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М.А. Ус*, Ю.Ю. Карпенко

ФГБОУ ВО ВГМУ имени Н.Н. Бурденко Минздрава России,
кафедра госпитальной терапии и эндокринологии, Воронеж, Россия

ИДИОПАТИЧЕСКАЯ ЛЕГОЧНАЯ ГИПЕРТЕНЗИЯ И ТРОМБОЭМБОЛИЯ IN SITU: ТРУДНЫЙ СЛУЧАЙ В КЛИНИЧЕСКОЙ ПРАКТИКЕ

M.A. Us*, Ju.Ju. Karpenko

State Budgetary Educational Institution of High Professional Education «Voronezh State Medical University n.a. N.N. Burdenko» of the Ministry of Health of the Russian Federation, Department of Hospital Therapy and Endocrinology, Voronezh, Russia

Idiopathic Pulmonary Hypertension and in Situ Thromboembolism: A Difficult Case in Clinical Practice

Резюме

Легочная гипертензия представляет собой сложный для дифференциальной диагностики синдром, являющийся исходом различных патологических состояний. При исключении двух наиболее распространенных причин развития легочной гипертензии, таких как патологии левых камер сердца и тромбоэмболии легочной артерии, дальнейший поиск этиологии зачастую становится проблематичен. Несмотря на появление ряда международных и отечественных рекомендаций, а также определенные успехи в медикаментозной терапии, долгосрочный прогноз у пациентов с легочной артериальной гипертензией остается неблагоприятным. Представлен клинический случай пациентки, 39 лет, страдающей идиопатической легочной артериальной гипертензией (иЛАГ). Пациентка не могла выносить ребенка; все ее попытки, продолжительностью более 19-ти лет, оставались безуспешными. У данной пациентки наблюдалось «подострое» течение легочной артериальной гипертензии и достаточно быстрое прогрессирование заболевания со значительным ухудшением качества жизни, что повлекло за собой невозможность вынашивания беременности. Также имелись признаки, негативно влияющие на прогноз, такие как нарастание одышки, потери сознания, значительное снижение работоспособности и высокая степень легочной артериальной гипертензии (по данным эхокардиографии систолическое давление в легочной артерии (СДЛА) составило более 128 мм ртутного столба). В связи с неэффективностью стандартной терапии селективным ингибитором циклогуанозинмонофосфат (цГМФ) — специфической фосфодиэстеразы 5-го типа (ФДЭ5) — силденафилом; был рассмотрен вариант лечения двойной специфической терапией, что позволило изменить ситуацию, получить положительную динамику и определить акушерско-гинекологический прогноз.

Ключевые слова: *идиопатическая легочная артериальная гипертензия, экстракорпоральное оплодотворение, легочная артерия, правый желудочек, специфическая терапия*

Конфликт интересов

Авторы заявляют, что данная работа, её тема, предмет и содержание не затрагивают конкурирующих интересов

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*Контакты: Маргарита Андреевна Ус, e-mail: dr.margatitaas@gmail.com
*Contacts: Margarita A. Us, e-mail: dr.margatitaas@gmail.com
ORCID ID: https://orcid.org/0000-0002-6331-4598

Abstract

Pulmonary hypertension is a complex syndrome for differential diagnosis, which is the outcome of various pathological conditions. With the exclusion of the two most common causes of pulmonary hypertension, such as pathology of the left heart chambers and pulmonary embolism, further search for etiology often becomes problematic. Despite the emergence of a number of international and domestic recommendations, as well as certain successes in drug therapy, the long-term prognosis in patients with pulmonary arterial hypertension remains unfavorable. In the description of this clinical case in a 39-year-old woman suffering from idiopathic pulmonary arterial hypertension, the main complaint of the patient was very non-specific. The woman could not bear the child, all her attempts, lasting more than 19 years, remained unsuccessful. Even in absolutely healthy women, pregnancy is associated with the highest risks and is a powerful "test" of the body, not to mention patients suffering from rare diseases. The patient has a "subacute" course and a fairly rapid progression of the disease with a significant deterioration in the quality of life, which led to the impossibility of carrying a pregnancy. There were also signs that aggravated the prognosis, such as increased dyspnea, loss of consciousness, a significant decrease in working capacity and a high degree of pulmonary hypertension (according to echocardiography, systolic pressure in the pulmonary artery > 128 mm Hg). Due to the ineffectiveness of standard therapy with a selective inhibitor of cycloguanosine monophosphate — specific phosphodiesterase type 5 — sildenafil; the option of specific therapy for pulmonary hypertension was considered, which made it possible to change the situation and bring the patient into a stable state and draw conclusions about the pregnancy.

Key words: *idiopathic pulmonary hypertension, in vitro fertilization, pulmonary artery, right ventricle, specific therapy*

Conflict of interests

The authors declare no conflict of interests

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BNP — brain natriuretic peptide; FBG — fibrinogen; FV — factor V Leiden mutation; ITGA2 — integrin-alpha-2; MTRR — methionine -synthase-reductase; MTR — methionine synthase; NT-proBNP — N-terminal pro B type natriuretic peptide; PAI-I — plasminogen activator inhibitor-1; CCB — calcium channel blockers; VRT — vasoreactive test; iPAH — idiopathic pulmonary arterial hypertension; PA — pulmonary artery; PAH — pulmonary arterial hypertension, PH — pulmonary hypertension; LV — left ventricle; PV — pulmonary valve; PVR — pulmonary vascular resistance; MRI — magnetic resonance imaging; INR — international normalised ratio; RV — right ventricle; PASYS — pulmonary artery systolic pressure; TV — tricuspid valve; PATE — pulmonary artery thromboembolia; FDE-5 — phosphodiesterase, type 5; CTEPH — chronic thromboembolic pulmonary hypertension; CVP — central venous pressure; cGMP — cyclic guanosine monophosphate; IVF — in vitro fertilisation; ERA — endothelin receptor antagonists; echo-CG — echocardiography; EEG — electroencephalography

Relevance

Idiopathic pulmonary arterial hypertension (iPAH) is a severe chronic and rapidly progressing disease characterised by an increase in pulmonary vascular resistance (PVR) as a result of a number of pathogenic processes in the vascular wall, that causes obstructive remodelling of small pulmonary arteries and arterioles. [1] Idiopathic arterial hypertension accounts for a minor number of all pulmonary hypertension (PH) cases. Median survival of patients with idiopathic pulmonary arterial hypertension before PAH-specific therapy is 2.8 years, and the period from disease manifestation to final diagnosis is 2 to 3 years. [2]. Idiopathic arterial hypertension is an orphan disease; however, there are no accurate global epidemiological data [6]. The international registries show that iPAH morbidity is 0.9–7.6 per million people, whereas the incidence rate is 5.6–26 per million of people. Pulmonary artery thromboembolia or thrombosis in situ can be a result of impaired clotting cascade, including endotheliocyte and platelet dysfunction. Platelet pathology and pro-coagulation changes can have a role to play in formation of local thromboses in chronic thromboembolic pulmonary hypertension (CTEPH) [4]. Current PAH-specific therapy aims to restore the balance of vascular mediators (nitrogen oxide, prostacyclin, endothelin) — main pathogenic links in the development of pulmonary arterial hypertension [3]. Clinicians use 5 classes of products: endothelin receptor antagonists (ERA), type 5 phosphodiesterase inhibitors, soluble guanylate cyclase stimulants, prostacyclin analogues and prostacyclin receptor agonists [3]. Management of patients with pulmonary arterial hypertension involves regular assessment of therapy efficacy, after which a dose escalation and two or three products from various classes can be required, especially for patients with intermediate or high risk of death [5, 7].

This article describes a case study of a patient with idiopathic pulmonary hypertension, thrombosis in situ, which are induced by miscarriages and ten procedures of in vitro fertilisation (IVF) and are refractory to standard therapy with selective cyclic guanosine monophosphate (cGMP) inhibitor — specific type 5 phosphodiesterase, and diuretics.

Outpatient and inpatient medical records of the patient with pulmonary arterial hypertension were analysed retrospectively. On March 28, 2022, a 39-year-old

woman was referred for the first time to the cardiologist at Voronezh Regional Cardiology Dispensary (at the Budgetary Healthcare Institution Voronezh Regional Clinical Hospital No. 1) from the Budgetary Healthcare Institution of the Voronezh Region Voronezh Regional Clinical Hospital No. 11, where primary healthcare providers had unsuccessfully attempted to control the patient's condition. (Fig. 1) The woman complained of shortness of breath after ascending just 3–4 stairs (1 flight of stairs), walking for up to 10 m, during household chores, also of swollen legs, dizziness, blood pressure fluctuations between 140/90 mm Hg and 90/70 mm Hg, episodes of rhythmic tachycardia up to 90–100 bpm, episodes of fainting.

Medical history: the patient considers herself ill from 2009, after the third miscarriage (pre-syncope was observed: dizziness, "congested" back of the head). From summer 2020, she has been having syncopal condition (several times a year) during physical load, forward bends, during hot weather. Brain magnetic resonance imaging (MRI) and electroencephalography (EEG) did not show any pathologies; however, the neurologist diagnosed syncope with spastic component due to arterial hypertension and hyperventilation. At the same very moment, the patient noted reduced tolerance to physical loads. In February 2021, examinations during her fourth pregnancy (in vitro fertilisation (IVF)) revealed changes in trombophilia gene polymorphism, Leiden mutation; the patient was prescribed enoxaparin sodium and acetylsalicylic acid. The patient had miscarriage at week 15–16 of gestation. By December 2021, she had 8 unsuccessful IVF procedures. During a routine examination in summer 2021, echocardiography showed enlarged pulmonary heart ***for the first time***. In December 2021, the patient underwent a ninth IVF procedure. In January 2022, she had hysteroscopy, after which the patient noted significant deterioration in her condition, episodes of syncope became more frequent (5 episodes in January–March 2022), worsened shortness of breath (even at minimal physical loads, e.g. body twists in bed), swollen legs.

Life history: no family history of cardiovascular diseases. Comorbidities: inherited multiple-factor trombophilia caused by factor V Leiden mutation (FV), heterozygous variant, methionine synthase (MTR), heterozygous variant, methionine -synthase- reductase (MTRR), homozygous variant, fibrinogen (FBG), heterozygous variant, plasminogen activator inhibitor-1

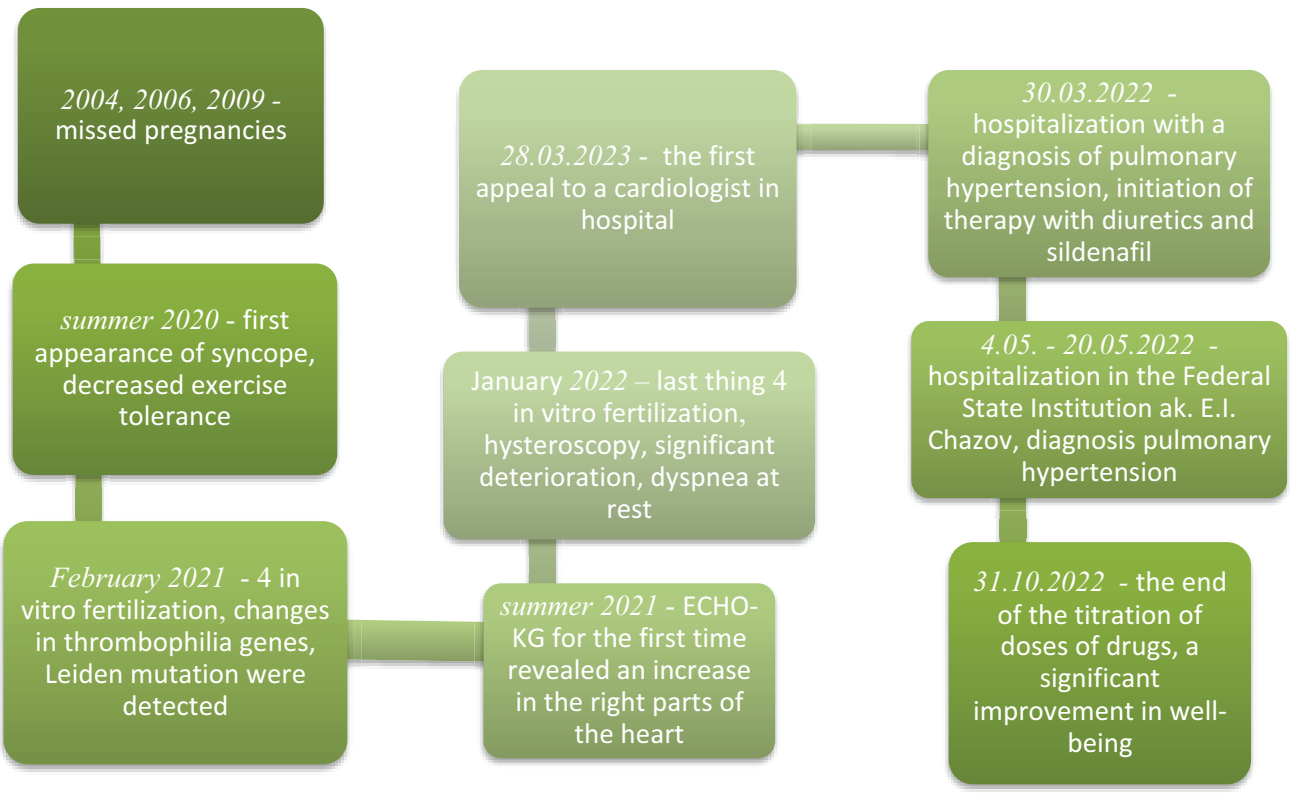


Figure 1. *Chronology of events*
Note: ECHO-KG — echocardiography

(PAI-I), heterozygous variant, integrin-alpha-2 (ITGA2), homozygous variant (diagnosed in 2020 during the fourth IVF procedure). Concomitant pathologies included superficial gastritis, reactive duodenitis, esophagitis. Mild obstructive apnoea syndrome was diagnosed in April 2022 after cardiorespiratory monitoring. Compensated chronic Hashimoto's thyroiditis (Euthyrox 125–150 μg daily). After unsuccessful attempts to conceive and carry pregnancy to term naturally (in 2004, 2006, 2009: missed miscarriages at weeks 5–6 of pregnancy), in 2020–2022 the patient was treated in the Budgetary Healthcare Institution of the Voronezh Region Voronezh Center for Family Health Protection and Reproduction, where the patient had 9 unsuccessful in vitro fertilisation procedures (from February 2021 to January 2022). History of allergies: acute essential oedema after ceftriaxone (as a child). TB, hepatitis B, C, human immunodeficiency virus, diabetes mellitus, typhus, paratyphoid fever, psoriasis, cancer — denies. No blood transfusions. Smoking and alcohol consumption — denies.

After an outpatient consultation by the cardiologist (March 28, 2022) due to conditions deterioration, the patient was referred to computed tomography angiography, which showed signs of pulmonary artery thromboembolia (PATE) in small branches on both sides. The patient was hospitalised to the Cardiac Defect Surgery Department of the Budgetary Healthcare Institution Voronezh Regional Clinical Hospital No. 1 with the diagnosis "thromboembolia of small branches of pulmonary artery (March 30, 2022). Circulatory inefficiency 2A. Functional class 3. High pulmonary hypertension. Trombophilia gene polymorphism (inherited multiple-factor thrombophilia caused by factor V Leiden mutation (FV), heterozygous variant, methionine synthase (MTR), heterozygous variant, methionine-synthase-reductase (MTRR), homozygous variant, fibrinogen (FBG), heterozygous variant, plasminogen activator inhibitor-1 (PAI-I), heterozygous variant, integrin-alpha-2 (ITGA2), homozygous variant" (from March 30 to April 6, 2023). After initiation of inpatient diuretic therapy (torasemide 5 mg daily, spirolacton 50 mg daily) and specific therapy (cyclic guanosine monophosphate inhibitor — type 5 phosphodiesterase (sildenafil) 20 mg three times daily), the patient noted short-term improvement in her health condition. Anticoagulant therapy with warfarin was prescribed. No surgery for pulmonary artery thromboembolia (PATE) was performed. The patient was consulted by pulmonologist, neurologist, somnologist. Under the recommendation of pulmonologist, the patient was referred for a consultation to the Federal State Budgetary Institution E. I. Chazov National Medical Research Institute of Cardiology of the Ministry of Health of the Russian Federation (Moscow) (Pulmonary Hypertension Department) for differential diagnosis of iPAH and chronic thromboembolic pulmonary hypertension (CTEPH) (Table 1), as well as therapy adjustment.

The patient was hospitalised to the Federal State Budgetary Institution E. I. Chazov National Medical Research Institute of Cardiology of the Ministry of Health of Russia from May 4 to May 20, 2022, where she underwent the following laboratory tests and instrumental examinations:

Complete blood count dd May 5, 2022: WBC — 9.8×10^9/L (N: 4.8–10.8); NEU — 5.3 K/μL (N: 1.9–8.0); LYMPH — 3.5 K/μL (N: 0.9–5.2); MON — 0.75 K/μL (N: 0.20–1.00); EOS — 0.14 K/μL (N: 0.00–0.80); BAS — 0.05 K/μL (N: 0.00–0.20); RBC — 4.36×10^{12}/L (N: 4.20–5.40); Hb — 12.80 g/dL (N: 12.00–16.00); HCT — 37.6 % (N: 37.0–47.0); mean corpuscular volume — 86.2 fL (N: 81.0–99.0); mean corpuscular haemoglobin — 29.4 pg (N: 27.0–31.0); mean corpuscular hemoglobin concentration — 34 g/dL (N: 33–37); RBC anisotropy factor — 14.5 % (N: 11.5–14.5); platelets — 345 $\times10^9$/L (N: 130–400); mean platelet volume — 10.3 fL (N: 7.2–11.1); PCT — 0.34 % (N: 0.02–1.00).

Blood biochemistry dd May 5, 2022: total bilirubin — 25.7 μmo/L (N: 1.7–20.5); K — 4.4 mmol/L (N: 3.5–5.3); Cl — 108.0 mmol/L (N: 98.0–108.0); Na — 139.0 mmol/L (N: 138.0–153.0); creatinine — 74.1 μmol/L (N: 50.0–98.0); K — 4.7 mmol/L (N: 3.5–5.3); Cl — 106.0 mmol/L (N: 98.0–108.0); Na — 142.0 mmol/L (N: 138.0–153.0).

D-dimer quantification dd May 5, 2022: D-dimer — 0.47 μg/mL (N: 0.00–0.50).

NT-proBNP (N-terminal pro B type natriuretic peptide) dd May 5, 2022): 1,893.0 pg/mL (N: 0.0–150.0).

Coagulation profile dd May 5, 2022: prothrombin time — 18.4 s (N: 5.0–15.0); international normalised ratio — 1.66 (N: 0.80–1.27); Quick's value — 49.0 % (N: 70.0–130.0).

Coagulation profile dd May 9, 2022: prothrombin time — 28.5 s (N: 5.0–15.0); international normalised ratio — 2.50 (N: 0.80–1.27) (patient was prescribed warfarin 5 mg).

Urinalysis dd May 5, 2022: colour — yellow; acidity — 5.5/faintly acid (N: 5.0–7.0); protein — 0.10 g/L; glucose — 0.3 mmol/L (N: 0.0–0.8); ketone bodies — neg (N: 0–1); bilirubin — neg; urobilinogen — 0 μmol/L (N: 0–34), squamose epithelium — 1 cell/μL (N: 0–28); WBC — 10 cell/μL; non-lysed RBC — 4 cell/μL; mucus — little per HPF; specific gravity — 1,023; clarity — completely clear.

Table 1. Classification of pulmonary hypertension, necessary for the standardization of diagnostic and treatment approach

Group 1 Pulmonary arterial hypertension	Refers to the number of orphan diseases. Clinical features: younger patients, family history, risk factors, associated diseases ECG: Rotation of the electrical axis to the right, hypertrophy of the pancreas. ECHO-KG: the right ventricle is enlarged, the right atrium is larger than the left atrium, the interventricular septum is deflected to the left, the transmitral blood flow is E/A ≤ 1, the Dopplerogram of the lateral segment of the fibrous ring of the mitral valve is E/Em < 8. X-ray of the chest organs: enlargement of the right chambers, dilated pulmonary artery, depletion of pulmonary blood flow in the periphery. Biomarkers: BNP/NT-proBNP — increased. Perfusion lung scintigraphy in combination with ventilatory lung scintigraphy: used to rule out chronic thromboembolism. Transventional cardiac catheterization: pulmonary artery wedge pressure ≤ 15 mm Hg, pulmonary-vascular resistance> 3 units. Wood, diastolic pulmonary gradient >7 mm Hg. Treatment: we have the right to prescribe specific therapy (but only idiopathic pulmonary hypertension is included in the federal list of orphan diseases).
Group 2 Pulmonary hypertension associated with pathology of the left chambers of the heart	Clinical features: older patients, arterial hypertension, diabetes mellitus, coronary artery disease, body mass index > 30 kg/m^2, clinical picture of congestive heart failure, history of cardiac asthma/pulmonary edema, orthopnea. ECG: Rotation of the electrical axis to the left, left ventricular hypertrophy, atrial fibrillation. ECHO-KG: the right ventricle can be enlarged, the left atrium is enlarged, the interventricular septum is deflected to the right, the transmitral blood flow E/A > 1, Dopplerogram of the lateral segment of the fibrous ring of the mitral valve E/Em > 10. Chest X-ray: congestive changes in the lungs, Kerley lines, pleural effusion, enlargement of the left chambers of the heart. Biomarkers: BNP/NT-proBNP — increased. Perfusion pulmonary scintigraphy in combination with ventilatory pulmonary scintigraphy: used to rule out chronic thromboembolism. Transventional cardiac catheterization: pulmonary artery wedge pressure > 15 mm Hg., diastolic pulmonary gradient < 5 mm Hg.
Group 3 Pulmonary hypertension bound with lung disease and/or hypoxia	Causes: chronic obstructive pulmonary disease, interstitial lung disease, other lung diseases with mixed restrictive and obstructive disorders, hypoxia in the absence of lung disease, respiratory disorders during sleep, alveolar hypoventilation syndrome, high-altitude pulmonary hypertension, abnormal development of the lungs. Perfusion lung scintigraphy is used in combination with ventilation lung scintigraphy.
Group 4 Pulmonary hypertension due to obstruction of the pulmonary arteries	Causes: chronic thromboembolic pulmonary hypertension, other pulmonary artery obstructions (angiosarcoma, other intravascular tumors, arteritis, congenital anomalies, parasitic diseases) Perfusion lung scintigraphy is used in combination with ventilation lung scintigraphy Treatment: thromboendarterectomy is indicated for patients with chronic thromboembolic pulmonary hypertension.
Group 5 Pulmonary hypertension of unknown or mixed origin	Causes: hematological diseases (chronic hemolytic anemia, myeloproliferative diseases, splenectomy), systemic disorders (sarcoidosis, pulmonary histiocytosis, lymphangioleiomyomatosis, neurofibromatosis, vasculitis), metabolic disorders (glycogenosis, Gaucher disease) and others. Treatment: more often surgical — thromboendarterectomy, atrial septostomy is indicated for patients with valvular heart disease.

Note: BNP — brain natriuretic peptid, ECG — electrocardiography, ECHO-KG — echocardiography, NT-proBNP — N-terminal pro-brain natriuretic peptid. [Avdeev S.N., Barbarash O.L., Bautin A.E., et al. 2020 Clinical practice guidelines for Pulmonary hypertension, including chronic thromboembolic pulmonary hypertension. Russian Journal of Cardiology. 2021;26(12):4683. https://doi.org/10.15829/1560-4071-2021-4683].

Electrocardiogram dd May 4, 2022: sinus tachycardia, 109 bpm. Electric axis deviation to the right. Signs of myocardial changes as a result of right ventricle hypertrophy.

Chest X-ray dd May 5, 2022: changes are consistent with high pulmonary arterial hypertension. Enlarged pulmonary heart. Delated azygous vein.

Echocardiography (M- и B-mode, colour Doppler imaging, Doppler sonography) dd May 16, 2022: dilated right heart with signs of right ventricle (RV) pressure overload. Dilated pulmonary trunk and branches. Ejection fraction 60 % (Simpson's). Right ventricular (RV) myocardial hypertrophy. Hight pulmonary arterial hypertension (94–99 mm Hg). Moderately reduced systolic function of right ventricle (RV). Tricuspid valve (TV) insufficiency, grade 2–3, pulmonary valve (PV) insufficiency, grade 1–2. Signs of moderately increased central venous pressure (CVP). Small amount of liquid in pericardial cavity.

Abdominal ultrasound dd May 5, 2022: slightly enlarged liver due to left lobe thickness. Spleen: unremarkable. Moderate diffuse changes in liver and pancreas parenchyma. Ultrasound signs of venous stasis in the system of inferior vena cava. No ultrasound signs of portal hypertension, abdominal dropsy. Ultrasound signs of chronic calculous cholecystitis.

Holter ECG monitoring dd May 6, 2022 — May 7, 2022: 24-hour ECG monitoring recorded sinus rhythm with 90 bpm (minimal heart rate is 70 bpm at 04:30 am, maximum value is 133 bpm at 12:19 pm). 2 ventricular

extrasystoles, single supraventricular premature beat. Changes in ST segment cannot be assessed to the initially modified terminal section of the ventricular complex.

Spirometry with computer-aided data processing dd May 6, 2022: lung capacity and airway patency are above the age norm.

High frequency focus ultrasound of peripheral arteries dd May 11, 2022: atherosclerotic plaques in the carotid not observed. Atherosclerotic plaques in femoral arteries not observed.

CT angiography of pulmonary arteries (MSCT-pulmonary angiography) dd May 11, 2022: no signs of massive thrombosis of pulmonary artery (PA) trunk and large branches. Signs of pulmonary hypertension. Thrombosis of some small subsegmental branches next to right C3 branch cannot be ruled out. A hypodense mass in left adrenal gland; probably, an adenoma.

Duplex scanning of iliofemoral veins dd May 13, 2022: saphenofemoral junctions are not dilated on both sides, no signs of thrombosis, ostial valves are intact. Blood flow in both common femoral veins is phasic, synchronised with breath.

Perfusion lung scintigraphy dd May 16, 2022: scintigraphic signs of pulmonary hypertension; no signs of focal perfusion changes in lungs and right-to-left shunt.

After a comprehensive clinical and laboratory examination (including pulmonary heart catheterisation) at the Federal State Budgetary Institution E. I. Chazov National Medical Research Institute of Cardiology of the Ministry of Health of Russia, the purpose of which was to find the origin of pulmonary hypertension, there were no data evidencing pulmonary hypertension caused by left heart pathology, congenital heart disorder, lung pathology, chronic thromboembolic pulmonary hypertension. The patient was diagnosed with idiopathic pulmonary hypertension with pulmonary artery thrombosis in situ, functional class III (according to WHO guidelines). Taken condition severity, low functional class, signs of blood flow insufficiency and factors of poor prognosis, the medical panel decided to adjust the PAH-specific therapy: cyclic guanosine monophosphate inhibitor — specific type 5 phosphodiesterase was replaced with riociguat at an initial dose of 0.5 mg three times daily, and selexipag was initiated at an initial dose of 200 μg twice daily. The patient tolerated both products without side effects. Later, it was recommended to titrate riociguat at 0.5 mg three times daily every 2 weeks up to the maximum dose of 2.5 mg three times daily (systolic blood pressure should be controlled before every medication intake), and weekly selexipag titration as per algorithm until the dose is 1,600 μg twice daily (Table 2). This therapy is life-saving; it cannot be replaced or discontinued. Taking into account the presence of idiopathic pulmonary hypertension, the patient was prescribed anticoagulant therapy with warfarin; considering thrombosis of some small subsegmental branches of pulmonary arteries, the target value of international normalised ratio (INR) is 2.5–3.5. Since the patient had sinus tachycardia, ivabradine was prescribed at an initial dose of 5 mg daily to maintain the heart rhythm. During the inpatient observation, the patient's condition remained stable, without circulatory inefficiency aggravations; blood pressure was 110–120/70–80 mm Hg. The patient was discharged in satisfactory condition.

Table 2. *Dose titration of of specific therapy for pulmonary hypertension (riociguat and selexipag)*

Дата/препарат Date/drug	мг в сутки/ mg per day	мкг в сутки/ mkg per day
	Риоцигуат/ Riociguat	Селексипаг/ Selexipag
25.07.2022	3,75	400
26.07.2022	3,75	400
27.07.2022	3,75	400
22.08.2022	6	400
23.08.2022	6	400
24.08.2022	6	400
05.09.2022	7,5	400
06.09.2022	7,5	400
07.09.2022	7,5	400
19.09.2022	7,5	800
20.09.2022	7,5	800
21.09.2022	7,5	800
26.09.2022	7,5	1200
27.09.2022	7,5	1200
28.09.2022	7,5	1200
03.10.2022	7,5	1600
04.10.2022	7,5	1600
05.10.2022	7,5	1600
10.10.2022	7,5	2000
11.10.2022	7,5	2000
12.10.2022	7,5	2000
17.10.2022	7,5	2400
18.10.2022	7,5	2400
19.10.2022	7,5	2400
24.10.2022	7,5	2800
25.10.2022	7,5	2800
26.10.2022	7,5	2800
31.10.2022	7,5	3200
01.11.2022	7,5	3200
02.11.2022	7,5	3200

Outpatient follow-up dd October 16, 2022: the patient does not complain of shortness of breath at rest and while speaking; shortness of breath appears at fluent speech and when ascending 10 and more stairs; she can tolerate household chores well; no syncope was observed.

Objective findings: the general condition is relatively satisfactory. The patient's consciousness is clear. Height: 167 cm. Weight: 82 kg. Body mass index: 29 kg/m^2 (overweight). Skin is of normal colour; mucous membranes are wet and of normal colour. The oropharynx is not hyperaemic. The subcutaneous fat layer is moderately developed; palpable lymph nodes are not enlarged. Breasts: visually unremarkable. Bones, joints and muscles: visually unremarkable. Thyroid gland: visually and palpatory unremarkable. Shank pastosity, more in the left shank.

6-min walk distance: pre-test SpO2 - 98 %, heart rate - 85 bpm; post-test SpO2 - 100 %, heart rate - 132 bpm. The patient walked 370 m. Borg Dyspnoea Scale: 5 points.

Respiratory system: the chest in normosthenic. Respiratory rate: 16 respirations per minute. Both hemithoraxes are evenly engaged in respiration; vocal fremitus is normal. Percussion sound is clear above all pulmonary fields; auscultatory vesicular respiration in all chest sections, without stridor. Shortness of breath on exertion is significant.

Circulation organs: the apex beat is in the 5th intercostal space along the left midclavicular line. Cardiac dullness border: right — at the right sternum edge; left — in the 5th intercostal space along the left midclavicular line; upper — in the 3rd intercostal space; the cardiac sound is clear; the loud second heart sound is above the pulmonary vein; diastolic murmur is in the auscultation point of tricuspid valve; the rhythm is regular, with a heart rate of 80 bpm; pulse: 80 bpm (no deficit); filling and exertion are normal. Blood pressure, right arm: 110/70 mm Hg, blood pressure, left arm: 114/70 mm Hg.

GIT: hearty appetite; the tongue is moist and clear; on palpation, the abdomen is soft and non-tender in all sections; the liver is palpable 1 cm below the right costal arch; spleen is not palpable; bowel movement: unremarkable.

Urinary system: urination is unobstructed; kidneys are not palpable; kidney punch is negative on both sides.

Neuropsychological status: memory is normal, the patient is lucid; sleep is normal; the patient understands her condition; no signs of severe disorders in 12 pairs of cranial nerves.

Sensory organs: eyesight, hearing and olfaction are normal.

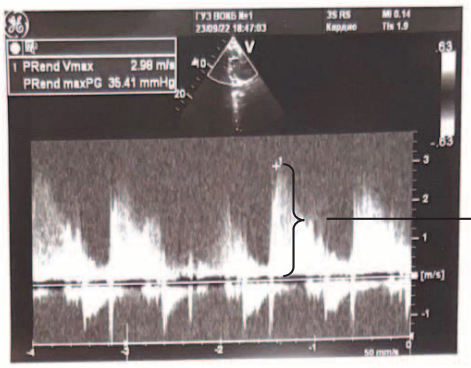
Based on clinical findings, results of laboratory and instrumental tests, the patient was diagnosed with the primary diagnosis "Idiopathic pulmonary hypertension. Functional class III (WHO). Thrombosis in situ of pulmonary arteries. Relative incompetence of tricuspid valve, grade 2–3, pulmonary artery valve insufficiency, grade 1–2. ***Complications.*** Chronic heart failure, grade IIB, NYHA functional class III. ***Comorbidities.*** Inherited multiple-factor thrombophilia caused by factor V Leiden mutation (FV), heterozygous variant, methionine synthase (MTR), heterozygous variant, methionine synthase reductase (MTRR), homozygous variant, fibrinogen (FBG), heterozygous variant, plasminogen activator inhibitor-1 (PAI-I), heterozygous variant, integrin-alpha-2 (ITGA2), homozygous variant. Superficial gastritis. Reactive duodenitis. Esophagitis. Mild obstructive apnoea syndrome. Chronic Hashimoto's thyroiditis".

The patient was recommended to modify her lifestyle: flu and pneumococcal disease vaccination; supplemental oxygen is recommended for air travel; in scheduled surgeries, epidural is preferable (not inhalation anaesthesia); excessive physical activity, changes of climatic regions and staying in high mountain regions should be avoided, as they can cause clinical deterioration. Also, a healthy diet is recommended: animal fats and cholesterol-rich products should be limited; spicy, fried and smoked products as well as easily digested carbohydrates should be avoided. Daily water intake should not exceed 1.2–1.3 L. Monitoring of consumed fluid and urination, weight monitoring. Sodium chloride consumption should be limited to 3 g/day; optimal work and rest schedule, limited emotional and physical load, which can cause condition decompensation. The most important recommendation for the patient was that, due to a high risk of complications, pregnancy is absolutely contraindicated. The patient was strongly encouraged to use barrier contraception; she was consulted by a psychologist. A professional psychologist noted positive changes and acceptance by the patient of her chronic condition, adherence to treatment is satisfactory.

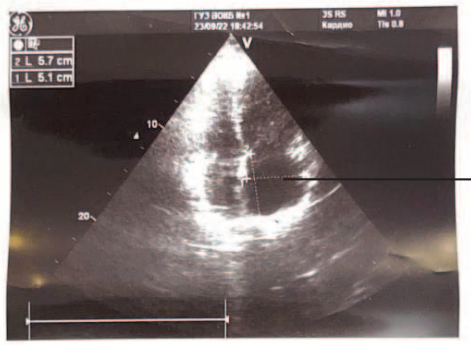
The following medicinal products are recommended permanently: selexipag 200 mg twice daily (riociguat during titration); riociguat 1 mg three times daily, the dose should be increased bu 1.5 mg/day every 2 weeks (0.5 mg for each intake) up to a dose of 2.5 mg three times daily (up to 7.5 mg/day); warfarin 2.5 mg 2 tablets daily with INR monitoring; furosemide 40–80 mg to be alternated with torasemide 20 mg (with daily weight and diuresis monitoring; electrolytic profile (K, Na) monitoring once every 3 weeks) (this diuretic therapy regimen was selected and titrated during hospitalisation

at the Federal State Budgetary Institution E. I. Chazov National Medical Research Institute of Cardiology of the Ministry of Health of Russia); ivabradine 5 mg (1 tablet) in the morning and 2.5 mg (half a tablet) in the evening; if required, 5 mg (1 tablet) in the evening (with heart rate monitoring); spironolactone 100 mg daily.

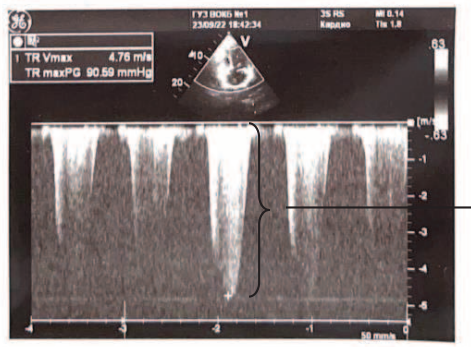
During the six-month follow-up after verification of the final clinical diagnosis and prescription of PAH-specific therapy (it is well tolerated), the patient's condition stabilised, disease activity decreased. The clinical presentation comprised disappearance of dyspnoea at rest, reduced dyspnoea during physical activity; episodes of syncope disappeared after completion of medicinal product titration. Once the general condition stabilised, the patient was referred to the Budgetary Healthcare Institution of the Voronezh Region Voronezh Regional Clinical Centre for Exercise Therapy and Sport Medicine 'Rehabilitation' for training under supervision of a rehabilitation physician, where she had a set of special exercises with soft physical load and elements of yoga. Laboratory and instrumental tests demonstrated some positive results: NT-proBNP reduced to 243.0 pg/mL (dd November 29, 2022), pulmonary artery pressure reduced to 90 mm Hg, regurgitation in pulmonary valve corresponds to grade 1 (echocardiography dd September 23, 2022) (Figure 2).



The pressure in the outflow section of the right ventricle is 35 mm Hg.



Right atrium 51 mm x 57 mm



Peak velocity of tricuspid regurgitation - 4.76 m/s

Figure 2. *Echocardiography data of patient P, 40 years old, dated from 09/23/2022 y.*
Note: Dilatation of the right chambers is noted. Ejection fraction 62 % (according to Simpson). Hypertrophy of the right ventricular myocardium. High arterial pulmonary hypertension. Right ventricular systolic function is moderately reduced. The pumping function of the left ventricle isn't reduced. Insufficiency of the tricuspid valve 2-3 degrees, pulmonary valve 1 degree

Discussion

Chronic conditions in women of reproductive age can negatively affect the course and outcome of pregnancy; however, they are not an absolute contradiction for having a baby. Modern healthcare makes it possible for women with multiple, sometimes severe, conditions to have a term pregnancy and healthy children. However, high pulmonary hypertension syndrome is *an exception*. Scarce literature data indicate that recently the number of mothers lost to this pathology is 12–36 %. Diagnosis of high pulmonary hypertension in a patient is *an absolute contraindication* to pregnancy. Termination of pregnancy is mandatory both in first and second trimesters (especially for patients with an estimated pulmonary systolic pressure of over 50 mm Hg) [14]. Pregnant women with high PH account for 0.54 % of all hospitalised patients with cardiovascular diseases. Maternal mortality in PAH reaches 56 % [11]. Mortality in patients with pulmonary circulation hypertension during pregnancy and immediately after birth is very high (material mortality) (in primary pulmonary hypertension — 30–40 %; in Eisenmenger's syndrome — 30–60 %) [14].

Literature reviews present the global experience with management of female patients with PH of functional class 1 and 2 during pregnancy and postpartum period. According to a majority of experts, female patients with this pathology (especially of high risk, functional class 3–4) are strongly encouraged to undergo sterilization or use a reliable method of contraception, and if a woman becomes pregnant, pregnancy must be terminated [12]. That is why it is very important to inform women with pulmonary hypertension about risks associated with pregnancy and provide them with recommendations from a woman health specialist and an expert in PH regarding adequate contraception [13]. Also, it is essential to take into account that a majority of PAH-specific medications can cause deformities and congenital abnormalities [1].

In this case study, it is undeniable that numerous pregnancies contributed to manifestations of pulmonary hypertension symptoms, which caused deterioration of general condition and functional class of PAH. In recurrent miscarriages, healthcare professionals should include pulmonary hypertension into a differential diagnosis [1,13,15]. Also, taken a high risk of PH progression during pregnancy, it is absolutely unacceptable to plan and maintain pregnancy in patients with an expected systolic pulmonary pressure of over 50 mm Hg. [15].

Unlike common diseases, in which risk identification and classification, treatment and observation are performed by primary healthcare providers, delivery of care to patients with a rare pathology, including pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension, requires involvement of specialists, who are not only aware of the problem, but also have practical experience in management of such conditions. An efficient solution can be cardiovascular risk management centres operating at tier 3 (specialised) medical institutions [10]. For a number of regions, these will be centres for cardiac failure or rare diseases, where specifically trained specialists in PH can render their services. An advantage of such an approach is a possibility to form a multidisciplinary team, which decides on an optimal management of a patient with pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension. At the next routing stage (tier 3 specialised centres), results of examinations and tests performed in a regional medical institution as part of specialised medical assistance, where PAH or CTEPH is suspected, are forwarded to a federal expert centre, using telemedicine technologies [10] (in this case, the patient was referred to the Federal State Budgetary Institution E. I. Chazov National Medical Research Institute of Cardiology of the Ministry of Health of the Russian Federation in Moscow, Pulmonary Hypertension Department).

Current management approach for patients with PAH is aimed at reduction of mortality; in other words, the aim is to achieve the low PAH functional class (I–II), good tolerability of physical activities, low NT-proBNP levels (< 330 ng/L) and absence of any signs of right ventricle dysfunction. The management strategy for patients with PAH can be divided into three stages. According to the current Russian guidelines, patients should be included into special rehabilitation programs in order to improve their physical condition. Stage one includes general measures: discussion of routine physical activity, family planning, contraception and postmenopausal hormone replacement therapy, preparation for scheduled surgeries, infection prevention, psychological and social support, ability to travel and therapy compliance [1]. Also, maintenance therapy (oxygen therapy, diuretics, digoxin) and follow-up by specialists from a PH centre are required, where catheterisation of the pulmonary heart can be performed for continuous monitoring of therapy efficiency. Since patients with PAH often have depression, psychological and social rehabilitation and classes for clinical and psychological

adaptation are required in order to reduce the risk of anxiety and depression [9].

According to the current Russian guidelines, there are two components of the drug therapy for patients with PAH: maintenance therapy (indirect anticoagulants (vitamin K antagonists), diuretics, cardiac glycosides, oxygen therapy) and specific therapy, including calcium channel-blocking agents (CCB), antihypertensive agents for pulmonary arterial hypertension (bosentan, macitentan, ambrisentan), iloprost for inhalation, phosphodiesterase inhibitors (iFDE-5), riociguat and selexipag [1].

Stage two is PAH-specific therapy with high doses of calcium channel blockers in patients with positive vasoreactive test (VRT) or with approved PAH medications in patients with negative test results. This recommendation is applicable to patients with idiopathic pulmonary arterial hypertension.

Stage three is associated with response to therapy, determination of comprehensive therapy with approved drugs or presence of indications for lung transplantation [9].

According to the theory of PAH development, simultaneous impact on various paths of pathogenesis can not only prevent disease progression, but also can make it possible to manage the outcomes more efficiently [3]. Modern PAH-specific medications have not only vasodilatory effect, but also a number of other actions — cytoprotective, antiproliferative, antiaggregatory, etc. Riociguat belongs to a new drug class, soluble guanylate cyclase stimulants [4]. Selexipag is the only non-prostanoid selective IP-receptor protagonist, an oral drug [8]. These drugs, if titrated correctly and provided the highest individual maintenance dose is achieved, result in vasorelaxation, inhibition of proliferative, inflammatory and fibrous effects.

PAH-specific therapy initiated in this case study at the federal expert centre stabilised the patient's condition (blood pressure and heart rate, circulatory inefficiency). This is a combination of a selective IP-receptor protagonist (selexipag) and a soluble guanylate cyclase stimulant (riociguat), titrated to their target values, that improved the patient's quality of life.

In addition to drug therapy, patient rehabilitation is important as well. In 2017, N. R. Morris et al. conducted a meta-analysis of the impact of physical rehabilitation on physical capability and quality of life of patients with PAH, who were prescribed adequate specific therapy with antihypertensive drugs for PAH management. Physical rehabilitation programs included aerobic exercises, power load, breathing exercises and elements of yoga [1]. Our patient was also provided with recommendations for physical activities. The patient decided to take classes with a specialist from the Budgetary Healthcare Institution of the Voronezh Region Voronezh Regional Clinical Centre for Exercise Therapy and Sport Medicine 'Rehabilitation', and she noted improvements both in her physical, mental and emotional state.

Conclusions

This case study demonstrates advisability of a complex clinical and laboratory assessment (including pulmonary heart catheterisation) in order to clarify the aetiology of pulmonary hypertension and decide whether PAH-specific therapy is required. Comprehensive therapy of pulmonary hypertension uses maintenance therapy, that does not impact the survival rate of patients with pulmonary hypertension, and specific drugs, the use of which prolongs the patient's life, reduces the number of hospitalisations and prolongs the period to clinical deterioration and transplantation. Timely therapy initiation after the final clinical diagnosis improves the long-term prognosis for patients with PAH. Pregnancy in women with pulmonary hypertension is of specific interest. However, unfortunately, at this stage, the modified WHO classification states: in terms of the risk of cardiovascular complications for the mother and children, pregnant women with PH are included in risk category IV, and we can claim that pregnancy is very dangerous for patients with PH. Pregnancy planning and carrying should be discussed and decided by an obstetrician-gynaecologist together with a cardiologist. Pregnancy is a risk for women with any pulmonary hypertension, especially with idiopathic PAH, because it is associated with high maternal mortality. Therefore, women with PH are recommended to use reliable contraception to prevent pregnancy or to consider immediate pregnancy termination, in order to prevent pulmonary hypertension progression and deterioration.

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Ус М.А. (ORCID ID: https://orcid.org/0000-0002-6331-4598): формирование идеи и концепции статьи, обзор публикаций по теме статьи, написание статьи, окончательное утверждение рукописи для публикации, ответственность за все аспекты статьи

Карпенко Ю.Ю. (ORCID ID: https://orcid.org/0000-0003-4757-2738): обзор публикаций по теме статьи, научная консультация, одобрение окончательной версии статьи перед подачей для публикации

Author Contribution:

All the authors contributed significantly to the study and the article, read and approved the final version of the article before publication

Us M.A. (ORCID ID: https://orcid.org/0000-0002-6331-4598): formation of the idea and concept of the article, review of publications on the topic of the article, writing an article, final approval of the manuscript for publication, responsibility for all aspects of the article

Karpenko Ju.Ju. (ORCID ID: https://orcid.org/0000-0003-4757-2738): review of publications on the topic of the article, scientific consultation, approval of the final version of the article before submission for publication

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