FEATURES OF THE HISTOLOGICAL STRUCTURE OF TROPHOBLAST AND CHORIONIC VILLI WITH RECURRENT PREGNANCY LOSS IN WOMEN WITH THROMBOPHILIAS

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The frequency of recurrent pregnancy loss does not tend to decrease. This pathology continues to be one of the important problems of modern medicine. It is known that thrombophilia can play a significant role in the etiology of spontaneous reproductive losses. However, the pathogenesis of recurrent spontaneous loss of pregnancy in the presence of maternal thrombophilia is not fully understood. *Aim*. To identify the features of the histological structure of trophoblasts and chorionic villi in the first trimester of pregnancy in women with thrombophilia and recurrent pregnancy loss, with careful exclusion of other possible causes of fetal loss syndrome. *Material and Methods*. Histological examination of 49 chorion tissue samples from 24 patients with thrombophilia and recurrent pregnancy loss in the first trimester (study group) was performed. The controls were samples of chorion tissue taken during artificial abortion in 33 healthy women who had a history of 2 or more spontaneous labor without significant complications. Thrombophilia diagnosis and hemostasis system state evaluation was performed for all patients on the basis of analysis of 30 parameters according to standard methods. All studies were conducted at the Regional clinical hospital № 8 in Ryazan as well as the scientific and clinical center of hematology, oncology and immunology of the Ryazan State Medical University named after academician I.P. Pavlov of Health Ministry of the Russian Federation. Statistical processing of the obtained results was carried out with the help of computer program package Statistica (version 10). *Results*. Significant differences in the histological structure of trophoblast and chorionic villi in the studied women were revealed, in comparison with those in the control group. It is proved that the presence of thrombophilia negatively affects the process of embryogenesis and contributes to a significant reduction in the area of the chorionic villus vessels in the first trimester of pregnancy. *Conclusion*. It is proved that the presence of thrombophilia has a negative effect on the process of embryogenesis and significantly reduces the vascular area of chorionic villi that can probably play a significant role in the pathogenesis of recurrent pregnancy loss.

Keywords: *thrombophilia and pregnancy, the trophoblast, chorionic villi, spontaneous abortion, missed abortion, pregnancy loss, recurrent pregnancy loss (fetal loss syndrome).*

Despite the constant improvement of medical technologies and improving the quality of obstetric-gynecological care, the frequency of recurrent pregnancy loss does not tend to decrease. This pathology makes up 5 to 20% structure of spontaneous reproductive losses, and continues to be one of the urgent problems of modern medicine, not only in our country, but also in the world [1,2].

Numerous recent studies have confirmed the important role of thrombophilia in the pathogenesis of spontaneous loss of preg-

nancy [3-9]. Maternal thrombophilia plays a significant role in the pathogenesis of habitual miscarriage including: mutations of gene V factor (Leiden) G1691A, prothrombin G20210A, inhibitor of plasminogen activator SERPINE (PAI) 1; antiphospholipid syndrome (APS); hyperhomocysteinemia; deficiency of natural anticoagulants – proteins C, S (PC, PS) and antithrombin (AT) III; increase in activity of von Willebrand factor (v. Willebrand) more than 150% and others.

According to a number of scientists, today considerable scientific knowledge has been accumulated, which makes it possible to isolate hereditary thrombophilia into an independent group of causes of miscarriage [3-5]. Multiple failures of in vitro fertilization (IVF) are also often associated with a high incidence of thrombophilia [10]. Studies conducted by O.V. Bitsadze, S.V. Akinshina, A.D. Makatsariya and co-authors (2014), revealed thrombophilia in 90% of patients with unsuccessful IVF attempts in history.

It has been scientifically proven that the process of formation and development of the placenta is the most important for the life-support of the embryo and fetus [2,11-14]. It is also known that maternal thrombophilia can disrupt formation, growth and development of the placenta [1-3,15-18]. The result of their negative impact may be complications that significantly disrupt the exchange between the blood of the mother and fetus (Fig. 1). Such complications include: perivillous fibrinoid deposition, fetal thrombotic vasculopathy, subchorial thrombosis, retrochoric or retroplacental hematoma, chorionic or placental marginal hematoma, maternal floor infarction (fibrin deposition on the placenta maternal surface) [2,19].

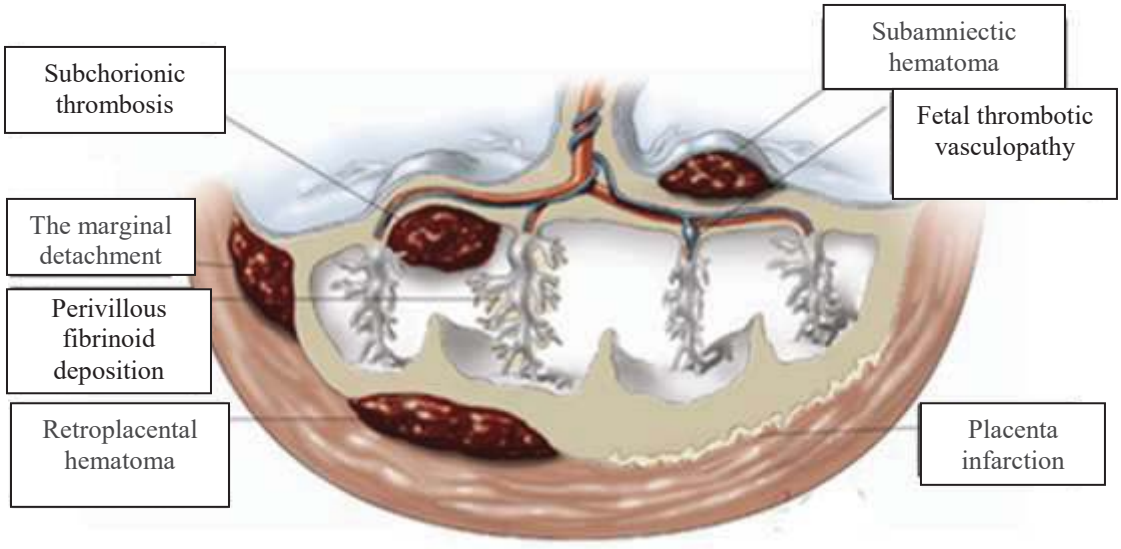

Fig. 1. Placental pathologies that can be caused by maternal blood hemostasis disorders [2]

Therefore, clarification of the main links in the pathogenesis of spontaneous reproductive losses in the presence of maternal thrombophilia is an important task. In the current scientific literature there are publications devoted to this problem [3,8,11]. However, the features of the histological structure of the placenta at different stages of its development in women with thrombophilia and the usual loss of pregnancy are not fully understood. At the same time, it is obvious that the results of such studies can be useful for identifying new links in the pathogenesis of reproductive losses and planning for correction of gestational complications.

Aim of Research**.** The study aim was to identify the features of the histological structure of trophoblasts and chorionic villi in first trimester of pregnancy in women with thrombophilia and recurrent pregnancy loss, with careful exclusion of other possible causes of fetal loss syndrome.

Materials and Methods

Histological examination of 49 chorion tissue samples from 24 patients with thrombophilia and recurrent pregnancy loss in the first trimester (study group) was performed. The controls were samples of chorion tissue taken during artificial abortion in 33 healthy women who had a history of 2 or more spontaneous labor without significant complications.

The study design consisted of 4 steps:

First step. Laboratory diagnosis or exclusion of thrombophilia in patients with a habitual loss of pregnancy in the anamnesis, as well as in women who independently gave birth 2 or more times without significant complications and reproductive losses;

Second step. Formation of the main and control groups of the study;

Third step. Study of histological structure of trophoblast and chorionic villi in patients of the main and control groups. In patients of the main group, this stage was retrospective, by morphometric evaluation of trophoblast in histological preparations of tissue of spontaneously interrupted or frozen pregnancies. In the control group, a prospective histological study of chorionic tissue taken at a planned official abortion was performed, which was carried out at the request of the woman.

The fourth step included statistical processing of the study results and their comparative analysis in the study groups.

The criteria for the inclusion of patients in the study groups and their exclusion from the groups are presented in Table 1.

Table 1

Criteria for inclusion of patients in groups and exclusion from groups

Criteria	Study group, n=24	Control group, n=33
Inclusion criteria	● 2 or more spontaneous or missed abortions in anamnesis; ● The presence of one or more confirmed incidence of thrombophilia by the results of laboratory diagnostics.	● Twice term pregnancy and childbirth independently without significant complications; ● Good/favourable obstetric and gynecological anamnesis. ● Absence of thrombophilia.
	● Absence of abnormalities of fetal development confirmed by ultrasound and biochemical screening or genetic examination of fetal (or embryos) tissues. ● Absence of clinically significant extragenital pathology and an ectopic pregnancy in anamnesis.	
Exclusion criteria	● The presence of obstetric and extragenital causes of miscarriage, including isthmicocervical insufficiency, endocrine disorders and infectious pathology.	● Complicated/unfavourable obstetric-gynecological anamnesis ● Presence of one or more incidences of thrombophilia.
	● The presence of fetal anomalies in the anamnesis; ● Presence of clinically significant gynecological and extragenital diseases; ● An increase in blood concentrations of acute phase inflammation proteins (C-reactive protein (CRP), antistreptolysin-O (ASLO), rheumatoid (RF), ceruloplasmin, haptoglobin, fibrinogen); ● Ectopic pregnancy in anamnesis.	

The main group consisted of 24 patients with a fetal loss syndrome, who had 2 or more spontaneous abortions or recurrent pregnancy loss in the anamnesis. The control group consisted of women without complicated (high risk) obstetric and gynecological anamnesis and extragenital pathology, who had 2 independent term deliveries without significant complications. Patients of both groups were excluded from obstetric and extragenital causes of pregnancy loss, including isthmicocervical insufficiency, endocrine disorders and infectious pathology. The absence of fetal abnormalities was confirmed by ultrasound and biochemical screening or genetic examination of fetal (or embryo) tissues in both groups. The increase of acute inflammation proteins concentration in the blood was excluded in all women according to the following criteria: CRP less than 8 mg/l, ACLO less than 250 U/ml, RF less than 18 U/ml, ceruloplasmin not more than 0.3 g/l haptoglobin not more than 1.2 g/l, fibrinogen not more than 4.2 g/l.

Ectopic pregnancy in the anamnesis, as well as the presence of clinically significant

gynecological and extragenital diseases were the general criteria for exclusion from study groups.

The parameters of age, anthropometric data and body mass index (BMI) in the examined women are presented in Table 2.

Table 2

Age and anthropometric data in the surveyed women

Indicators	Clinical groups	
	Main	Control
Age, years – *M±m* – *dispersion (min–max)*	 31.0±1.06 (23–39)	 30.2±0.85 (23–38)
Height, cm – *M±m* – *dispersion (min–max)*	 166±1.2 (156–175)	 165±0.9 (152–174)
Body weight, kg – *M±m* – *dispersion (min–max)*	 62.3±2.03 (51–85)	 63.1±1.66 (50–95)
BMI, kg/m^2 – *M±m* – *dispersion (min–max)*	 23.4±0.84 (19.5–33.0)	 23.1±0.58 (19.5–337)

The age of the patients of the main and control groups did not differ significantly and amounted, respectively, to 31.0±1.06 and 30.2±0.85 years ($p_{t\text{-}test}$>0.05). Also, there were no significant differences between anthropometric and BMI in both groups ($p_{t\text{-}test}$>0.05).

Comparative characteristics of parity and pregnancy outcomes in groups are presented in Table 3.

Table 3

Comparative characteristics of parity and pregnancy outcomes in groups

Indicators	Clinical groups	
	Main	Control
Parity, *M±m (t-test)*	3.0±0.29*	2.3±0.09
Total women with reproductive losses, *n (%)* *Of these, with the number of losses:* *– 1* *– 2* *– 3* *– 4* *– 5 and more*	24 (100)** – *13 (54.2)*** *5 (20.8)*** *3 (12.5)*** *3 (12.5)***	–
Total number of women who gave birth without loss, *n (%)* *Of these, with the number of deliveries:* *– single* *– two* *– 3 and more*	2 (8.4)** *2 (8.4)*** – –	33 (100) – *24 (72.7)*** *9 (27.3)***

Note: n – the absolute number of women, % – their proportion in the study groups; * – statistically significant differences by the criterion of Student's (*t-test*) between groups ($p_{t\text{-}test}$<0.05); ** – statistically significant differences according to the criterion of the correspondence of $\chi 2$ between groups ($p_{\chi 2}$<0.01)

The average parity of pregnancies in the main group was significantly higher than the control values (3.0±0.29 и 2.3±0.09, accordingly, $p_{t\text{-}test}$<0.05). Reproductive loss was present in all women of the main group and absent in the control group ($p_{\chi 2}$<0.01). Pregnancies that ended without reproductive loss were registered in 2 (8.3%) patients of the

main group, which was significantly less than the control values (33 (100%), $p_{\chi 2}$<0.01). All patients of the main group had multiple loss of pregnancy, of which 2 losses – 13 (54.2%), 3 – 5 (20.8%), 4 – 3 (12.5%), 5 or more – 3 (12.5%). Ectopic pregnancy was absent in all women, according to exclusion criteria.

Clinical, laboratory, instrumental and statistical methods of research were used in this study. All studies were conducted at Regional clinical hospital № 8 in Ryazan and the scientific and clinical center of hematology, oncology and immunology of the Ryazan State Medical University named after academician I.P. Pavlov of Health Ministry of the Russian Federation.

The state of the hemostatic system was evaluated on the basis of analysis of 30 parameters according to conventional methods: D-dimers, prothrombin time, activated partial thromboplastin time (APTT), international normalized ratio (INR), prothrombin complex factor activity, kaolin time, lebetox time, concentration fibrinogen, hematocrit, peripheral blood thrombocytes, antithrombin III (AT III), protein C (PC), protein S (PS), fibrinolysis, lupous anticoagulant (LA), antibody titres (IgM, IgG) to cardiolipin, β2-glycoprotein 1 and prothrombin, mutation of the factor V gene (Leiden) – G1691A, mutation of the prothrombin gene – G20210A, mutation of the plasminogen activator inhibitor (PAI), homocysteine concentration, platelet aggregation with 4 inducers (ristomycin, collagen 20,0 μmol/l, adrenaline – 5.0 μmol/l and ADP 2 μg/lL), the activity of f. Willebrand. The study of hemostasis was performed by using an automatic analyzer of the ACL 7000 System manufactured by the Instrumentation Laboratory Company. Blood samples for the study were taken from the cubital vein on the 19-21st day of the ovulatory menstrual cycle 6 and 9 months after the completion of the last pregnancy.

For histological examination, samples of chorionic tissue 0.5 x 0.5 cm were fixed in 10% formalin. Filling in paraffin was carried out according to the generally accepted method. Paraffin blocks were prepared on a microtome with slices 4-5 microns thick and stained with hematoxylin and eosin. All studies were performed using conventional methods [5].

In the stained preparations, morphometric evaluation of new chorionic villi generation was carried out in cross section according to the Adobe Photoshop Cs3 Extended program using an Olympus CX42 microscope with a digital camera (the image of the villi was transmitted 100 times to the computer screen). All measurements were taken in units/mm^2 of the shear area. The algorithm for the morphometric evaluation of chorionic villi is presented in the scheme (Fig. 2).

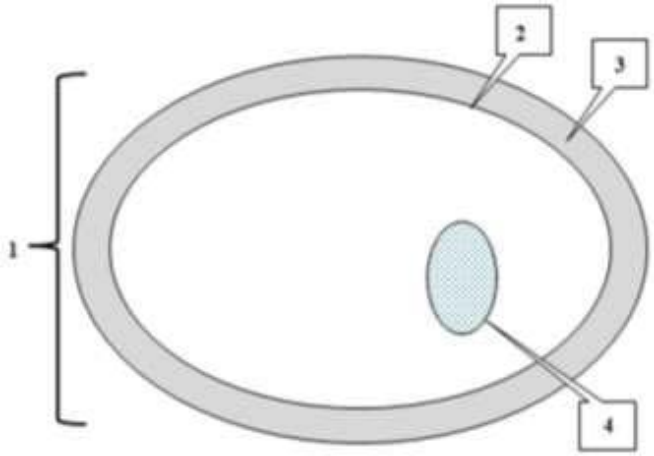

Fig. 2. Algorithm for the morphometric evaluation of chorionic villi, where
1 – is the determination of the chorionic villus area, 2 – total area of the chorionic villus stroma,
3 – area of the trophoblastic epithelium, 4 – area of the chorionic villus vessels

The algorithm for the morphometric evaluation of chorion villi included: 1) the determination of their area along the outer contour of the epithelial cover; 2) measurement of the total area of the stroma of the villi along the inner contour of their epithelial cover; 3) calculating the area of trophoblastic epithelium by the difference in the area of villi and the total area of the stroma; 4) measuring the area of the vessels by their outer contour.

In all the examined women, the pregnancy was interrupted surgically by vacuum aspiration or by routine curettage of the uterus. On the day of the operation, ultrasound was performed to determine the duration of pregnancy on the Medison 8000 EX or Medison ACCUVIX V10.

Statistical analysis of the results was carried out using the STATISTICA computer software package (version 10) using parametric and nonparametric statistical methods.

Results and Discussion

Congenital and acquired thrombophilia were laboratory diagnosed in all 24 (100%) patients in the main group, single – in 7 (29.2%), multiple – in 17 (70.8%) (Tab. 4).

Table 4

The structure of diagnosed thrombophilias in the main patient group

Thrombophilias enumeration	Thrombophilias structure			
	singular		multiple	
	n	%	n	%
All thrombophilias	**7**	**29.2**	**17**	**70.8***
Mutation of the plasminogen activator inhibitor SERPINE (PAI) 1	3	12.5	15	62.5*
APS	2	8.3	4	16.7
AT III deficiency	1	4.2	5	20.8*
Hyperhomocysteinemia	1	4.2	6	25.0*
PC and (or) PS deficiency	–	–	6	25.0*
Willebrand factor increase activity (>150%)	–	–	12	50.0*
FV gene mutation (Leiden) G1691A	–	–	1	4.2

Note: n – absolute number of thrombophilia; % – specific weight of thrombophilia; * – statistically significant differences according to the criterion of the correspondence of χ^2 ($p_{\chi 2}$<0.05) between thrombophilia in singular and multiple composition

All diagnosed thrombophilias, except for APS and mutation of the factor V gene (Leiden) G1691A, were statistically significantly more frequent in the multiple group of patients in the main group ($p_{\chi 2}$ <0.05). The overall rating of thrombophilias was as follows. The first rating place was taken by the mutation IAP SERPINE (PAI) 1, which was detected more often than the others and was 18 (75%) cases (homozygous and heterozygous – 9 (37.5%) cases each). The second ranking place was the hyperactivation of the f. Willebrand more than 150% – 12 (50%) cases, which was also much more frequent following it in the ranking of mutations. Third place was occupied by hyperhomocysteinemia – 7 (29.2%) of observations. The fourth rating place was shared by APS deficiency of PC, PS and AT III – with 6 (25%) cases each. The mutation Leiden G1691A (heterozygous) – 2 (8.3%) was significantly less common than other thrombophilias. The mutation of the prothrombin gene was not detected.

Comparative characteristics of the timing of termination of pregnancy, determined by the date of the last menstruation (LM) and the results of ultrasonic diagnostics (USD), in groups is presented in Table 5.

Gestational terms of termination of pregnancy in women of the main and control groups did not differ significantly and amounted to 9.5±0.29 and 9.3±0.35 weeks according to LM dates ($p_{t\text{-}test}$>0.05). The spread of the indicator from the minimum to the maximum values by LM dates was also the same and was 6-12 weeks in both groups.

Term of interrupted pregnancy according to USD in patients of the main group

Table 5

Comparative characteristics of the timing of abortion in the main and control groups, full weeks of gestation

The timing of abortion	Clinical groups	
	Main	Control
By the date of LM: − *min – max* − *M±m (t-test)*	 6 – 12 9.5±0.29*	 6 – 12 9.3±0.35
By the results of USD: − *min – max* − *M±m (t-test)*	 3 – 9 ❖,♦ 6.1±0.18**	 6 – 12 8.9±0.3

Note: LM – the last menstruation; USD – ultrasonic diagnostics; Statistically significant differences according to the Student's test ($p_{t\text{-}test}<0.05$): * – between the terms of gestation, determined by the date of LM and the results of USD in the group, ** – between groups; Statistically significant differences according to the $\chi 2$ matching criterion ($p_{\chi 2}<0.05$): ❖ – between the terms of gestation, determined by the date of the last menstruation and the results of ultrasound diagnosis in the group, ♦ – between groups

was significantly less (6.1±0.18 weeks) than in the control (8.9±0.39 weeks $p_{t\text{-}test}<0.01$) and by LMP dates in of them ($p_{t\text{-}test}<0.01$), which was due to the presence of a frozen pregnancy in the main group. Thus, the spread of the indicator from the minimum to the maximum values in the main group was from 3 to 9 weeks, and in the control – from 6 to 12 weeks ($p_{\chi 2}<0.05$).

Comparative characteristics of histological structure of trophoblast and chorionic villi in the women of the main and control groups were as follows (Tab. 6).

Table 6

Comparative characteristics of histological structure of trophoblast and chorionic villi in women in the main and control groups

Groups of women (statistics functions)	Area of trophoblasts and chorionic villi, units/mm^2			
	Trophoblast	Chorionic villus vessels	Chorionic villus stroma	
			without vessels	total
Main: • *min – max* • *M±m (t-test)*	 182 – 1717 869.2±61.20*	 0 – 18 4.3±0.63*	 1723 – 4152 2839.5±142.09	 1726 – 4152 2843.8±141.81
Control: • *min – max* • *M±m (t-test)*	 602 – 1426 1062.3±51.49	 46 – 180 97.1±7.90	 1447 – 4455 2876.0±175.57	 1523 – 4635 2973.1±178.72

Note: min–max – range spread from minimum to maximum value, * – Statistically significant differences according to the Student's test (*t-test*), $p_{t\text{-}test}<0.05$

There were significant differences in the histological structure of trophoblast and chorionic villi in women with thrombophilia and recurrent pregnancy loss, in comparison with control. Thus, the trophoblast area in the main group was statistically significantly lower than in the control group (869.2±61.20 and 1062.3±51.49 units/mm^2, according, $p_{t\text{-}test}<0.05$). The area of the chorionic villus vessels in the main group was also significantly less than the control values (4.3±0.63 and 97.1±7.90 units/mm^2, according, $p_{t\text{-}test}<0.01$). The photographs show the histological structure of the trophoblast and the vessels of the chorionic villi in terms of gestation of 6 and 10 weeks in the patients of the main and control groups (Fig. 3 and 4).

The histological picture of trophoblast and vessels of chorionic villi at the gestation period of 6 weeks had the following characte-

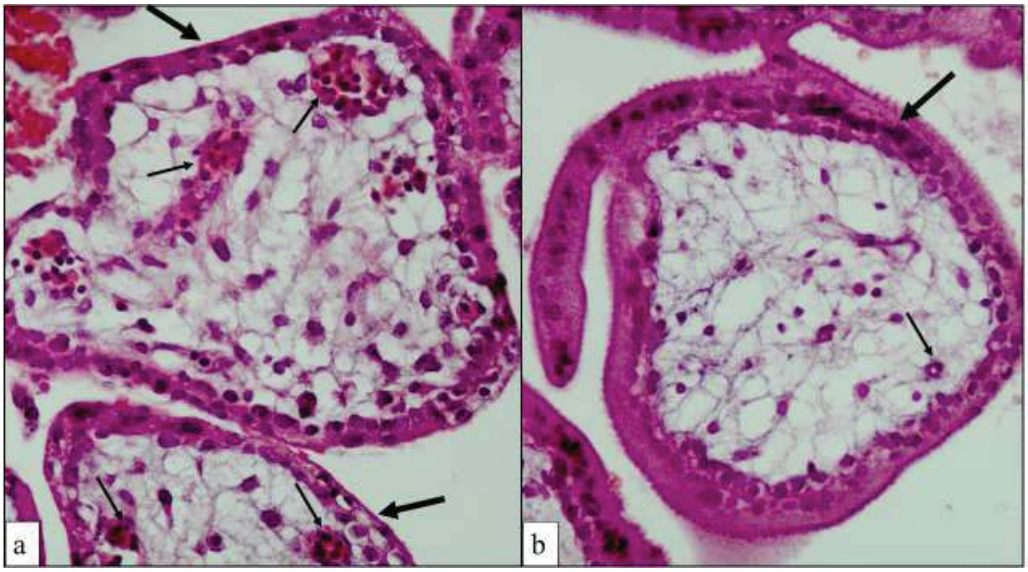

Fig. 3. Histological structure of the trophoblast and vessels of the chorionic villi at the gestation period of 6 weeks in patients of control (a) and main (b) groups: thick arrows – cytotrophoblast, thin arrows – chorion vessels

ristic differences between groups. In the control, the presence of a double-row cytotrophoblast with forming syncytial buds was registered, as well as growing vessels with a moderately enlarged lumen (Fig. 3a). The main group was characterized by a single-row hypoplastic species trophoblast and single hypoplastic-looking vessels with a collapsed lumen (Fig. 3b).

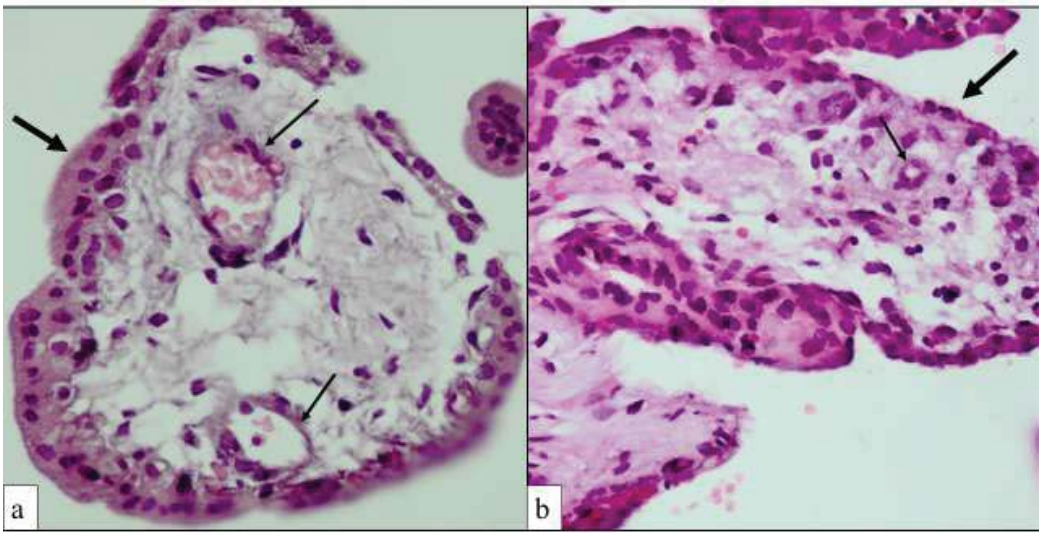

Fig. 4. Histological structure of trophoblast and vessels of chorionic villi in gestation period of 10 weeks in patients of control (a) and main (b) groups: thick arrows – cytotrophoblast, thin arrows – chorion vessels

The histological picture of the trophoblast and the vessels of the chorionic villi at the gestation period of 10 weeks also had distinctive differences between the groups. In the control group, the presence of a double-row cytotrophoblast with forming syncytial buds and well-formed full-blood vessels was recorded (Fig. 4a). In the main group, the histological picture did not essentially differ from that in the gestation period of 6 weeks (Fig. 4b and 3b).

The results of this study confirm the important role of thrombophilia in the pathogenesis of spontaneous loss of pregnancy through the development of disturbances in the histological structure of the trophoblast and the vessels of the chorionic villi in the first trimester of pregnancy. In scientific publications F.A. Beeksma, et al. (2012), G. Demirel, et al. (2012), M.R. Raspollini, et al. (2007), B.B. Rogers, et al. (2010) a conclusion was also made about the possible role of thrombophilia in the formation of embryonic thrombotic vasculopathy [6-9]. However, the authors indicated that they did not make exceptions to other possible causes of habitual loss of pregnancy, which prevented them from making an unambiguous conclusion about the thrombophilic origin of the revealed disorders in the formation of trophoblasts and chorionic villi. A review of L. Marsden, J. Comstock (2015), devoted to this problem, concluded that controlled prospective studies are necessary, with complete and careful exclusion of other possible causes of embryonic thrombotic vasculopathy [20].

Thus, the conducted study differs by excluding other possible causes of habitual miscarriage and a comprehensive examination of thrombophilia in both patients of the main and control groups.

Conclusions

1. All 24 (100%) patients in the main group had laboratory diagnoses of thrombophilia, of them single thrombophilia – in 7 (29.2%) patients, multiple thrombophilias – in 17 (70.8%). Among them were the following: mutation inhibitor activator plasminogen SERPINE (PAI) 1 – 18 (75%) (homozygous and heterozygous – 9 (37.5%) each); mutation Leiden G1691A heterozygous – 2 (8.3%); deficiency of PC and / or PS-6 (25%); deficiency of AT III – 6 (25%); antiphospholipid syndrome (APS) – 6 (25%); hyperhomocysteinemia – 7 (29.2%). Hyperactivation of f. Willebrand more than 150% was present in 12 (50%) women.

2. Gestational terms of termination of pregnancy in the women of the main and control groups did not differ significantly and amounted to 9.5±0.29 and 9.3±0.35 weeks according to LMP dates, respectively ($p_{t\text{-}test}<0.05$). Term of pregnancy according to ultrasound in patients of the main group was significantly less than in the control (6.1±0.18 and 8.9±0.39 weeks, respectively, $p_{t\text{-}test}<0.01$) and according to the dates of LMP in them ($p_{t\text{-}test}<0.01$), which, certainly, is associated with the presence of a missed abortion.

3. The characteristic differences in histological picture of trophoblast and chorionic villi in women with thrombophilia and recurrent pregnancy loss, in comparison with control, in the first trimester of pregnancy, are revealed. In the control, the presence of a double-row cytotrophoblast with forming syncytial kidneys, as well as growing, well-pronounced, full-blooded vessels was recorded. The main group was characterized by a single-row hypoplastic species trophoblast and single hypoplastic-looking vessels with a collapsed lumen. Dynamics of the histological pattern at the 6^{th} and 10^{th} weeks of gestation were absent.

4. It is proved that thrombophilia negatively affects the process of embryogenesis. Thus, the trophoblast area in patients with thrombophilia was statistically significantly lower than in the control group (869.2±61.20 and 1062.3±51.49 units/mm^2, respectively, $p<0.05$). Also, the area of chorionic villi vessels in women with thrombophilia was significantly less than the control values (4.3±0.63 and 97.1±7.90 units/mm^2, respectively, $p<0.01$).

5. The revealed features of the histological structure of trophoblast and chorionic villi in patients with thrombophilia probably can play a significant role in the pathogenesis of recurrent pregnancy loss.

Authors have no conflict of interest to declare.

References

1. Ailamazyan EK, Kulakov VI, Radzinsky VE, et al., editors. *Akusherstvo: nacional'noe rukovodstvo.* Moscow: GEOTAR-Media; 2014. (In Russ).

2. Cunningham FG, Leveno KJ, Bloom S.L., et al. *Williams Obstetrics.* 24th ed. New York: McGraw-Hill; 2005.

3. Gogia N, Machin GA. Maternal thrombophilias are associated with specific

placental lesions. *Pediatr Dev Pathol.* 2008; 11(6):424.

4. Makacarija AD, Beloborodova EV, Bajmuradova SM, et al. *Hyperhomocysteinemia and complications of pregnancy.* Moscow: Triada-H; 2005. (In Russ).

5. Momot AP. Problema trombofilii v klinicheskoj praktike. *Rossijskij zhurnal detskoj gematologii i onkologii.* 2015;2(1):36-48. (In Russ). doi:10.17650/2311-1267-2015-1-36-48.

6. Beeksma FA, Erwich J, Khong TY. Placental fetal vascular thrombosis lesions and maternal thrombophilia. *Pathology.* 2012; 44(1):24-8.

7. Demirel G, Celik IH, Zergeroglu S, et al. Neonatal outcome of the pregnancies associated with placental villous thrombosis–thrombophilic status of the mothers and the infants. *The Journal of Maternal-Fetal & Neonatal Medicine*. 2012;25(11):2225-9.

8. Raspollini MR, Oliva E, Roberts DJ. Placental histopathologic features in patients with thrombophilic mutations. *The Journal of Maternal-Fetal & Neonatal Medicine.* 2007;20(2):113-23.

9. Rogers BB, Momirova V, Dizon-Townson D, et al. Avascular villi, increased syncytial knots, and hypervascular villi are associated with pregnancies complicated by factor V Leiden mutation. *Pediatric and Developmental Pathology.* 2010;13(5):341-7.

10. Bicadze VO, Akin'shina SV, Makacarija AD, et al. Vspomogatel'nye reproduktivnye tehnologii i jatrogennye tromboticheskie oslozhnenija. *Voprosy ginekologii, akusherstva i perinatologii.* 2014;1:49-59. (In Russ).

11. Benirschke K, Burton GJ, Baergen RN. *Pathology of the Human Placenta.* 6th ed. New York: Springer; 2012.

12. Sills A, Steigman C, Ounpraseuth ST. Pathologic examination of the placenta: recommended versus observed practice in a university hospital. *J Womens Health.* 2013; 5:309-12.

13. Redline RW. Placenta and gestational trophoblastic disease. In: Cheng L, Bostwick DG, editors. *Essentials of anatomic pathology: fourth edition.* New York: Springer Cham Heidelberg; 2016. P. 1589-610.

14. Staun-Ram E, Shalev E. Human trophoblast function during the implantation process. *Reprod Biol Endocrinol.* 2005;3:56.

15. Roberts DJ. Placental pathology, a survival guide. *Arch Pathol Lab Med.* 2008;132(4):641.

16. Grand BE, Voto LS. Maternal issues in thrombosis and thrombophilia. In: Kurjak A, Chervenak FA, editors. *Textbook of Perinatal Medicine*. 3rd ed. New Delhi, London, Philadelphia, Panama: Jaypee Brothers Medical Publishers; 2015. P. 1738-43.

17. Sebire NJ, Backos M, El GS, et al. Placental pathology, antiphospholipid antibodies, and pregnancy outcome in recurrent miscarriage patients. *Obstet Gynecol* 2003; 101:258-63.

18. Soares MJ, Chakraborty D, Renaud SJ, et al. Regulatory pathways controlling the endovascular invasive trophoblast cell linear. *J Reprod Dev*. 2012:58(3):283.

19. Faye-Petersen OM, Heller DS, Joshi VV. *Handbook of Placental Pathology.* 2nd ed. London: Taylor & Francis; 2006.

20. Marsden L, Comstock J. Fetal Thrombotic Vasculopathy. *Journal of Fetal Medicine*. 2015;2(3):121-5.

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