Pathogenetic background of occurrence of venous thromboembolic complications in women with antenatal fetal death

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Improving the quality of medical services provided to pregnant women remains an urgent issue in modern obstetrics. Women with perinatal losses, especially in the second half of pregnancy, deserve special attention, mainly in connection with an increased incidence of thromboembolic complications in this group of patient.

***The aim** is to search for coagulation predictors of antenatal fetal death, to determine the main indicators of hemostasis and correlation between the case of antenatal fetal death and the risk of thromboembolic complications.*

***Materials and methods.** According to the goal, we examined 54 pregnant women with antenatal fetal death. Control group included 30 healthy primigravida women Comparative characteristics of the state of the hemostatic system during pregnancy and childbirth in the case of antenatal fetal death and during physiological pregnancy were conducted. Evaluation of the hemostatic system was performed before delivery and in the postpartum period with a dead fetus. The condition of the vessels of the pelvic organs was determined by dopplerometry of the internal iliac, uterine and ovarian veins.*

***Results.** The assessment of the hemostatic system parameters in the second group of pregnant women in 65% revealed a tendency to hypercoagulation, which manifested itself much earlier than in physiological pregnancy.*

***Conclusions.** Antenatal fetal death is a trigger for activation of coagulation and formation of blood clots, and, accordingly, is a factor of the occurrence of thrombotic exacerbations in the perinatal period. In pregnant women with antenatal fetal death, it is necessary to determine the soluble fibrinogen monomer complex and D-dimer parameters, which most informatively indicate the degree of intravascular coagulation. In pregnant women at high risk of antenatal fetal death at the stage of antenatal clinic should be performed duplex scanning of the pelvic veins with the determination of average blood flow velocity, cross-section diameter, cross-section area indicators and the calculation of volumetric blood flow velocity, and if there are changes venous thromboembolism prevention should be provided.*

Key words: *dead fetus, D-dimer, thromboprophylaxis, pelvic veins*

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Patogenetyczne podłoże występowania żylnych powikłań zakrzepowo-zatorowych u kobiet z przedporodową śmiercią płodu

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Istotną kwestią we współczesnym położnictwie pozostaje poprawa jakości świadczenia usług medycznych dla kobiet w ciąży. Na szczególną uwagę zasługują kobiety z porodami, zwłaszcza w drugiej połowie ciąży, głównie w związku ze zwiększoną częstością powikłań zakrzepowo-zatorowych w tej grupie pacjentek.

***Celem** jest poszukiwanie predyktorów krzepnięcia przedporodowej śmierci płodu, określenie podstawowych wskaźników hemostazy i określenie związku między przypadkiem przedporodowej śmierci płodu a ryzykiem wystąpienia powikłań zakrzepowo-zatorowych.*

***Materiały i metody.** Zgodnie z założonym celem przebadaliśmy 54 kobiety w ciąży z przedporodową śmiercią płodu. Grupę kontrolną stanowiło 30 zdrowych pierworudek. Przeprowadzono porównawczą charakterystykę stanu układu hemostazy podczas ciąży i porodu w przedporodowej śmierci płodu oraz w ciąży fizjologicznej. Ocenę układu hemostazy przeprowadzono przed porodem i po porodzie w martwym płodzie. Stan naczyń narządów miednicy określono przez wykonanie Dopplera żyły biodrowej wewnętrznej, macicy i jajnika.*

***Wyniki.** Podczas oceny wskaźników układu hemostazy w grupie badanej w ciąży wynoszącej 65% stwierdzono tendencję do hiperkoagulacji, która objawiła się znacznie wcześniej niż w ciąży fizjologicznej.*

***Podsumowanie.** Śmierć przedporodowa płodu jest wyzwalaczem aktywacji krzepnięcia i powstawania zakrzepów krwi, a zatem jest czynnikiem występowania powikłań zakrzepowych w okresie okołoporodowym. U kobiet w Śmierć przedporodowa płodu konieczne jest określenie wskaźników kompleks monomeru fibrynogenu i D-dimeru, co najbardziej pouczające wskazuje na stopień wewnątrznaczyniowego krzepnięcia krwi. U kobiet w ciąży z dużym ryzykiem przedporodowej śmierci płodu na etapie poradni przedporodowej należy wykonać skanowanie dupleksowe żył miednicy z określeniem średniej prędkości przepływu krwi, średnicy przekroju poprzecznego, wskaźników pola przekroju poprzecznego oraz obliczenia objętości krwi prędkość przepływu, aw przypadku zmian należy zapewnić zapobieganie żylnej chorobie zakrzepowo-zatorowej.*

Słowa kluczowe: *martwy płód, D-dimer, profilaktyka zakrzepowa, żyły miednicy*

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The preservation of the life and health of the mother and the future generation is a strategically important and priority task in the field of health care. Pregnancy loss remains one of the most pressing problems in obstetrics and gynecology. Despite numerous studies of the etiopathogenesis of perinatal losses, the frequency of spontaneous abortion in the population

ranges from 2 to 55%, with the majority occurring in the first trimester of pregnancy, antenatal fetal death (AFD) in Ukraine ranges from 1 to 3%, this is about 6.5 cases per 1000 births, compared to the EU level of up to 3‰ [4,13].

Perinatal losses, as a rule, is a consequence of one or multiple factors influences acting simultaneously or sequentially on the mother's body. Up to the main known causes of perinatal loss (unauthorized interruption pregnancy and antenatal fetal death) these include: genetic factors, endocrine disorders, hereditary and acquired disorders in the hemostatic system, immune factors, some nosologies of extragenital pathology, diseases of the genitals (uterine fibroids, developmental abnormalities, etc) [5,8].

Actual remains an adequate assessment and scientific justification the main causes and factors of influence on the level of antenatal mortality rate. In particular, this applies to organizational aspects functioning of the perinatal service at various levels providing specialized assistance (planning for future reproductive plans, antenatal fetal care, planning and management pregnancy and childbirth, care and recommendations for the introduction of the postpartum period.

Despite a large number of studies devoted to the pathogenesis of antenatal fetal death, the etiological factors of most cases of missed abortion remain unknown and are characterized as idiopathic. Recently, in the world literature, there are reasoned data on the influence of disorders in the hemostatic system on the occurrence of missed abortion. One of the main triggers in the occurrence of missed abortion is endothelial dysfunction, which leads to vascular spasm, increased permeability and impaired tissue perfusion, as well as activation of the coagulation system. this is a provoking factor in the development of chronic DIC syndrome [3,6]. DIC syndrome occurs as a result of the release of tissue thromboplastin. In most cases, tissue factor is secreted by damaged subendothelium and activated monocytes, which in turn induce cytokine secretion. In the case of focal damage, an increase in monocytes and platelets occurs, which contributes to the occurrence of local coagulation. However, with generalized endothelial activation, on the contrary, diffuse coagulation induction occurs, i.e. DIC-syndrome. Pregnancy is a hypercoagulable condition, which is provided by in particular, the presence of tissue thromboplastin, which is found in both endothelial cells, trophoblast and amniotic fluid [7].

The development of pregnancy is accompanied by a complex set of physiological changes in a woman's body, it is an adaptive mechanism for the functioning of the mother-placenta-fetus system. In particular, in the hemostatic system, there is an increase in blood clotting potential, which is an adaptive response of the pregnant woman's body aimed at limiting blood loss during childbirth. During pregnancy, there is a significant increase in the content of molecular activation factors (*von Willebrand* factor, β-thromboglobulin,) and secondary (tissue thromboplastin) links of hemostasis and fibrinolysis (thrombin-antithrombin III, SFC, D-dimer) with a decrease in physiological anticoagulants (antithrombin III, protein C) [1,11]. Thus, a state of increased vigilance against thrombosis develops. On examination of hemostasis, the so-called *Virchow* triad is noted, which is most clinically manifested in the third trimester of pregnancy: hypercoagulation (as a result of an increase in the level of blood clotting factors and inhibition of anticoagulant mechanisms); venous stasis (humoral and mechanical causes) and vascular wall damage.

It is noteworthy that the level of fibrinogen during pregnancy increases from the first trimester of pregnancy, and, in parallel with hyperfibrinogenemia, until the third trimester of pregnancy, there is a slowdown in the euglobulin and factor XIIa-dependent lysis of clots and an increased content of SFC and D-dimer. Compared with non-pregnant women, these indicators at the end of pregnancy are on the verge of thrombotic risk [12].

Prothrombin index (PI) is the ratio of the clotting time of a healthy person's plasma (control plasma) and the clotting time of the studied blood plasma. The indicator is expressed as a percentage (the norm is 90-105%). Prothrombin time (PT) is an indicator that characterizes the external pathway of blood clotting. If lengthens when there is a deficiency of plasma factors II, V, VII, X and fibrinogen; in the presence of inhibitors of these factors, treatment with anticoagulants, liver diseases, vitamin K deficiency.

Indicator activated partial thromboplastin time (APTT) is caused by the activation of factors VIII, IX, X, XI, XII and characterizes the internal pathway of blood clotting. This time is prolonged if there is a deficiency or abnormality in the production of factors XII, XI, IX, VIII, V, X, fibrinogen, and in the presence of coagulation inhibitors, including heparin. Shortening of APTT is observed in compensated and partially compensated forms of intravascular coagulation in the case of an increase in the level of factor VIII. It should be noted that this test indicates not only the procoagulant link of the hemostatic system, but also characterizes its antithrombin potential.

The D-dimer is a breakdown product of the fibrin protein present in the blood after a blood clot decay. The products are formed during clot lysis under the influence of plasmin and some fibrinolytics. The level of D-dimer increases in conditions that activate the coagulation system, such as DIC syndrome, deep vein thrombosis, pulmonary embolism, significant tissue damage or surgical interventions, infectious and inflammatory processes.

The soluble fibrinogen monomer complex (SFC) is a product of fibrin and fibrinogen degradation, which indicates an intensification of intravascular coagulation processes.

Mechanical compression of the vessels of the lower extremities and pelvic organs leads to blood stasis, which in turn is the framework for the occurrence of thrombosis during pregnancy. Venous thrombotic complications are attributed to uncontrolled causes of maternal mortality, which indicates that it is mandatory to predict and prevent venous thromboembolism (VTE) during pregnancy and childbirth [9]. The concept of VTE includes thrombosis of deep and superficial veins, and pulmonary embolism (PE). Frequency of the occurrence of such complications in pregnant women and women in labor is 0.3-0.5% of the total number of births [2].

To determine the need for thromboprophylaxis it is necessary to determine the degree of risk of occurrence VTE at the stage of an antenatal clinics at registration, in the second and third trimester of pregnancy and immediately before delivery. The presence of hereditary thrombophilia and / or a burdened family history of thrombosis is automatically considered a high-risk group for a pregnant woman and requires thromboprophylaxis and routine monitoring of hemostatic parameters during pregnancy and in the postpartum period. The British Royal College of obstetricians and gynacologists additionally determines the presence of additional factors such as age, obesity (BMI ≥30 kg/m^2), smoking, history of stillbirths, the use of assisted reproductive technologies, the presence of varicose veins of the lower extremities. With antenatal fetal death, the risk of VTE increases by 6 times compared to live birth [10].

The aim of our study is the search for coagulation predictors of antenatal fetal death, determination of the main indicators of hemostasis: fibrinogen level, D-dimer, an antigen of the tissue plasminogen activator (t-PA) and its inhibitor (PAI-1) and determining the parallel between the case of antenatal fetal death and the risk of thromboembolic complications.

MATERIAL AND METHODS

According to the goal, we examined 54 pregnant women with antenatal fetal death who were admitted to Kyiv City Maternity House No. 3 in the period from 2017 to 2020. The main group was divided into two subgroups: the first subgroup included pregnant women who had a burdened hereditary history of thromboembolism, the second subgroup had no history of thromboembolism. The control group consisted of 30 healthy primigravida pregnant women without any extragenital patho-

logy and complications during pregnancy. A comparative characteristic of the state of the hemostatic system during pregnancy and childbirth with antenatal fetal death and with a physiological pregnancy was conducted. In addition, we compared the state of the hemostatic system before delivery and during delivery. postpartum period with a dead fetus. The diagnosis of „antenatal fetal death" was established on the basis of a thorough examination of the pregnant woman's complaints, namely, the last episode of feeling fetal movements, the presence of pathological discharge from the genital tract; pain in the lower abdomen and lower back; external obstetric examination data, sonography data (no heartbeat, limbs in the extended position, the presence of fetal dropsy), lack of registration of heartbeat episodes during CTG recording; the amount and color of amniotic fluid. During collection of anamnesis, attention was paid to hereditary and thrombotic anamnesis: the presence of varicose veins of the lower extremities, the presence of past reproductive losses, complications in previous pregnancies, such as preeclampsia, cases of thrombosis, heart attack, and stroke in close relatives under the age of 40, clarified the presence of past extragenital and gynecological diseases.

To study the state of the hemostatic system in pregnant women and women in labor, the following biochemical tests were used: to assess the state of the procoagulant link of the hemostatic system – the content of fibrinogen (F), prothrombin index (PI), APTT, to characterize the antithrombin system, the content of antithrombin III (AT-III) and protein C (PC); to assess the state of the fibrinolytic link of the hemostatic system – the total fibrinolytic activity of blood, the content of plasminogen, α1-proteinase inhibitor (a1-IP), tissue plasminogen activator (t-PA), and D-dimer. Test parameters obtained in women with antenatal fetal death were evaluated in comparison with similar blood parameters of women with a physiological course of pregnancy and childbirth.

Comparative characteristics of hemostatic system parameters were performed when a case of antenatal fetal death was detected, immediately after delivery and 48 hours after delivery.

The condition of the vessels of the pelvic organs was determined by dopplerometry. Spectral analysis of the degree of dilatation of the pelvic vessels was performed using the device MyLab Seven Esaote SpA, a transabdominal sensor. Internal iliac veins (IIV), uterine veins (UV), and ovarian veins (OV) were examined. The following blood flow parameters were used: average blood flow velocity (ABF), cm/sec; cross-section diameter (CSD), cm; cross-section area (CSA), cm^2; $S= \pi r^2$, where r is the radius of the cross-section of the vessel; volumetric blood flow velocity (VBF) is the volume of blood flowing through the cross-section of the vessel per unit time, ml / min; VBF= Vcp S, where Vcp is the linear velocity, S is the cross-section of the vessel.

Statistical calculations of the obtained results were performed using the Microsoft Excel 2010 software and the Statistica 10 program; to determine the reliability, the Student's t-criterion was used at a significance level of $p \leq 0.05$.

RESULTS AND DISCUSSION

During the examination, anamnesis data, features of the course of this pregnancy in the case of AFD, and the course of previous pregnancies were obtained. The average age of pregnant women in the main group was in the range of 26-42 years, with the average of 32.8±4.5. The analysis of the medical and social characteristics of the group did not reveal statistically significant differences in the average age in indicators characterizing menstrual and reproductive functions. The main and control groups had a history of non-specific inflammatory infections of the urinary and genital tracts. It is worth noting that 48% (26) of women in the main group had a burdened hereditary thrombotic history (the presence of first-and second-line relatives of heart attacks, ischemic strokes, varicose veins of the lower extremities), and every 4 women had a burdened family history of hypertension.

Due to the polyethological nature and pathophysiological pathogenesis of the occurrence of antenatal fetal death, it is necessary to obtain a clear picture of the nature of disorders in the hemostatic system in these pregnant women. According to the results of the survey of pregnant women, the main group is divided into subgroups. The first subgroup included women with AFD who had signs of blood stasis and varicose veins of the lower extremities and pelvis. The second subgroup consisted of women with antenatal fetal death without signs of impaired blood outflow from the vessels of the pelvic organs.

We considered it necessary to assess the state of the coagulantion system, in particular its endothelial-platelet link. The results of the conducted studies in pregnant women of the examined groups upon admission to the hospital are shown in table 1.

One of the indicators that characterize microcirculatory hemostasis is the number of platelets. Although the platelet count does not directly indicate the activity of platelet factors, it does indirectly indicate the hemostatic potential of platelets. The total platelet count in pregnant women of both subgroups of the main group was (115±1.55) $*10^9$/l (in the main group) and (124±1.32)$*10^9$/l – II of the main group, respectively. Although, according to the data, in the I main group, the average platelet counts were 42% lower compared to women in the control group, these changes were significant (p<0,05).

Attention is drawn to the fact that in patients of both subgroups of the main group and the control group, an increase in the prothrombin index of more than 100% is observed. This test

Table 1. Indicators of the hemostatic system of the examined patients, M±m
Tabela 1. Wskaźniki układu hemostazy badanych chorych, M±m

Indicator	Main group		Control group (n=30)
	I main subgroup (n=34)	II main subgroup (n=20)	
Platelets in venous blood10^{109}/l	115±1,55*	124±1,32*	198±3,2
Platelet aggregation with ristomycin, %	48,7±1,9	42,1±2,1	36,4±2,6
Fibrinogen g / l	4,15±0,53	4,44±0,39*	3,01±0,2
D-dimer mg / ml	4,4±0,25	3,8±0,14	1,7 ±0,16
PI %	102,4±1,26	101,37±1,1	107,6±2,26
Antithrombin III	71,43±0,28*	73,30±0,64*	115,2±0,7
SFC mg / ml	13.3±0.2	14.5±0.23	4.5±0.15
Protein C %	32,8±0,35	34,4±0,71	40,3±2,66
t-PA antigen ng / ml	1,62±0,53*	1,46±0,41*	0,38±0,12
PAI-1 ng / ml	64,6±14,1*	52,4±13,8*	12,5±9,6

Note. Reliability of p relative to the control group: *p<0,05

characterizes the external pathway of blood clotting. Indicators of this test are determined by the content and functional activity of a number of clotting factors (II, V, VII, X, fibrinogen). This fact is explained by physiological changes in the hemostatic system, namely, an increase in the level of fibrinogen, SFC and D-dimer, which makes it possible to determine the group of pregnant women by being particularly wary of the occurrence of disorders in the hemostatic system during pregnancy.

According to our data, pregnant women with antenatal fetal death showed a decrease in the antithrombin reserve of the hemostatic system (AT-III and protein C). The content of AT-III varies within 71.43±0.28% in the first main group and 73.30±0.64% in the second, protein C – 32.8±0.35% and 34.4±0.71, which in both cases is significantly lower than in the control group (p=0.006). It should be noted that in 13% (7) pregnant women with AFD, the content of AT-III is equal to or below 55%, and in 10 pregnant women with AFD, the level of protein C is below 55%. We considered such a significant deficiency of natural anticoagulants in the plasma of pregnant women with AFD as the thrombophilic condition is the pathogenetic background for the development of thrombosis and embolism in the postpartum period.

D-dimer content attracts attention by the fact that in women with AFD it is at significantly higher levels and indicates one of the possible etiopathogenetic factors of AFD occurrence, such as preeclampsia, placental abruption, thrombosis of the placental spiral arteries. In the main group, high platelet aggregation activity with ristomycin was observed in comparison with the control group (p<0,005). Also, increased levels of tissue plasminogen activator inhibitor and high content of tissue activator antigen in the main group compared to the control group were observed.

There is no doubt that changes in the hemostatic system that are observed in women with AFD even before childbirth are the main pathogenetic factor for the occurrence of thrombotic complications in the postpartum period. Early diagnosis of the pre-thrombotic state and its timely correction is the key to a satisfactory course of the postpartum period and prevention of thrombotic complications in this contingent of pregnant women.

The next stage of our study was duplex scanning of the vessels of the lower extremities and small pelvis. In the course of the survey, the results presented in table 2 were obtained.

results showed that the internal iliac vein dilation in pregnant women of the control group is within the normal range (0.9-1.2 cm), while 34 (64%) pregnant women with AFD were diagnosed with iliac vein dilation up to 1.5 cm. In 8 pregnant women with AFD (14.8%), a difference was found between the right and left internal iliac veins, which is confirmed by calculations of the cross-sectional area, where in the control group the CSA does not exceed 0.1 cm. The received data indicates, that two-thirds of patients in both study groups had low ABF of the iliac veins (4.9-10.0 cm/s), without significant differences in both the left and right veins. Studies have shown that the ovarian vein CSD in healthy pregnant women is within the acceptable norm. While in more than 85% of the examined pregnant women, this indicator has medium and high degree of expansion (more than 0.4-0.6 cm). Similar changes in the CSA and AVB parameters indicate a more pronounced degree of violation in the left ovarian vein and in the right one, which is probably due to the features of the venous anatomy of the small pelvis. The results of ultrasound Doppler examination showed that this method of examination allowed obtaining objective confirmation of signs of morphological changes in the vascular wall and manifestations of venous stasis that occur during pregnancy, especially if it was complicated by antenatal fetal death.

CONCLUSION

ADF is a trigger for activation of coagulation and formation of blood clots, and, accordingly, is a factor of the occurrence of thrombotic complications in the peripartal period.

In pregnant women with AFD, it is necessary to determine the indicators of SFC and D-dimer what is most informative indicates the degree of intravascular coagulation. In our study changes in SFC and D-dimer indicators was detected in 53.7% of pregnant women with AFD.

Doppler examination of the pelvic veins showed that 85.1% of pregnant women with AFD have significant signs of venous blood stasis and dilatation of the pelvic veins, which is manifested by the difference in indicators between the left and right iliac veins, a decrease in ABF in the iliac and uterine veins.

In pregnant women at high risk of AFD at the stage of antenatal clinic should be performed duplex scanning of the pelvic

Table 2. Comparative characteristics of the state of pelvic veins during Doppler examination
Tabela 2. Porównawcza charakterystyka stanu żył miednicy w badaniu dopplerowskim

Pelvic veins	Indicator	Main group (n=54)		Control group (n=30)		Reference values
		Left side	Right side	Left side	Right side	
Internal iliac vein	ABF, cm/sec	5,8±0,92	7,9±1,5	8,2±0,77	10,3±0,67	10 – 16 cm/sec
	DCS, cm	1,6±0,14	1,3±0,16	1,12±0,06	0,92±0,08	0,9 – 1,2 sec
	CSA, cm^2	0,22±0,03	0,17±0,02	0,14±0,01	0,1±0,02	0,1 – 0,15[2]
	VBF, ml / min	144±3,0	140±4,0	126±3,0	128±2,0	50 – 150ml / min
Uterine vein	ABF, cm/sec	7,6±0,68	8,4±0,74	9,8±0,87	11,4±0,69	10 – 16 cm/sec
	DCS, cm	1,43±0,11	1.36±0,09	1,1±0,12	1,08±0,07	0,9 – 1,2 sec
	CSA, cm^2	0,25±0,04	0,19±0,01	0,12±0,02	0,11±0,02	0,1 – 0,15[2]
	VBF, ml / min	156±2,0	148±3,0	139±3,0	127±5,0	50 – 150ml / min
Ovarian vein	ABF, cm/sec	9,7±0,89	10,2±0,79	12,4±0,91	13,2±0,83	10 – 16 cm/sec
	DCS, cm	1,47±0,13	1,44±0,06	1,0±0,09	1,1±0,12	0,9 – 1,2 sec
	CSA, cm^2	0,16±0,02	0,13±0,004	0,11±0,01	0,12±0,001	0,1 – 0,15[2]
	VBF, ml / min	153±4,0	149±3,0	137±2,0	124±2,0	50 – 150ml / min

Note. Reliability of p relative to the control group: *p<0,05

In pregnant women with AFD, the results of Doppler scanning of the pelvic veins indicate the violations of blood outflow from the lower extremities. As can be seen from table 2, the veins with the determination of ABF, DCS, CSA indicators and the calculation of VBF, and if there are changes VTE prevention should be provided.

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