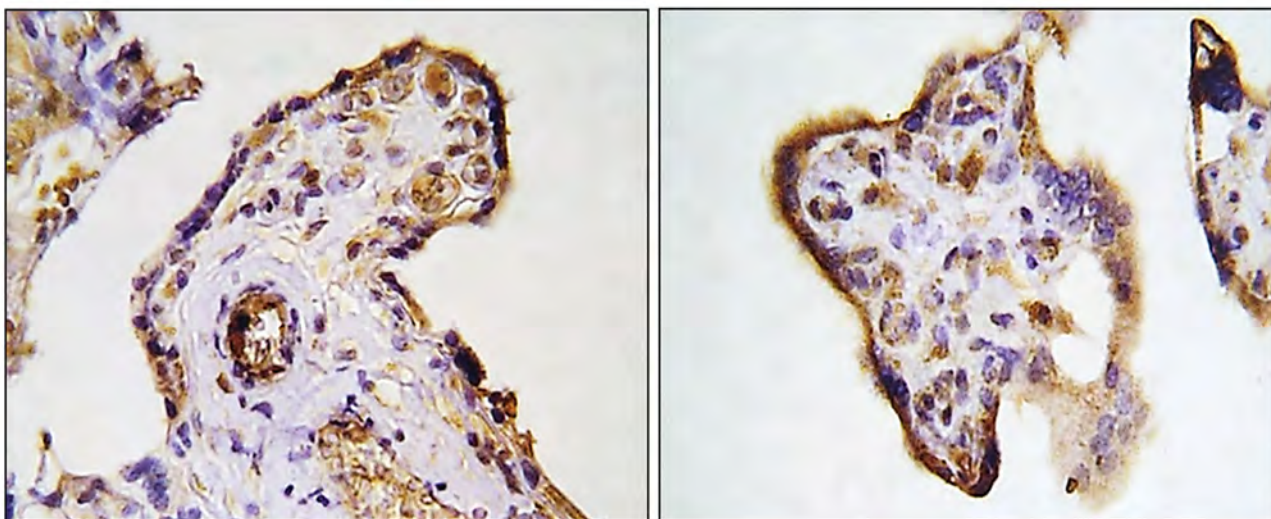
density of immunohistochemical staining on protein Bax in a trophoblast of chorionic villi at comorbid IDA concerning an inflammation without anemia increase.

**Discussion.** The intensification of proliferative processes in the trophoblast of the chorionic villi of the placenta in IDA is confirmed by the results of other



**Figure 1** – Ki-67-positive nuclei in the trophoblast of the chorionic villi in acute chorioamnionitis in IDA (left) and chronic chorioamnionitis in IDA (right). Optical zoom: Ob. 40x. Oc. 10x





**Figure 2** – Expression of the Bax protein in the trophoblast of the chorionic villi in chronic chorioamnionitis in IDA (left) and chronic basal deciduitis in IDA (right). Optical zoom: Ob. 40 $\times$ . Oc. 10 $\times$

researchers who showed that according to the degree of IDA there was a significant quantitative proliferative response of cytotrophoblast of placental villi, with certain features depending on the type [12]. In addition, in our other studies [1], we have shown that proliferative activity in IDA varies with gestational age and placental prematurity, but iron-deficiency anemia in gravidas and chorionic tree maturation both individually and in combination lead to the intensification of these processes.

Our research data on the increase of apoptosis processes in the trophoblast of the chorionic villi of the placenta in IDA, which are identical to the results of other researchers [4, 14], can be related to the development of hypoxia in response to anemia which quickly depletes cell energy systems and leads to its death [14]. The intensification of Bax-dependent apoptosis processes in acute inflammation of the chorionic and basal plates of the placenta probably occurs with the contribution of cytotoxic leukocytes, which are able to use a special transmembrane respiratory chain of the plasma membrane to form superoxides and bombard the target cell stimulating apoptosis, in particular through oxidation in particular due to the oxidation of phosphatidylserine in the plasma membrane of the target cell [15]. In chronic inflammation, the intensification of apoptotic processes is mainly due to the increasing severity of inflammation and increased activity of free radical processes, which is confirmed by our previously obtained data on high levels of nitroperoxides in placental structures [16], which begin to induce apoptosis. In this case, the side effect of IDA, taking into account the even greater intensity of free radical processes, insufficient oxygen transport with the depletion of the energy systems of the cell, more intensely triggers the mechanism of apoptosis. The same apoptotic activity in the trophoblast of the

chorionic villi was shown by scientists who studied the inflammatory processes of the placenta as a result of infection with *Mycobacterium tuberculosis* [17].

According to the scientific works, when the trophoblast surface is damaged, it stimulates proliferative processes [9]. Since the inflammation of the placenta alters the surface of the trophoblast, which may be due to the intensification of free radical processes [16] in the maternal blood of placental intervillous spaces due to damaged syncytiotrophoblast and primarily the surface of microvilli, this confirms placenta in various forms of chorioamnionitis and basal deciduitis. According to our scientific research in immunohistochemical study of the proliferative antigen Ki-67 in IDA, in comorbid iron-deficiency anemia in gravidas, hypoxia is aggravated by strong cross-links between these conditions. The inflammation creates hypoxic conditions due to increased metabolic activity, and hypoxia at the site of inflammation can cause vascular damage, blood coagulation, and blood flow blockage, which ultimately inhibit the proliferation.

Consequently, based on the results of proliferative activity reduction with activation of Bax-dependent apoptosis in the trophoblast of the chorionic villi of the placenta in acute, as well as in chronic chorioamnionitis and basal deciduitis in combination with IDA, we also obtained a justification for the arithmetic mean thickness and volume of the placenta relative to observations of placenta with inflammation without anemia in this comorbid pathology [18].

**Conclusion.** The results of our research can serve as additional criteria for the pathological diagnosis of acute and chronic forms of chorioamnionitis and basal deciduitis with the determination of morphological differences caused by iron-deficiency anemia in gravidas out of the inflammatory foci.

Iron-deficiency anemia in gravidas leads to the intensification of proliferative processes and Bax-dependent apoptosis in the trophoblast of the chorionic villi of the placenta relative to the placenta from physiological pregnancy. In acute as well as in chronic chorioamnionitis and basal deciduitis, the proliferative activity and apoptotic processes in the trophoblast of the chorionic villi of the placenta increase,

while comorbid iron-deficiency anemia in gravidas intensifies only the processes of Bax-dependent apoptosis.

**Perspective for further research** is to establish the features of proliferation and apoptosis in the trophoblast of the chorionic villi of the placenta at other stages of gestation in chorioamnionitis and basal deciduitis in iron-deficiency anemia in gravidas.

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### ИММУНОГИСТОХИМИЧЕСКОЕ ИССЛЕДОВАНИЕ ПРОЦЕССОВ КЛЕТочНОЙ РЕГУЛЯЦИИ ТРОФОБЛАСТА ПРИ ХОРИОАМНИОНИТЕ И БАЗАЛЬНОМ ДЕЦИДУИТЕ НА ФОНЕ ЖЕЛЕЗОДЕФИЦИТНОЙ АНЕМИИ БЕРЕМЕННЫХ

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**Резюме.** Цель исследования. Иммуногистохимическим методом установить количественные параметры клеточной пролиферации и апоптоза в трофобласте хориальных ворсинок плаценты при остром и хроническом хориоамнионите, а также базальном децидуите при железодефицитной анемии беременных.

**Материалы и методы исследования.** Исследовано 198 плацент. Иммуногистохимическую методику выполняли с применением первичных антител против антигена Ki-67 и Вах с визуализацией полимерной системой с красителем диаминобензидином. Подсчитывали количество Ki-67-позитивных ядер трофобласта хориальных ворсинок, а для антигена Вах, методом микроденситометрии измеряли оптическую плотность иммуногистохимической окраски (в относительных единицах оптической плотности). Сравнение различий в средних тенденциях осуществляли с помощью двустороннего непарного критерия Стьюдента с предварительной проверкой нормальности распределения в статистических выборках. Статистически значимыми считали различия при  $p \leq 0,05$ .

**Результаты исследования.** Количество Ki-67-позитивных ядер трофобласта при остром хориоамнионите с железодефицитной анемией беременных составило  $56 \pm 3.8 \%$ , а относительные единицы оптической плотности иммуногистохимической окраски протеина Вах –  $0.234 \pm 0.0012$ , при хроническом –  $59 \pm 3.6 \%$  и  $0.230 \pm 0.0014$  соответственно. При остром базальном децидуите на фоне анемии количество Ki-67-позитивных ядер трофобласта составила –  $56 \pm 3.2 \%$ , средние показатели оптической плотности иммуногистохимической окраски протеина Вах –  $0.236 \pm 0.0016$ , при хроническом –  $57 \pm 3.7$  и  $0.249 \pm 0.0015$  соответственно.

**Выводы.** Железодефицитная анемия беременных интенсифицирует пролиферативные процессы и Вах-зависимый апоптоз в трофобласте хориальных ворсинок плаценты. При остром, а также хроническом хориоамнионите и базальном децидуите растет пролиферативная активность и апоптотические процессы в трофобласте хориальных ворсинок плаценты, при этом железодефицитная анемия беременных при воспалении интенсифицирует только процессы Вах-зависимого апоптоза.

**Ключевые слова:** воспаление плаценты, трофобласт хориальной пластинки, анемия.

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### ИМУНОГИСТОХІМІЧНЕ ДОСЛІДЖЕННЯ ПРОЦЕСІВ КЛІТИННОЇ РЕГУЛЯЦІЇ ТРОФОБЛАСТА ПРИ ХОРІОАМНІОНІТІ ТА БАЗАЛЬНОМУ ДЕЦИДУЇТІ НА ТЛІ ЗАЛІЗОДЕФІЦИТНОЇ АНЕМІЇ ВАГІТНИХ

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**Резюме.** Мета дослідження. Імуногістохімічним методом встановити кількісні параметри клітинної проліферації та апоптозу в трофобласті хоріальних ворсинок плаценти при гострому та хронічному хоріоамніоніті, а також базальному децидуїті на тлі залізодефіцитної анемії вагітних.

**Матеріали і методи дослідження.** Досліджено 198 плацент. Імуногістохімічну методику виконували із застосуванням первинних антитіл проти антигену Ki-67 та Вах із візуалізацією полімерною системою із барвником діамінобензидином. Підраховували кількість Ki-67–позитивних ядер трофобласта хоріальних ворсинок, а для антигену Вах, мікроденситометричним методом вимірювали оптичну густину імуногістохімічного забарвлення (у відносних одиницях оптичної густини). Порівняння розбіжностей у середніх тенденціях здійснювали за допомогою двобічного непарного критерію Стьюдента з попередньою перевіркою нормальності розподілу у статистичних вибірках. Статистично значущими вважали розбіжності при  $p \leq 0,05$ .

**Результати дослідження.** Кількості Ki-67–позитивних ядер трофобласта при гострому хоріоамніоніті із залізодефіцитною анемією вагітних становила  $56 \pm 3.8 \%$ , а відносні одиниці оптичної густини імуногістохімічного забарвлення на протеїн Вах –  $0.234 \pm 0.0012$ , при хронічному –  $59 \pm 3.6 \%$  та  $0.230 \pm 0.0014$  відповідно. При гострому базальному децидуїті на тлі анемії кількість Ki-67–позитивних ядер трофобласта склала –  $56 \pm 3.2 \%$ , середні показники оптична густина імуногістохімічного забарвлення на протеїн Вах –  $0.236 \pm 0.0016$ , при хронічному –  $57 \pm 3.7$  та  $0.249 \pm 0.0015$  відповідно.

**Висновки.** Залізодефіцитна анемія вагітних інтенсифікує проліферативні процеси та Вах-залежний апоптоз у трофобласті хоріальних ворсинок плаценти. При гострому, а також хронічному хоріоамніоніті та базальному децидуїті зростає проліферативна активність та апоптотичні процеси у трофобласті

хоріальних ворсинок плаценти, при цьому коморбідна залізодефіцитна анемія вагітних інтенсифікує тільки процеси Вах-залежного апоптозу.

**Ключові слова:** запалення плаценти, трофобласт хоріальної пластинки, анемія.

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