MINISTRY OF HEALTH OF UKRAINE

ODESA NATIONAL MEDICAL UNIVERSITY

International faculty

Faculty of Medicine and Pharmacy

Department of General and Clinical pharmacology with Pharmacognosy

Abrazi Hanae

Medical and pharmaceutical support for patients with coagulopathies in reproductive gynecology / Медико-фармацевтична підтримка пацієнтів з коагулопатіями в репродуктивній гінекології

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ЗАТВЕРДЖУЮ
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ВИСНОВОК

Комісії щодо запобігання академічного плагіату
від «19» лютого 2026 р., протокол № 2

Комісія щодо запобігання академічного плагіату Одеського національного медичного університету (голова – Олена РУДИНСЬКА, секретар – Катерина ОСТАПЧУК та 5 членів комісії) розглянула науковий текст магістерської роботи на тему: «MEDICAL AND PHARMACEUTICAL SUPPORT FOR PATIENTS WITH COAGULOPATHIES IN REPRODUCTIVE GYNECOLOGY», HANAE Abrazi здобувача освіти другого (магістерського) рівня вищої освіти кафедри загальної і клінічної фармакології та фармакогнозії зі спеціальності 226 «Фармація, промислова фармація» на наявність академічного плагіату із застосуванням автоматичного сервісу «StrikePlagiarism» (https://panel.strikeplagiarism.com) та визначила наступне:
наданий текст є оригінальним – **94,95 % оригінальності (висока унікальність).**

Комісією рекомендовано роботу до публічного захисту.
Рішення прийнято одноголосно.

Голова Олена РУДИНСЬКА

Секретар Катерина ОСТАПЧУК

RESPONSE

for the master's thesis Abrazi Hanae

«Medical and pharmaceutical support for patients with coagulopathies in reproductive gynecology»

for the OQR "Master" in specialty 226 "Pharmacy, Industrial Pharmacy"

Disturbances in the hemostatic system in general, and thrombophilia in particular, are considered one of the main etiopathogenetic factors of obstetric and gynecological diseases: miscarriage, preeclampsia, thromboembolic complications of hormonal contraception and hormone replacement therapy, obstetric hemorrhage, disseminated intravascular coagulation syndrome, etc. This work was devoted to the study of issues of disturbances of local and general hemostasis.The above-mentioned determined the relevance of choosing the topic of the master's thesis.

The master's work was completed in accordance with the work plan and approved by the Academic Council of the International and Pharmaceutical Faculty of the University in the specialty 226 "Pharmacy, Industrial Pharmacy".

The master's thesis was completed and designed by a student who conducted a theoretical search of literature sources to study the main etiopathogenetic issues and methods of diagnostics and treatment of pathology of blood coagulation, mastered the methods of pharmacological, clinical, laboratory analysis, scientific and practical experiment, and interpretation of data, proved active, creative, thinking and capable of scientific work as a student.

The work consists of 2 sections, conclusions, list of references. The conducted research was embodied in the analysis of the literature sources stated by clinical and pharmacological results. The work is of great scientific and practical importance and can be implemented in the practical activities of the obstetrics and gynecology departments, specific reproductive clinics and the educational process at the Faculty of Pharmacy.

Abrazi Hanae master's thesis "Medical and pharmaceutical support for patients with coagulopathies in reproductive gynecology" was performed at a certain scientific level using modern research methods, the volume of which is adequate. The work is performed in the traditional style, is a completed

scientific work, the design meets the established requirements and is recommended for defense in the EC ONMedU for OQR "Master" in specialty 226 "Pharmacy, Industrial Pharmacy".

Supervisor,

Candidate of Medical Sciences, Associate professor  Strechen S.B.

REVIEW

for the master's thesis of the 5th group student of the 5th year of the Faculty of Pharmacy full-time Abrazi Hanae

on the topic: "Medical and pharmaceutical support for patients with coagulopathies in reproductive gynecology"

(Scientific adviser - PhD, Associate Professor Strechen S.B.)

Abrazi Hanae master's thesis is devoted to the topical issue of theoretical and practical medicine and clinical pharmacy - optimization of methods, measures, and principles to improve the efficiency and effectiveness of diagnostics and pharmacotherapy of gynecology and obstetrics coagulopathy, which is very important, given the prevalence and danger of these pathological conditions.

The decision of the main purpose and sequence of tasks led to the content of the master's thesis, the transition from defining the etiology and pathogenesis of various types of hemostatic disturbances, main groups of drugs for their correction, to analysis of clinic-laboratory and pharmacological methods to assess the effectiveness and safety of the proposed schemes. Based on the main areas of research, the topic of the master's thesis should be considered unconditionally disclosed.

The content of the master's thesis corresponds to the set purpose, the set tasks are solved, the purpose of the work is achieved. The material is presented consistently, in accordance with internal logic. The results of the work are relevant, deepen the understanding of the problem of pathogenetic treatment, compliance with its effectiveness in terms of clinical and laboratory-instrumental parameters, and at the same time safety.

Evaluating the work based on completeness, validity of conclusions and proposals, it is worth paying attention to the diligence in developing theoretical and practical material on the problem under consideration. The presented master's thesis takes the form of an independent study. In general, the work of Abrazi Hanae meets the established requirements. There are some comments that do not affect the overall positive impression of the master's thesis.

In this regard, the master's thesis of Abrazi Hanae deserves a positive assessment - good/180.

Reviewer,

Doctor of medical sciences, Professor  Peter ANTONENKO

Abstract

The master's thesis reviewed modern literary sources on the problem of women's reproductive health, identified the main pathological mechanisms of failures in self- and artificial insemination, clarified blood clotting disorders in the form of bleeding and thrombosis in obstetric practice, determined the location of hemocoagulation disorders in the processes of conception, progression and gestation of pregnancy, and delivery. The main pathophysiological mechanisms were identified, which were subsequently the subject of practical research both at the diagnostic and pharmacocorrection stages.

The practical part of the work was carried out by means of a comparative analysis of the diagnosis and treatment of the relevant disorders in the conditions of specialized reproductive clinics of Ukraine and Morocco, which allowed us to identify similar problems, the solution of which also took place at modern world diagnostic and treatment levels, which allowed us to increase the effectiveness and efficiency of assistive technologies. The hemostasis chart, which was used for laboratory monitoring of the state of hemocoagulation, allowed for a comprehensive dynamic assessment of the level of antithrombin, D-dimer, fibrinogen, clotting time, and subsequently to select drugs for pharmacoprophylaxis and pharmacotherapy of the corresponding disorders: direct-acting anticoagulants, antierythrocyte and antiplatelet antiaggregants, anti-inflammatory immunosuppressants. As a result, correction of hemostasis increased the effectiveness of in vitro fertilization methods by an average of 4%.

Keywords: reproductive health, blood clot disorders, hemocoagulation, thrombophilia, antithrombotic drugs and procoagulants.

CONTENT

LIST OF ABBREVIATIONS AND SYMBOLS

APS - antiphospholipid syndrome

AFA -antiphospholipid antibodies

AFD - antenatal fetal death

DIC – disseminated intravascular coagulation syndrome

FGR - fetal growth retardation syndrome

TGF - transforming growth factor

LMWH and UFH - low molecular weight and unfractionated heparins

MMPs - matrix metalloproteinases

ART - assisted reproductive technologies

IVF - in vitro fertilization

ICSI - intracytoplasmic sperm injection

WHO - World Health Organization

LA - lupus anticoagulant

APTT - activated partial thromboplastin time

AT III - antithrombin

IGF - insulin-like growth factor

INTRODUCTION

Relevance of the topic: A wide range of clinical syndromes and diseases is caused by blood clotting problems. The pathogenesis of hemostasis disorders is diverse and occupies a leading place in the pathology of the cardiovascular system, the development of oncological and autoimmune diseases. Today, an increased risk of thrombotic complications in coronavirus infection has been clearly proven. There are many antithrombotic drugs (thrombolytics, direct and indirect anticoagulants, antiplatelet agents), about coagulants, which, depending on the leading link in the disorders, are used for pharmacotherapy of the corresponding changes.

The female body is more prone to thrombosis (genetic factors, pelvic anatomy, functional anatomy of the veins of the lower extremities and pelvic veins, overflow of the venous bed during menstruation), female sex hormones (estrogens) significantly increase the activity of the coagulation system and thrombogenicity of the vascular wall; during ovulation stimulation during in vitro fertilization, high estrogen levels increase the risk of microthrombosis and reduce the success of implantation; the appointment of combined hormonal contraceptives as therapeutic and prophylactic agents increases the risk of venous thrombosis, which is why women's health, as well as fertility, attract considerable attention from researchers.

Hemostasiogram is a method that provides the most complete integrated simultaneous assessment of the blood coagulation and anticoagulation systems, selection of the correct treatment tactics and timely response to the occurrence of any critical conditions. This biochemical laboratory method occupies a leading position among methods for assessing fibrinolysis, platelet and plasma components of the blood coagulation system, which led to its choice for determining reproductive hemocoagulation problems and selecting appropriate correction agents.

The above was the rationale for choosing the topic of research and defining the main purpose and objectives of the work.

Main purpose: Determining the place of the hemostasiogram in the diagnosis and pharmacocorrection of hemocoagulation disorders in women of reproductive age to increase the effectiveness of assistive technologies.

To achieve this purpose, the following **tasks** were formulated:

1. To investigate and conduct a comparative analysis of the use of methods of laboratory and instrumental examination of hemocoagulation disorders in women of reproductive age.

2. To study the possibility and practical use of hemostasiogram assessment for the diagnosis of thrombophilia and the use of the method to monitor the effectiveness of assisted reproductive technologies.

3. To develop practical recommendations for monitoring the effectiveness and safety of appropriate corrective therapy and prophylaxis with an analysis of the state of hemostasis.

4. To conduct a comparative analysis of the state of reproductive technologies in different countries (using the example of Ukraine and Morocco); to draw appropriate conclusions.

Object of research: clinical pharmacology of drugs with the antiplatelets, anticoagulants acitivity, steroidal anti-inflammatory drugs; patients – female with the hemocoagulation problem in the specific reproductive clinic; medical documentation, lists of prescriptions.

Research methods: general clinical, laboratory, instrumental, statistical, pharmacological.

Practical significance of the work. The obtained clinical and laboratory results complemented the comprehensive and full implementation of preparatory recommendations for conception, and the constant dynamic monitoring of the effectiveness and safety of pharmacotherapy methods in chronic miscarriage, in

spontaneous natural pregnancy, and in the implementation of assisted reproductive technologies.

Approbation of master's work results. The main provisions of the masters work were presented at the meeting of the Department of General and clinical pharmacology with the pharmacognosy ONMedU; in the materials of the XIII All-Ukranian Scientific and Practical Conference with International Participantion "Clinical pharmacology as an integral factor in achieving positive outcomes in medical and pharmaceutical practice" (13-14 November 2025, Vinnytsia, Ukraine).

CHAPTER 1. Hemocoagulation disorders in gynecological practice - pathophysiology and pharmacotherapy (literature review)

According to the plan, main goal and objectives of the master's thesis, we considered a problem that exists in many countries of the world - the issue of demography, a problem that is not only medical, but also social, the solution of which is aimed at the actions of states, legislative acts, regulatory orders, large financial and material costs. We always say that any medical problem depends on non-medical factors by more than 80%, and 15-20% are due to the modern development of the relevant medical field, in this case - reproductive medicine, reproductive gynecology.

Reproductive function is a reliable criterion of the social and biological health of society, bioecology of the environment [1]. Most research in the field of reproductive problems concerns miscarriage: when examining patients with infertility of unclear genesis, in 15% of cases, a pregnancy is detected that is interrupted in the early stages [2, 3], and with each subsequent miscarriage, the risk of miscarriage increases significantly [4].

Analysis of modern data on optimizing the diagnosis and treatment of various forms of fertility disorders allows us to present a general algorithm for studying the causes of reproductive function disorders, as a multicomponent examination that involves studying possible factors of both male and female infertility [5, 6].

Among the causes of reproductive health disorders can be anatomical, infectious, immunological, endocrine, genetic factors. Modern gynecology identifies the following main causes that lead to female infertility:

- obstruction of the fallopian (uterine) tubes;

- disorders in the endocrine system;

- congenital or acquired pathology of the structure of the uterus;

- immunological incompatibility of partners;

- age factor;

- diseases of the thyroid gland, adrenal glands, pituitary gland cause infertility as a side effect of hormonal imbalance;

- diabetes mellitus, kidney and liver dysfunction, systemic diseases;

- chronic sexually transmitted infections that are asymptomatic;

- excess or insufficient weight;

- unbalanced diet, lack of vitamins and trace elements necessary for the functioning of the reproductive system;

- bad habits, namely smoking, drug addiction, alcohol abuse.

It should be noted that today, to a large extent, reproductive failures are also considered from the standpoint of andrology - the male problem, which exists, tends to increase, and in the conditions of Ukraine - it prevails over the female one. It should also be noted the negative consequences of the transferred coronavirus infection, which are accompanied by long-term violations of the immune response, immune defense, the presence of autoimmune issues before physiological fertilization, and then pregnancy [12]. Moreover, the latter issues are characteristic not only for the population of Ukraine, but also for the whole world.

From the point of view of immunology and experimental data, pregnancy is the so-called "Th2 phenomenon", that is, a shift towards the Th2-type of the immune response, which protects against premature abortion [7, 8], however, the results of recent studies in this aspect do not allow to extend it to all immunological aspects of the gestational process and put forward the role of the main regulatory link in physiological pregnancy cells of innate immunity [9]. As is known, the female genital organs are the entrance gates for bacterial, viral and fungal infections and have a unique ability to regulate immune defense against

potential pathogens without harm to the life of the fetus and the health of women. Being a physiological barrier, epithelial cells of the reproductive tract express receptors that recognize pathogens - RAMP (TLR, NOD, RIG, etc.), secrete chemokines and cytokines that regulate innate and adaptive immunity, and also secrete an endogenous antibacterial factor - lysozyme) [10]. Thus, infectious and inflammatory processes of the reproductive tract can lead to impaired fertility, to pathological pregnancy and defects in local immunity of women in the postpartum period. It has been established that in women with complicated postpartum endometritis there is a decrease in the expression of a number of Toll receptors (TLRs 4,5), as well as regulatory transcription factors (MyD88, NFkB), which leads to a violation of the activity of cytokines and defensins on the membrane of the epithelium of the reproductive tract with subsequent increased use of pathogens. Along with this, TLRs are able to interact with ligands of normal microflora, receiving signals stimulating local immunity from various strains of lactobacilli, bifidobacteria, which significantly activates the synthesis of interferons, interleukins and initiates the maturation of antigen-presenting dendritic cells [11].

When listing possible factors that affect the negative results of fertilization and pregnancy progression, we did not mention the influence of the coagulation-anticoagulation system on the course of these processes. However, the pathological role of hemostasis disorders is one of the leading and is always considered to improve reproductive outcomes. During a pregnancy that proceeds normally, a certain balance between the activity of coagulation and anticoagulation is maintained. At the beginning of pregnancy, for various reasons, there is activation of blood clotting factors and inhibition of the activity of anticoagulant factors, which can be accompanied by the formation of numerous microthrombi in the vessels of the uterus or placenta, which leads to disturbances in the uteroplacental circulation system up to the cessation of pregnancy development. The female body is more prone to thrombosis (genetic factors, pelvic anatomy, functional anatomy

of the veins of the lower extremities and pelvic veins, overflow of the venous bed during menstruation), female sex hormones (estrogens) significantly increase the activity of the coagulation system and thrombogenicity of the vascular wall; when stimulating ovulation during in vitro fertilization, a high level of estrogen increases the risk of microthrombosis and reduces the success of implantation; the appointment of combined hormonal contraceptives as therapeutic and prophylactic agents increases the risk of venous thrombosis, therefore women's health, as well as fertility, attract considerable attention from researchers. It was these questions that determined the choice of topic and the tasks of the work, which were solved by analyzing modern literature and further analyzing certain results of hemostasiogram indicators and pharmacological methods of correction.

1.1. The problem of blood clotting in obstetrics and gynecology on the example of thrombophilia

Hemostasis is a complex biological system that maintains a stable (liquid) state of blood in the body in the norm and stops bleeding when blood vessels are damaged. There are two mechanisms (or links) of hemostasis:

1. Vascular-platelet hemostasis (primary, it is triggered first when a vessel is damaged);

2. Coagulation hemostasis (secondary, triggered as a result of the activation of the first mechanism and is responsible for the formation of a stable blood clot).

The blood clotting system is several interdependent reactions that occur in the form of a cascade (chain reaction). At the same time, a balance is constantly maintained between the activity of the blood system - coagulation-anticoagulation. At each stage of the process, a certain proenzyme (inactive form of the enzyme) is activated. 13 such proteins (blood clotting factors) make up the coagulation system. They are designated by Roman numerals from I to XIII.

In disorders of the vascular-platelet link of hemostasis, conditions are determined that are accompanied by:

• increased bleeding;

• a tendency to hematoma formation with minor trauma or even spontaneously, for no apparent reason;

• a tendency to excessive thrombus formation.

There are factors that stimulate the formation of a primary thrombus and disrupt it, we can consider them as controlled factors. These include the inflammatory process - the content of biologically active substances in the blood increases and the permeability of the vessel wall is disturbed. This leads to the activation of platelets, which ensure the formation of a primary thrombus, and in severe infectious diseases the coagulation link of hemostasis may also be reactivated [13]. When the number of platelets decreases (thrombocytopenia) or their qualitative inferiority (thrombocytopathy), the process of primary thrombus formation is disrupted. This condition can occur with prolonged use of certain medications: for example, nonsteroidal anti-inflammatory drugs, such as aspirin or analgin, as well as some antibiotics. Thrombocytopathy also develops in kidney diseases. The use of strong alcohol, various spices can reduce the functional activity of platelets.

When the coagulation system of hemostasis is disturbed, changes occur in the amount or activity of clotting factors, which may be hereditary, i.e. associated with a change in the structure (mutation) of genes responsible for the activity of certain blood clotting factors. This may be accompanied by increased bleeding (for example, hemophilia, Hageman syndrome, von Willebrand disease) or excessive activation of the coagulation link of hemostasis - a tendency to thrombus formation, thrombophilia.

The cause of hereditary thrombophilia is mutations in the genes of factors V (Leiden mutation), factor II (prothrombin), as well as deficiencies of proteins C, S and others [14]. At the same time, there are conditions that are the cause of acquired thrombophilias - this is older age, smoking, obesity, prolonged immobilization during and after complex operations, oncological diseases. In hereditary thrombophilia, which can be diagnosed using a blood test to detect the G1691A mutation in the factor V gene of coagulation (Leiden mutation), the G20210A polymorphism in the prothrombin gene (factor II of blood coagulation), as well as determining the activity of the protein. With mutations in the folate cycle genes, when the metabolism of folic acid and its compounds is disrupted, which leads to an increase in the level of homocysteine in the blood. Homocysteine damages the endothelium (inner layer) of blood vessels, which initiates thrombus formation. The causes of increased homocysteine levels may be a deficiency in the diet of folic acid and vitamin B12, kidney disease, thyroid disease. With antiphospholipid syndrome, this is an autoimmune disease in which the body synthesizes antibodies to its own clotting factors, and as a result of this process, blood clots are spontaneously formed in the vessels. Therefore, it is important to determine the content of antibodies to cardiolipin, antibodies to beta-2-glycoprotein, lupus anticoagulant in the blood.

Analysis of literary sources shows several mechanisms of hemostasis disorders in gynecology. Suppression of the immune link of the hemostasis system develops due to the suppression of steroid and immunosuppressive substances [15]. In response to the violation of the transplacental barrier, pro-inflammatory cytokines (IL-1α), T-suppressors (CD8+), natural killers with suppression of B-lymphocyte release (CD22+) are released into the bloodstream, which activate the hypercoagulable cascade [16].

When placental ischemia occurs, the so-called “endothelial toxin” is released, resulting in angiopathy, which increases the risk of thrombosis [17, 18]. The risk of developing subacute DIC syndrome within 2 weeks after delivery is 1.5

times more likely to develop in antenatal fetal death (AFD), compared with pregnancy with a live child [19]. The literature contains data on the activation of the complement system, low levels of protein Z, with a significant increase in the content of the C5 fraction in the blood plasma in pregnant women with ADP [20]. Protein Z is considered a vitamin K-dependent protein that has procoagulant and anticoagulant properties. Its main properties are the regulation of coagulation and fibrinolysis processes, inhibition of factor X, interaction with proteins of the anticoagulant link of the blood coagulation system (protein C and S) [21]. The development of thrombosis in thrombophilias develops due to a violation of the balance of redox reactions with the development of endotheliopathy, microthrombosis and placental infarction, with subsequent disruption of uteroplacental circulation [22]. At the end of the 20th century, O. Egeberg first described this pathology as a predisposition to thromboembolism, which is associated with changes in the blood coagulation system, especially the FV Leiden gene mutation, the prothrombin mutation (G20210A), polymorphisms of genes controlling the fibrinolysis system: PAI-1 (G6754), polymorphisms of tissue plasminogen activator (t-PA I/D), fibrinogen (G455A), factor XII and antiphospholipid syndrome [22]. When classifying thrombophilias depending on the risk of thrombosis during pregnancy, high-risk and low-risk thrombophilias are distinguished. High-risk thrombophilias include: antithrombin III deficiency, factor V Leiden homozygotes, prothrombin gene mutation and compound heterozygotes of FVL and PGM [22]. Low-risk thrombophilias include heterozygous factor V Leiden, heterozygous PGM, protein C deficiency, and protein S deficiency [23]. Inherited thrombophilias are risk factors for the development of a prethrombotic obstetric condition in pregnant women, especially in the third trimester and for up to 6 weeks postpartum. The most common form of inherited thrombophilia is factor V Leiden, a heterozygous mutation (1–15%), also known as activated protein C resistance [22]. Between 20% and 50% of women who develop venous thrombosis during pregnancy or postpartum have an identified underlying genetic

disorder. Because the overall absolute thrombotic risk is low, routine screening for thrombophilia is not recommended during pregnancy [24, 25].

Special attention deserves the acquired form of thrombophilia - antiphospholipid syndrome (APS), in which the risk of thrombotic complications is significantly increased in the case of insufficiency of the antithrombin system and the occurrence of a concomitant provoking factor, which leads to an imbalance in the hemostasis system [23]. Antiphospholipid antibodies (AFA) bind to thrombin, blocking the interaction with AT III, protein C and S, inhibiting their anticoagulant function, as well as by affecting platelets, increasing the potential of thromboxane A2, glycoprotein 2b-3a. When acting on the endothelial wall, they provoke the formation of adhesion molecules [26]. According to the literature, in the presence of AFA in the area of uteroplacental circulation, endothelial dysfunction, microthrombosis and vasospasm develop, which leads to the development of local ischemic placental complex. Subsequently, an imbalance of pro-inflammatory and anti-inflammatory cytokines occurs, which activate collagenase in the process of remodeling the extracellular matrix of the cervix, which in the future leads to structural changes in the cervix, premature birth and ADP [26]. Thus, a review of the literature indicates a multifactorial nature of the occurrence of ADP, among which the main predictors are: extragenital pathology, infectious and inflammatory diseases of bacterial and viral etiology, congenital and acquired forms of thrombophilia. Pathogenetically, one of the main complications of ADP remains disorders in the hemostasis system, which are usually not diagnosed in the postpartum period and do not allow predicting the occurrence of complications during the next pregnancy.

The hemostasis system is a complex of threshold-dependent, highly regulated physical, biochemical and cellular interactions [27, 28]. This complex combines procoagulant factors, anticoagulant proteins, inhibitors and activators of coagulation, fibrinolysis, interleukins, platelet, leukocyte, receptor-molecular, and humoral reactions, antithrombotic and procoagulant activity of the endothelium,

hemodynamic and vascular changes [28]. The severity of disorders in this multicomponent system is determined by various thrombophilic or hemorrhagic states in the woman's body. The prevalence of thrombosis and thromboembolism is 3–12 cases per 1000 pregnant women. Pregnancy is accompanied by the development of complex complexes of physiological changes, in particular in the hemostasis system, which create conditions for the functioning of the mother-placenta-fetus system, which are caused by various factors and are considered an adaptive reaction of the pregnant woman's body to compensate for the costs during fetal development and possible blood loss during childbirth [27]. In the woman's body, changes occur in the blood coagulation system with a tendency to hypercoagulability. In particular, the so-called "Virchow's Triad" occurs: hypercoagulability, which occurs as a result of an increase in the level of blood coagulation factors and inhibition of anticoagulant mechanisms, venous stasis (humoral and mechanical causes), damage to the vascular wall [29]. It is worth noting that changes in the hemostasis system should be considered as a prethrombotic state, since during pregnancy the risk of venous thrombosis increases 5–6 times compared to the general population of women of reproductive age [29]. The main changes in the hemostasis system during pregnancy are: increased platelet activity, increased procoagulant properties of the endothelium, increased content of blood clotting factors, decreased anticoagulant activity [30]. When an imbalance occurs in the hemostasis system, conditions that provoke the mechanisms of thrombophilia, which is clinically manifested by thrombosis or bleeding. The development of systemic endothelial dysfunction, activation of the pro-inflammatory response and, as a result, the occurrence of DIC syndrome are observed [30]. According to the literature, with increasing gestational age, the concentration of fibrinogen increases, starting from the first trimester, which is manifested by a slowdown in euglobulin and XIIa-dependent clot lysis, an increase in the level of D-dimer and soluble fibrinogen monomer complex (RFMC) [31]. A significant contribution to the development of thrombotic complications during pregnancy and in the postpartum period was made by the pandemic of the 21st

century - coronavirus infection [32]. The frequency of thrombotic complications in this group of patients with COVID-19 is 3 times higher than in the absence of this infectious disease. In coronary artery disease, there is an increase in the procoagulant link of the hemostasis system, an increase in the level of fibrinogen, fibrin degradation products, D-dimer and is manifested by the formation of thrombi against the background of endothelial dysfunction [32]. As a result of these changes, there is a disruption of the vascular endothelium nutrition, which contributes to the regression of antithrombotic activity. There is a disorienting synthesis of substances that have antiaggregatory (prostacyclin, nitric oxide, endothelin), anticoagulant (AT-III, thrombomodulin, protein C) and fibrinolytic activity (tissue plasminogen activator), as well as the ability of the endothelium to remove activated blood coagulation products, fibrin monomer complexes, from the bloodstream [33]. The combination of hemodynamic changes determines the development of thrombosis of the deep and superficial veins of the lower extremities, iliofemoral and pelvic veins [33].

The hemostasis system is a chain of complex cascade-complex enzymatic reactions that occur with the involvement of a large number of cellular and humoral agents with certain mechanisms of neuroendocrine regulation [34]. The main components of the hemostasis system are: coagulant (plasma factors) and anticoagulant (physiological anticoagulants) links, activators and inhibitors of fibrinolysis, cellular factors of blood formed elements (platelets, leukocytes, erythrocytes), coagulation and fibrinolysis factors of the vascular wall and tissues surrounding them. The interaction of these components allows maintaining a stable balance between hypocoagulation and hypercoagulation [35]. The endothelium is a protective barrier that prevents the entry of thromboplastin and the activator of Hageman factor (factor XII) into the bloodstream; is one of the sources of production of natural anticoagulants (AT III, plasminogen activator) and platelet aggregation activator – ADP and von Willebrand factor. When the vascular wall is damaged, vasoconstriction occurs and a powerful procoagulant surface is formed,

which promotes adhesion of formed blood elements to form a primary clot. Platelets are non-nucleated biconvex cell fragments with a diameter of 2–4 μm, which are formed in the red bone marrow from megakaryocytes and are responsible for the key stages of the hemocoagulation process [36]. Large-scale studies have shown that the number of platelets during pregnancy decreases, especially in the third trimester - gestational thrombocytopenia. Thus, the lower limit of the normal platelet count in late pregnancy is recommended to be 140×109/l. The platelet count decreases due to the physiological increase in circulating blood volume, and the mean platelet volume becomes an unbiased indicator of their size [36]. The number of leukocytes during pregnancy increases to the range of 6-16×109/l. Leukocytosis is usually manifested by neutrophils, in particular by immature forms. There is evidence in the literature of increased oxidation processes in neutrophils during pregnancy. The number of lymphocytes is reduced in the first trimester of pregnancy, and their level increases with increasing gestational age. Studies of T- and B-lymphocyte subpopulations in peripheral blood and the proliferative capacity of these cells in response to mitogens have established an increase in the proportion of helpers and suppressors and a decrease in killer cells during pregnancy. Leukocytes accelerate the process of cell aggregation, activate coagulation hemostasis due to the presence of thromboplastin, antiheparin and fibrin-stabilizing factors in them [29]. In pregnant women, the number of erythrocytes increases due to the stimulating effect of erythropoietin, which is synthesized in the kidneys under the influence of progesterone. However, increased hematopoiesis and an absolute increase in erythrocytes in the blood increases the total oxygen capacity of the blood, which the pregnant woman compensates for by accelerating its transportation through the circulatory system [34]. Erythrocytes influence the process of activation of vascular-platelet hemostasis in two ways: by releasing ADP, increasing the adhesive and aggregation properties of platelets when changing the size and deformation of erythrocytes. The activating effect of erythrocytes on the intrinsic

pathway of thrombus formation persists even with reduced activation of Hageman factor [37].

The coagulation mechanism of hemostasis includes 13 coagulation factors. The main part of which are proteins that circulate in small quantities in the blood plasma as inactive proenzymes. When vessels are damaged, the factors begin to activate each other in a certain order. Activation of the coagulation mechanism of the hemostasis system begins with the formation of tissue prothrombinase and occurs in two ways: “extrinsic” and “intrinsic” [38]. Their difference is based on the source of phospholipids, which are the matrix for fixing coagulation factors and their catalysts. The “extrinsic” path is initiated by tissue factor – TF (thromboplastin), which is released from the damaged vessel wall, from the subendothelial space and surrounding tissues. Thromboplastin activates factor VII, forming the FVIIa-TF complex, and triggers a further cascade that leads to the activation of factors IX and X. The initial reaction for the formation of blood prothrombinase is the activation of factor XII, which occurs when blood comes into contact with the phospholipids of the outer membrane of activated platelets. Factor XIIa, in turn, activates factor XI, under the influence of which, together with Ca2+ ions, factor IX is activated. In turn, it activates factor X and a complex is formed: factor X + factor V + factor IV (calcium ions), which completes the formation of blood prothrombinase. FXa together with factor V form a proteolytic complex that participates in the reaction of converting prothrombin into thrombin and the formation of a fibrin clot. The final stage is the formation of insoluble fibrin. Under the influence of thrombin, fibrin-monomer complexes are formed, which then undergo polymerization under the influence of calcium to form an insoluble fibrin polymer [38]. The “internal” coagulation pathway is activated by components of the intravascular space. Under the influence of collagen, factor XII (FXII) is activated and protein complexes kallikrein and high-molecular-weight kininogen are formed. Fibrinase compacts the fibrin mesh, in which the formed elements of the blood that form the thrombus are retained. After some time, the

clot retraction occurs with its subsequent tight attachment to the vascular wall [38]. The anticoagulant system ensures limitation of the area of thrombus formation and prevents their spread beyond the lesion. This system includes blood coagulation inhibitors such as: AT-III, proteins C and S, α2-macroglobulin. AT-III is the most important anticoagulant - an inhibitor of serine proteinases, primarily thrombin, which forms stable complexes with factors XII, XI, X, IX, II. Increased activity of this component is observed in the presence of negatively charged heparinoids and heparin. Heparin forms a complex with AT-III and increases its anticoagulant properties by 1000 times [38]. Thus, the heparin-antithrombin complex directly affects the intrinsic pathway of blood coagulation, and protein C, protein S and thrombomodulin cleave non-enzymatic factors V and VIII [29]. On the surface of endothelial cells, under the action of the thrombin-thrombomodulin conglomerate, protein C is activated and the action of these factors is blocked. During the physiological course of pregnancy, the level and activity of AT-III do not change, but when systemic complications occur, such as preeclampsia, its content is significantly reduced. Protein S is a non-enzymatic vitamin K-dependent cofactor of activated protein C. In its absence, the anticoagulant properties of protein C are reduced and there is a high probability of thrombotic complications both during pregnancy and in the postpartum period [42, 43]. The fibrinolytic link of the blood coagulation system is one of the regulators of the hemostasis system during pregnancy, which plays a crucial role in maintaining the blood in a liquid state, thereby preventing intravascular thrombus formation. The fibrinolytic system consists of activators, inhibitors and plasmin, which is formed from plasminogen. Activation of this protein occurs through the extrinsic and intrinsic pathways. The internal pathway is provided by urokinase, streptokinase, and the external pathway is provided by tissue plasminogen activator [45]. The main component of the fibrinolytic system of hemostasis is the proteolytic enzyme plasmin, which circulates in the blood as the enzyme plasminogen. The state of fibrinolytic activity of the blood is determined not so much by the level of plasminogen, but by the ratio of its activators and inhibitors. That is, fibrinolysis is based on the

phenomenon of plasminogen activation, which occurs against the background of a powerful inhibitory potential of the blood. The level of plasminogen increases maximally in the first trimester of pregnancy and remains on a plateau until the end of pregnancy. The process of physiological activation of plasminogen occurs only in the presence of a fibrin clot. When insoluble fibrin is broken down by plasmin, D-dimers are formed, and fibrinogen fragments X, Y, D, E are formed. Fibrinolysis is limited by the presence of its inhibitors - plasminogen activator type I, thrombin-activated fibrinolysis inhibitor, alpha2-antiplasmin, alpha2-macroglobulin and alpha1-antitrypsin. According to the authors, fibrinolytic activity of the blood decreases with increasing gestational age. In particular, laboratory-confirmed changes are diagnosed in the third trimester of pregnancy [45]. The content of tissue plasminogen activator (t-PA) in the endothelium of the vascular wall is high, but its release from the vascular wall is weakened. The action of vascular components of fibrinolysis in pregnant women is limited to parietal effects in the vessels. A decrease in t-PA synthesis and an increase in the level of inhibitors and plasminogen activator may indicate a decrease in the fibrinolytic potential of the blood, and therefore thrombus formation [40, 44].

Thus, the hemostasis system is a chain of complex cascade-complex enzymatic reactions that occur with the participation of cellular and humoral components with certain mechanisms of neuroendocrine regulation. During pregnancy, fibrinolytic activity of the blood is suppressed, especially in the presence of additional factors that provoke hypercoagulation, and an increase in the level of fibrin degradation products and D-dimer are not indicative during pregnancy for the diagnosis of hypercoagulation [38, 39]. Assessment of thrombinemia using tests for the detection of fibrin monomers and fibrinogen/fibrin cleavage products is considered a probable risk of developing DIC syndrome or thrombosis [41]. The occurrence of complications during pregnancy in combination with increased thrombotic potential of the blood is an unfavorable background in the development of DIC syndrome, and therefore

requires the development of an algorithm for early diagnosis and assessment of the hemostasis system in obstetrics [40, 44]. Timely detection of the limit of the hemostasis system of the level of “appropriate” hypercoagulation and transition to the level of thrombophilia may be the key to preventing the occurrence of thrombotic complications during pregnancy planning, during embryo transfer, during pregnancy, and also in the postpartum period [40, 44].

1.2. Thrombophilia – a predictor of the ineffectiveness of reproductive technologies

The term “thrombophilia” means a predisposition to thrombosis due to genetic or acquired defects in the hemostasis system. Thrombophilias can occur at all stages of the blood coagulation process, which is the result of a complex interaction of blood cells, coagulation factors and endothelium, which has both anticoagulant and procoagulant properties. According to the results of population studies, the prevalence of thrombophilias in medical practice is 15-20% [46, 52]. It should be noted that pregnancy itself is a condition that is a kind of trigger for the presence of latent thrombophilia, since pregnancy itself is accompanied by physiological hypercoagulability, and during this period the risk of thrombosis increases 5-6 times, which leads to the appearance of clinical manifestations of previously asymptomatic thrombophilia [47]. The manifestation of thrombophilias during pregnancy has a different spectrum of disorders: from macrothrombosis in large vessels to microthrombosis and impaired microcirculation in vital organs.

With the beginning of the rapid development of clinical hemostasis and immunology in the 80-90s of the 20th century, a number of genetic forms of thrombophilia were discovered one after another, including:

- FV Leiden mutation, prothrombin G20210A mutation, polymorphisms of genes controlling the fibrinolysis system: PAI-1, 4G/5G, polymorphisms of tissue plasminogen activator t-PA I/D, fibrinogen-455 A/G, factor XII, etc., and antiphospholipid syndrome (APS). The role of hyperhomocysteinemia in the

development of atherothrombosis and venous thromboembolism began to be studied.

- acquired thrombophilia - in the etiopathogenesis of not only thrombotic, but also typically obstetric complications began to be studied: miscarriage, fetal growth retardation syndrome (FGR), antenatal fetal death (AFD), which determine perinatal morbidity and mortality [47-49].

From a modern point of view, thrombophilia is considered as an etiopathogenetic factor for a wide range of diseases and syndromes: fetal loss syndrome, preeclampsia, thromboembolic complications of hormonal contraception and hormone replacement therapy, etc. [52]. Thrombophilia is an integral etiopathogenetic risk factor for the development of most obstetric complications, which is often combined with other systemic syndromes, including SIRS, metabolic syndrome, DIC syndrome, oxidative stress, endotheliopathy [48, 51]. If earlier the participation of thrombophilia in the pathogenesis of obstetric complications was considered only from the point of view of the processes of microthrombosis of the vascular bed and, accordingly, disorders of uteroplacental blood flow, in recent years the non-thrombotic effects of thrombophilia in the pathogenesis of obstetric complications have begun to be considered and studied even at the stage of implantation of the fetal egg and in the early embryonic phase [49, 50]. Implantation, invasion of the trophoblast and subsequent functioning of the placenta appear to be multi-stage processes of endothelial-hemostasiological interactions with complex autocrine-paracrine regulation, which are objectively disrupted in the case of thrombotic tendency and in the case of genetic coagulation defects.

In normal pregnancy, changes in the blood coagulation system are represented by a weak local activation of thrombus formation in the uterine vascular bed, with increased synthesis of fibrinogen and other coagulation factors in combination with a slight decrease in the level of natural inhibitors of blood coagulation [52]. Intra- and extravascular fibrin deposition is part of the

physiological process during implantation of the fetal egg and invasion of the trophoblast in the placental bed. However, recent studies have shown that trophoblast cells are responsible not only for controlling the physiological deposition of fibrin in the placental bed, but also for the increased deposition of fibrin, which is observed in complicated pregnancy. The process of fibrinolysis regulation depends primarily on the activity of plasminogen activators (t-PA, u-PA) and on the level of synthesis and secretion of plasminogen activator inhibitor and their interaction. In the process of preparation for implantation under the influence of progesterone, the endometrium increases the content of plasminogen activation inhibitor type 1 (PAI-1), tissue factor (TF) and decreases the level of tissue and urokinase-type plasminogen activators, matrix metalloproteases and vasoconstrictor – endothelin 1. These physiological mechanisms of regulation of hemostasis, fibrinolysis, extracellular matrix and vascular tone are aimed at preventing bleeding during subsequent invasion of the trophoblast [50-52]. For its part, the blastocyst synthesizes tissue and urokinase-type plasminogen activators and proteases, which are necessary for the destruction of the extracellular matrix during implantation. Their excessive synthesis is regulated by chorionic gonadotropin. In the process of "dosed" destruction of the matrix under the action of enzymes secreted by the blastocyst, endometrial cells containing a certain amount of extravascular fibrin are not phagocytosed, but are "rejected" as it were by means of "contact" inhibition. In the case of hypofibrinolysis (as a result of PAI-1 polymorphism, and other reasons), desynchronization of local processes of fibrinolysis and fibrin formation occurs during implantation. Circulation of antiphospholipid antibodies (APA) aggravates the situation, since they stimulate prothrombotic mechanisms and therefore desynchronize fibrinolysis processes, change the surface preimplantation parameters of the fetal egg - charge, configuration, block the production of hCG by the trophoblast and exhibit endocrine effects [51].

Proinflammatory mediators impair the barrier function of the endothelium and induce TF expression on endothelial cells and various immune cell populations. Thus, coagulation activation occurs in the “zones” of inflammation, and TF/FVIIa/FXa not only induces coagulation but also sends a signal into the cell via PAR-2 receptors. Inhibition of TF-cell signaling “preserves” pregnancy [52].

Anticoagulant therapy with heparinoids (fondaparinux) or selective thrombin inhibitors (hirudin) does not prevent recurrent fetal loss. LMWH effects are mainly associated with inhibition of complement activation and anti-TF effects. Inhibition of C3, C4 and C5a prevents the development of APA-mediated thrombosis. Passively overcoming the placental barrier, APAs activate the complement system. Interestingly, even subanticoagulant or low molecular weight doses of heparin in early pregnancy are effective in APS due to non-anticoagulant (anti-inflammatory, anti-TF, anti-complementary, anti-fibrinolytic) effects [52]. APAs activate complement in decidual tissue, disrupting adequate inhibitory mechanisms and inducing inflammation and fetal damage. Thus, heparin prevents recurrent miscarriages by limiting complement activation and reducing the inflammatory response in the fetal-uterine space rather than by inhibiting thrombus formation in early pregnancy. At the same time, in the II and III trimesters of pregnancy, the anticoagulant effects of LMWH are extremely important to prevent vascular thrombosis in the uteroplacental space, since in the conditions of AFA circulation and the progression of physiological hypercoagulation, the risk of thrombosis of both microcirculation and macrothrombosis increases significantly. Therefore, the nonthrombotic and thrombotic pathological effects of AFA determine and pathogenetically justify the use of low molecular weight heparin with its non-anticoagulant and anticoagulant effects from early pregnancy [52]. Non-anticoagulant effects of LMWH: Inhibits the production of TNF-α; Increases serum TNF-α-binding protein I and thereby suppresses systemic effects (SSBO); Has an anti-inflammatory effect on the vascular wall in conditions of thrombosis;

Restores the ability of trophoblast to secrete hCG, which is suppressed under conditions of circulating AFA. This, in turn, expands both the theoretical justification and its practical use in thrombophilia.

1.3. Clinical pharmacology of drugs for the treatment of thrombophilia

Considering the existing data on the pathogenesis of hemostasis disorders in general in problems with pregnancy, fertilization, physiological gestation, and, in particular, in thrombophilia, taking into account modern data on pharmacotherapy and pharmacoprophylaxis of the described changes, taking into account the obtained practical results that were subjected to retrospective analysis in the work, we have identified the following groups of drugs and directly the drugs of choice: direct-acting anticoagulants - low molecular weight heparin analogues (enoxaparin (Clexane)), natural heparin analogues (heparin), antiplatelet agents - cyclooxygenase-1 inhibitors (acetylsalicylic acid (aspirin-cardio)), antiplatelet and antierythrocyte antiplatelet agents, methylxanthine derivatives with myotropic vasodilator activity - pentoxifylline (Trental), anti-inflammatory drugs with immunosuppressive activity – methylprednisolone (methypred). It is on the clinical and pharmacological characteristics of these drugs that we will focus in the next section of the work, the justification of their use with further assessment of therapeutic efficacy and, at the same time, the safety of use in disorders of reproductive function in women.

In order to increase the number of embryos available for transfer and freezing, women receive massive therapy with exogenous gonadotropins, which increases the risk of thrombosis [37]. Changes in hemostasis during ovarian stimulation are similar to those observed during pregnancy and are caused by a rapid (more than 100-fold in 2 weeks) increase in estradiol levels [55]. At the same time, the concentrations of endogenous coagulation factors (factor V, fibrinogen, von Willebrand factor) increase, and the levels of antithrombin and protein S decrease. However, despite the procoagulant changes, the reduction in clotting time remains within normal limits and there are no changes in fibrinolysis.

In the case of ovarian hyperstimulation syndrome, the changes become more significant: higher levels of fibrinogen, von Willebrand factor, D-dimers, thrombin-antithrombin complexes, and decreased levels of prekallikrein and tissue factor (III) inhibitor are observed [53].

Despite the significantly altered coagulation parameters, thromboembolism during ovarian stimulation is a rather rare phenomenon (0.08–0.11%) [9]. With the development of ovarian hyperstimulation syndrome, complications occur more often - approximately in one in 128 women (20–40-fold increase in risk compared with physiological pregnancy) [34].

Low molecular weight and unfractionated heparins (LMWH and UFH) are used to prevent thromboembolic complications [50]. However, in a number of situations with hereditary thrombophilias, the recommended prophylactic and even therapeutic doses may be ineffective [54]. Resistance to anticoagulant therapy can be explained by local hyperactivation of coagulation and high concentrations of estradiol, which reduces the antithrombotic properties of the epithelium. Clinical progression of thromboembolism occurs in 10% of cases and requires immediate restoration of adequate hemostasis. As in pregnancy, the duration of treatment of venous thrombosis/thromboembolism with transient risk factors to prevent recurrence is an average of 6 months, with multiple risk factors anticoagulant therapy can continue throughout the woman's life. Prophylactic treatment should be carried out during pregnancy and for at least 6 weeks after delivery. The effectiveness of anticoagulant therapy for antiphospholipid syndrome with habitual miscarriage has contributed to the revival of interest in the use of LMWH in thrombophilic complications. A few studies show an increased risk of miscarriage, placental abruption, fetal growth restriction, and preeclampsia in association with inherited thrombophilias [1, 4].

Antiphospholipid syndrome is the most common acquired thrombophilia and is associated with frequent miscarriages and a high risk of recurrent miscarriage [25]. The role of antiphospholipid antibodies in the genesis of infertility is debated

due to the heterogeneity of the seropositivity of these antibodies. Agreement is needed on which antibodies should be evaluated and what titers should be considered positive [23].

Some studies have questioned the role of antiphospholipid antibodies in infertility, but the authors did not examine the results in women with recurrent miscarriages or consecutive losses after IVF [55]. Similarly to acquired thrombophilia, women who have not achieved a positive result after three embryo transfers have elevated levels of antiphospholipid antibodies [29]. Therefore, screening for thrombophilia in consecutive failures is clearly warranted, as anticoagulant treatment has a beneficial effect. Screening after one IVF-mediated miscarriage is not considered warranted [7], but positive serological results in women with two early IVF-mediated miscarriages are found with the same frequency as in patients with spontaneous habitual miscarriage (high-risk group for recurrence -19). Such cases are amenable to treatment [12]. Therefore, screening after two early IVF-mediated miscarriages is advisable.

Women with confirmed antiphospholipid syndrome or repeated implantation failures and positive antiphospholipid antibody tests are recommended to be given LMWH and ASA during ovarian stimulation and to continue this therapy throughout pregnancy [25]. Patients with a positive reaction to one type of antiphospholipid antibodies at the first attempt of IVF are not shown anticoagulant therapy due to the lack of data on the impact of antiphospholipid antibodies on infertility, while the detection of several types of antiphospholipid antibodies, on the contrary, requires the use of LMWH and ASA with a high complication rate of pregnancy [32].

Classically, the role of heparin in the use of ART in acquired and hereditary thrombophilias is considered from the point of view of thrombosis prevention. However, the effects of heparin are probably much broader due to its interaction with a large range of proteins that affect the physiological processes of implantation and trophoblast development. It is known that the risk of

complications and adverse perinatal outcomes in artificial insemination is higher than in pregnancy that has occurred physiologically. Impaired implantation and trophoblast development correlate with the risk of preeclampsia, gestational diabetes, placenta previa and the need for operative delivery. The prerequisites for these complications arise in the first trimester in case of disruption of the processes of implantation and trophoblast development[34]. The process of implantation is not fully understood, but anticoagulant therapy is proposed as a prophylaxis in women with a history of placental complications [20]. Given the high risks of complications with the use of ART, LMWH is often used in practice, also based on biological “plausibility”.

Selectins and heparin - the initiation of the interaction of the blastocyst with the endometrial epithelium is similar to the rolling of leukocytes. It is believed that selectins - cell adhesion molecules - can initiate the implantation process [53]. Heparin modulates the action of selectins. Heparins containing polyglycans with a higher molecular weight, such as dalteparin, tinzaparin, block the binding of selectins. Nadroparin calcium, enoxaparin - heparins with lighter fragments - do not affect the functions of selectins [53], therefore, theoretically they are the drugs of choice. At the same time, nadroparin calcium has better local tolerance compared to enoxaparin.

Cadherins and heparin - cadherins are a group of glycoproteins that provide calcium-dependent cell adhesion. E-cadherin is expressed by many tissues, including the endometrium. E-cadherin expression influences extravillous trophoblast migration and invasion [53]. Unfractionated heparin (UFH) and LMWH induce a decrease in decidual E-cadherin expression, potentially supporting extracellular trophoblast differentiation.

Insulin-like growth factor and heparin-induced insulin-like growth factors 1 and 2 (IGF-1 and IGF-2) are also involved in fetal implantation and development[14]. UFH and LMWH increase free IGF-1 in a dose-dependent manner without affecting total IGF-1 and IGF-binding protein [26]. In vitro, IGF-1

stimulates trophoblast cell migration, and therefore the local increase in free IGF-1 levels combined with the decrease in transforming growth factor (TGF) levels induced by LMWH may contribute to successful trophoblast invasion[21]. Similarly, increased expression of IGF-2 facilitates the implantation of extracellular cytotrophoblast cells into the decidual membrane and its vascularization, as shown in a mouse experiment [28].

Cytokines and heparin - transforming growth factor. Various cytokines are involved in the regulation of trophoblast invasion. TGF-β1-3 are expressed by both endometrial and trophoblast cells and inhibit trophoblast proliferation and invasion [22]. LMWH suppresses the expression of TGF-β1 by mesangial cells by preventing increased binding of nuclear proteins to the regulatory site of the TGF-β1 promoter [40].

Interleukin 1 and heparin - TGF-β1 promoter IL-1 is a proinflammatory cytokine that is also thought to be involved in the implantation process. Administration of a natural inhibitor of the IL-1 receptor antagonist prevents blastocyst implantation in mice by reducing integrin levels on the epithelial surface in the lumen of spiral vessels [36]. Addition of IL-1 to blastocysts in culture increases endometrial expression of integrin β3, which improves blastocyst adhesion [33]. The effects of UFH and LMWH on IL-1 expression by trophoblasts and blastocysts have not been demonstrated, but increased IL-1 expression in leukocytes in vitro in response to heparin administration has been reported [53], raising the possibility that similar effects may occur in the endometrium.

Matrix metalloproteinases (MMPs) and heparin - MMPs are a family of 22 endoproteases that can degrade components of the extracellular matrix and are important mediators of cell-cell and cell-matrix interactions. In vitro studies have shown that successful implantation and placentation are mediated by a balance between trophoblast expression of MMPs and their inhibition by natural tissue inhibitors of metalloproteinases [27]. Heparin has variable effects on MMPs [38], but LMWH at therapeutic doses induces transcription of MMP-2 and MMP-9,

which are essential for trophoblast invasion, and protein expression with a concomitant decrease in the expression of tissue inhibitors of metalloproteinases [41]. Thus, LMWH may enhance trophoblast cell invasion by regulating their destructive potential.

Aspirin (acetylsalicylic acid) is indeed an antiplatelet agent, i.e. a drug that prevents platelet aggregation and, consequently, the formation of blood clots. Its action is based on the inhibition of the enzyme cyclooxygenase 1 (COX-1) in platelets, which leads to a decrease in the production of thromboxane A2, a substance that causes platelets to stick together.

Low-dose aspirin has a modest benefit when used to prevent preeclampsia. This benefit is greater in early pregnancy [54]. Aspirin is widely used to increase the chances of a live birth in women undergoing ART. However, there is conflicting evidence regarding the effectiveness of this treatment, the appropriate time to start treatment, and its duration. Although aspirin is physiologically beneficial in some aspects necessary for a successful pregnancy, aspirin use has also been associated with miscarriage and vaginal bleeding. There is currently no evidence to support the use of aspirin to improve pregnancy rates in the general IVF population. The quality of the evidence for live birth was moderate, and for other outcomes was very low to moderate.

Pentoxifylline is a methylxanthine derivative that improves the rheological properties of blood by causing various changes in blood cells and the endothelium. It has been shown to improve the plastic properties of red blood cells by increasing their ATP. Later data were obtained indicating that, in addition to increasing the elasticity of red blood cells, leukocytes play an important role in reducing blood viscosity and increasing its flow properties. Their activation leads to a decrease in deformability, chemotaxis, decreased adhesion, degranulation and release of endoperoxides, a decrease in the production of tumor necrosis factor alpha (TNF-a), leukocyte sensitivity to interleukin, suppression of the activity of T and B lymphocytes, a decrease in As a result of damage to endothelial cells, the adhesive

properties of leukocytes are stimulated and the production of inflammatory mediators (cytokines) increases [55].

Pentoxifylline causes a dose-dependent increase in the concentration of cAMP in mononuclear and polymorphonuclear cells. It is believed that this effect is due to the inhibition of phosphodiesterase activity. The increase in adhesion of polymorphonuclear cells occurs due to the stimulating effect of TNF-a. There is evidence that it has a direct toxic effect on endothelial cells, which is blocked by pentoxifylline. TNF-α is also involved in the development of disseminated intravascular coagulation by stimulating endothelial production of procoagulant tissue factor and reducing the level of endothelial thrombomodulin, which leads to a decrease in protein C activation.

The formation and destruction of blood clots is a dynamic process that includes the interaction of the damaged vessel wall, platelets, the blood coagulation system, fibrinolysis, the kinin system, shear stress occurring in the bloodstream, and the development of an inflammatory reaction that is carried out with the participation of a large number of mediators. Improvement of conditions associated with increased blood coagulation also involves a decrease in platelet aggregation and adhesion, an increase in the level of plasminogen activator and plasmin, an increase in the level of antithrombin III, a decrease in fibrinogen, the level of a2-antiplasmin, a decrease in the level of a1-antitrypsin and a2-MA. Pentoxifylline actively intervenes in these processes.

Methylprednisolone (methypred) is a synthetic drug from the group of glucocorticoid hormones. The drug has anti-inflammatory, anti-shock, anti-allergic and immunosuppressive effects. After penetrating the cell, methylprednisolone interacts with specific receptors in the cytoplasm of the cell and forms a complex that binds to DNA and stimulates the formation of mRNA, which leads to changes in the formations on the ribosomes of proteins responsible for the properties of cells. Methylprednisolone stimulates the synthesis of lipocortin, which inhibits the enzyme phospholipase A2, which leads to the suppression of the synthesis of

prostaglandins and leukotrienes involved in the development of inflammatory reactions. Methylprednisolone stabilizes lysosomal membranes, inhibits the synthesis of hyaluronidase and reduces the synthesis of lymphokines. The drug has an antiproliferative effect due to a decrease in the migration of monocytes into the focus of inflammation and inhibition of fibroblast proliferation. Methylprednisolone inhibits the activity of the collagenase enzyme, which prevents the destruction of bone tissue and cartilage in rheumatoid arthritis. The antiallergic effect of methylprednisolone is due to a decrease in the number of basophils and a direct decrease in the synthesis and secretion of mediators of the immediate allergic reaction. The hormone causes involution of lymphoid tissue and the development of lymphopenia, which leads to immunosuppression [55]. Methylprednisolone increases the number of receptors in cells and increases their sensitivity to physiologically active substances (including catecholamines). The drug reduces the amount of proteins in the blood plasma, increases the catabolism of proteins in muscle tissue. The drug inhibits the absorption of calcium in the gastrointestinal tract and promotes its leaching from bones and increases the excretion of calcium in the urine. Unlike prednisolone, methylprednisolone does not have mineralocorticoid activity. The drug promotes the synthesis of enzymes in the liver; and also enhancing the production of fibrinogen, erythropoietin, surfactant, lipomodulin. Methylprednisolone promotes the synthesis of fatty acids and triglycerides, causes fat redistribution (reduction of fat deposits on the limbs and increase in fat deposits on the upper half of the trunk and face). The drug increases the absorption of carbohydrates in the gastrointestinal tract, promotes the mobilization of glucose into the bloodstream and enhances gluconeogenesis. Methylprednisolone has an anti-shock effect, stimulates the formation of some cells in the bone marrow. The drug increases the number of erythrocytes and platelets in the blood, reduces the number of lymphocytes, eosinophils, monocytes, basophils in the blood. Methylprednisolone suppresses the function of the pituitary gland, and also suppresses the production of ACTH. The anti-inflammatory effect of the drug is associated with a decrease in the release of arachidonic acid from

phospholipids of cell membranes, and a decrease in the amount of its metabolic products (prostaglandins, leukotrienes). It is due to its pronounced anti-inflammatory and immunosuppressive properties that metipred is used in disorders of the reproductive function of women caused by the presence of autoimmune diseases, or autoimmune mechanisms of disorders of egg implantation, fertilization, trophoblast, chorion, placenta functions.

CHAPTER 2. Results of practical application of various hemocoagulation correction schemes in women of reproductive age

2.1. Research materials and methods

Returning to the topic of the master's thesis, considering the main goals and objectives set during the planning stage, and evaluating current data on the assessment of the hemostatic system in various clinical conditions in general, and in obstetric and gynecological pathology in particular, the practical portion of the work was conducted by analyzing the medical records of 30 patients from a specialized reproductive medicine clinic. Women of reproductive age 30-40 years old presented with problems of primary conception and chronic miscarriage—the most common questions that arise during their first or repeat visits to a reproductive gynecologist. There is a standard screening examination that allows us to identify the problem, conduct laboratory and instrumental diagnostics, select the necessary correction method (pharmacological, surgical), offer a personalized method of assisted technologies (intrauterine insemination, use of own or donor material, in vitro fertilization) to solve and achieve the final medical, social, psychological result - pregnancy, childbirth, improvement of the demographics of the country and the world.

Among the pathological conditions affecting women, and specifically the female factor, problems with the coagulation system occupy a leading position.

Increased thrombus formation or a tendency to bleed impairs egg implantation, embryogenesis, gestation, and the progression of a physiological pregnancy. The end of the last century was marked by the discovery of antiphospholipid syndrome (APS) and genetic forms of thrombophilia, which allowed for a new assessment of the mechanism of thromboembolic complications in both general clinical and obstetric-gynecological practice. Impaired blood coagulation, along with chronic inflammatory diseases, congenital malformations of the external and internal female genitalia, and structural adhesions resulting from surgical interventions, are common causes of failure to conceive and maintain a desired pregnancy.

The standard examination algorithm for a woman during the initial consultation with a reproductive specialist includes information about both members of the couple, primary and secondary complaints, and reproductive history (number of pregnancies, births, contraceptive methods, surgeries, pharmacological methods – hormone therapy). A menstrual history is mandatory (at what age did menarche occur, regularity, heaviness, and painfulness of menstruation). A manual examination of the mammary glands is also included. The presence of extragenital pathology is also included. A history of infectious and sexually transmitted diseases is also included. A history of allergies and oncology is also included. Endocrine and genetic status (thyroid pathology, acne, hereditary diseases of the woman and man). Anthropometric indicators (height, weight, body mass index, waist-to-height ratio). Laboratory tests (anti-Müllerian hormone, follicle-stimulating hormone, luteinizing hormone, thyroid-stimulating hormone, estradiol, prolactin, ferritin, vitamin D, urogenital swab microscopy, Pap test, karyotyping, hemostasis). Instrumental tests (ultrasound of the pelvic organs on days 10-12 of the menstrual cycle, ultrasound of the mammary glands on days 5-7 of the menstrual cycle, hysterosalpingographic sonography).

Laboratory biochemical and hormonal blood tests and a hemostasiogram were performed at the Smartlab or Dila multidisciplinary network using automated equipment and diagnostic kits. The study's objectives focused on a comprehensive

assessment of the blood coagulation system. A hemostasiogram is a comprehensive, multicomponent test that allows for an objective assessment of the state of the blood coagulation system. A hemostasiogram is more informative than a coagulogram, as it includes an assessment of D-dimer as an indicator of thrombosis and antithrombin as a substance that ensures the normal function of heparin. This method is used in the diagnosis of many blood coagulation disorders (thrombosis, bleeding, disseminated intravascular coagulation, thrombophilia). It allows for the assessment of a person's condition in the pre- and postoperative periods, the identification of risks for various blood diseases and their complications, and is optimal for monitoring the treatment of coagulation disorders. A hemostasis test is a comprehensive study of the blood coagulation system to assess the risk of thrombosis, bleeding, monitoring anticoagulant treatment, or preparing for surgery. It includes determination of antithrombin (AT III), D-dimer, fibrinogen, thrombin time, prothrombin test, and activated partial thromboplastin time (APTT).

Antithrombin (AT III) is a natural anticoagulant that inhibits thrombin and other clotting factors. AT III is a serine protease synthesized by hepatocytes and vascular endothelium. Antithrombin III deficiency can be congenital or acquired. The main clinical manifestation of antithrombin III deficiency is thrombosis. In this case, it can be caused by both changes in the quantity and structural changes of antithrombin III.

D-dimer is a marker of fibrinolysis activation. It increases due to thrombosis, pulmonary embolism, disseminated intravascular coagulation, pregnancy, and postoperative complications.

Fibrinogen is a plasma protein that, under the action of thrombin and activated factor XIII (factor XIIIa), is converted into insoluble fibrin, forming the basis of a thrombus—a stable blood clot.

Thrombin time measures the rate of conversion of fibrinogen to fibrin. It is prolonged by fibrinogen deficiency, heparin exposure, or other coagulation disorders.

APTT – evaluates the effectiveness of the intrinsic coagulation pathway. It increases with deficiency of factors VIII, IX, XI, and XII, hemophilia, and anticoagulant therapy.

Prothrombin time – characterizes the extrinsic coagulation pathway. It is a control value during indirect anticoagulant therapy.

Indications for a hemostasiogram: before surgery, IVF; to select hormonal contraceptives or anticoagulant therapy; in case of taking anticoagulants, antiplatelet agents; in case of suspected pulmonary embolism, disseminated intravascular coagulation syndrome (DIC); in case of bleeding in any location; in case of severe liver disease; in case of recurrent miscarriages, chronic miscarriage.

For the study, venous blood was collected taking into account the following preparation rules to exclude the influence of certain factors on the results: donate blood on an empty stomach. 6-12 hours before donation, it is necessary to avoid food, alcohol, smoking, and limit physical activity. Drinking still water is allowed; do not take any medications. If discontinuing medication is not possible, the laboratory must be informed. Another well-known test for measuring blood coagulation properties is thromboelastography, but recently, a hemostasiogram has become more commonly used in reproductive medicine. A hemostasiogram is a comprehensive analysis of individual components of the blood coagulation system, while a thromboelastogram is a functional study of the entire thrombus formation process. A hemostasiogram evaluates individual parameters (e.g., clotting time, fibrinogen levels), while a thromboelastogram shows clot formation and its strength on a graph, allowing for the dynamic evaluation of hemostasis system function. The administration of appropriate medications to correct detected

changes was also monitored dynamically using hemostasiogram parameters. This will be demonstrated in the next section of the master's work.

2.2. Clinical efficacy and safety of antithrombotic drugs and procoagulants in thrombophilia

We want to present the practical part of the work on specific clinical examples that corresponded to the goal and objectives of the work and were registered at the stage of pregnancy planning, with previous unsuccessful attempts at pregnancy, with signs of miscarriage.

Normal pregnancy is accompanied by a large number of sequential processes that are involved in embryo transfer, embryogenesis, physiological formation of the chorion and placenta, ensuring fetal growth. Changes also occur in the hemostasis system, and any deviations from reference values can threaten serious complications for both the mother and the child. Thus, violations of placental function lead to gestosis, to premature termination, intrauterine development delay and intrauterine fetal death. Moreover, violations of hemostasis play a significant, and often even the main, role in all these cases.

In violations of placental function, preventive hypocoagulation is important. Prophylactic hypocoagulation in the first trimester reduces the risk of pregnancy complications in later terms. Effective correction of placental function in the early stages, but it makes no sense in the later ones. Doses and regimens of prophylactic hypocoagulation in pregnancy differ from doses and regimens of hypocoagulation therapy in other conditions (acute vascular complications, thromboembolism, prophylaxis in artificial heart valves):

1. Aspirin + heparin. At risks of placental dysfunction, prophylactic hypocoagulation includes aspirin preparations in low doses, heparin and their combinations. It should be borne in mind that each of them has a potentiating effect on the other. Their combination sharply enhances the effect, which can increase the risk of bleeding, especially during childbirth and cesarean section. Therefore, it is important to see hypocoagulation in advance to prevent

complications. It is also important to consider the patient's diet. Some foods significantly reduce platelet aggregation. Such products include, in particular, garlic, green tea, cranberries.

2. Drugs that have an anticoagulant effect. Aspirin is absolutely safe in doses up to 100 mg per day, which provides blocking of vascular spasm, which leads to chronic placental dysfunction.

Indications for prophylactic hypocoagulation:

a) A complicated history (infertility, miscarriage)

b) genetic thrombophilias

c) genetic risks of vasospasm (homozygotes for ACE, AGT)

d) stimulation of ovulation (including during IVF)

e) large doses of hormonal drugs.

Let us consider the example of patients planning pregnancy and in the early stages, the indicators of hemostasis and thromboelastography, which should be paid attention to when selecting therapy, and changes in their condition in dynamics.

1. A woman, 42 years old, examined at the stage of pregnancy planning. Two studies were conducted (Fig. 2.1), with an interval of 5.5 months. The latter demonstrates that the hemostatic potential (HP) of patient 1 is characterized by moderate structural hypocoagulation (MA = 362 rel. o.), chronometric (t5 = 43.3 min) normocoagulation at the stage of formed PFP (cross-linked fibrin). Gel point indicators (t3 = 43.3 min); ICD = 8.5 rel. o. and CTA = 7.3 rel. o. indicate a hypocoagulation trend of GP at the proteolytic stage of fibrinogenesis against the background of a decrease in thrombin activity.

The process of lateral fibrin folding (IPS = 1.0 rel. o.) is inhibited. Suspension stability of blood is normal (tl = 1.3 min). Aggregation activity of FEC

(formed blood elements) at the initiation stage is increased ICC = 0.77. Fibrinolytic activity of plasma is normal IRLS = -0.55%.

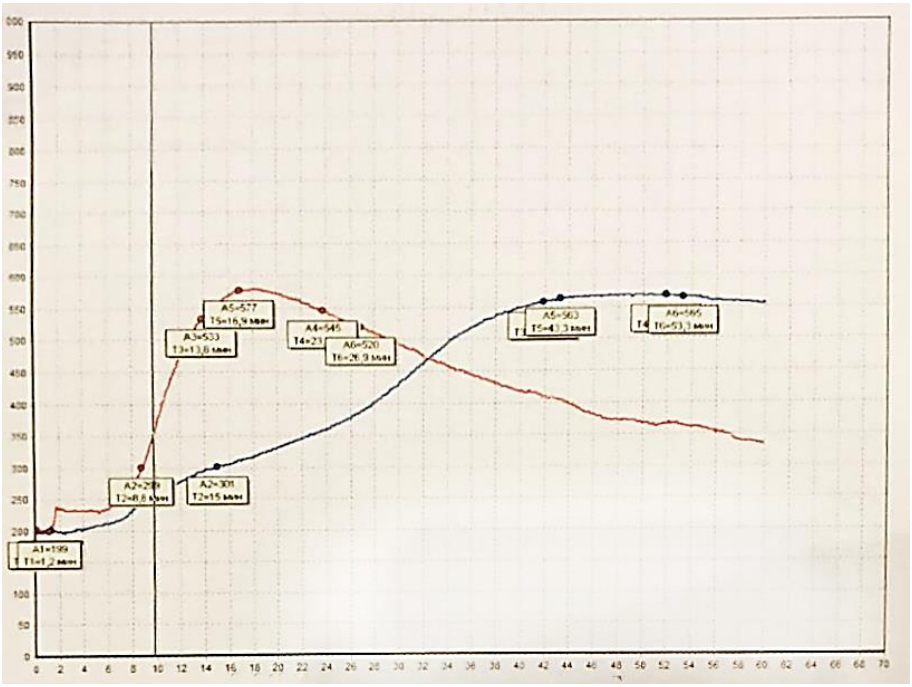


Fig. 2.1. Thromboelastogram curves of the patient: from 09.03 (red curve), 23.08 (blue curve).

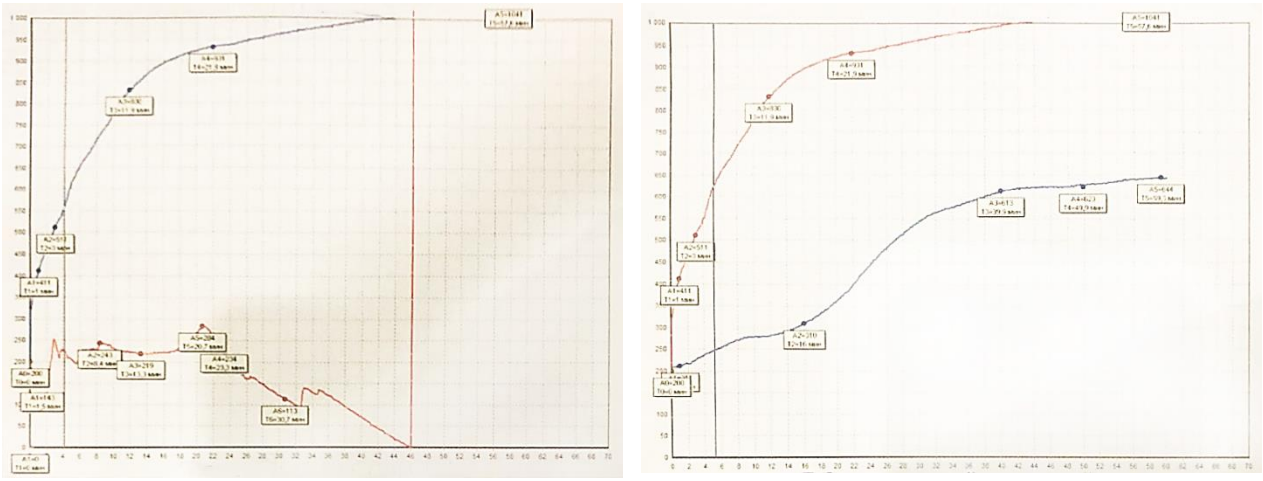
After the study, Kanavit 2.0 intramuscularly, one injection, vitamin K 2 tablets twice a day were recommended.

2. Woman, 42 years old, first month of pregnancy. Three studies were conducted (Fig. 2.2) on the third day after embryo transfer, two and four weeks later.

At the time of the last study, she was taking: Tranexam 500 mg twice a day, a week, vitamin K complex 1 capsule twice a day.

The result of the patient's second study, based on which a conclusion was made about structural normocoagulation (MA = 630 rel. units) and chronometric hypocoagulation (t5 = 57.6 min) at the stage of formed PFP. Gel point indicators (t3 = 11.9 min); ICD = 35.21 rel. units and CTA = 50 rel. units. indicate a normocoagulatory trend of GP at the proteolytic stage of fibrinogenesis against the

background of normal thrombin activity. The process of lateral fibrin folding (IPS = 10.10 rel. units) is slightly inhibited, corresponding to the general normocoagulatory trend of GP. Suspension stability of blood is normal (tl = 1.0 min); recommendations are given for the use of Cardiomagnyl, 1 tablet once a day (14 days). Control was carried out after 14 days.



а б

Fig.2.2. Thromboelastogram curves of patient 2: a – from 09.04 (red curve), 23.04 (blue curve); b – from 23.04 (red curve), 10.05 (blue curve).

After the study, Kanavit 1.0 intramuscularly every other day, five injections, ascorutin 2 tablets twice a day were recommended.

Diagnosis and correction of medication dosage using the thromboelastography method in hypercoagulable states

Hypercoagulable syndrome is a condition characterized by blood thickening. A slight deviation of the hemostatic system towards this syndrome has extremely negative consequences for the mother and fetus: from bleeding, miscarriage to premature birth and other complications.

Blood thickening develops as a result of the coincidence of a large number of risk factors at a specific moment: hypodynamia, obesity, impaired vascular tone, dehydration, overheating, stress.

Antiphospholipid syndrome (APS) deserves special attention. In this pathology, pathological activation of platelets occurs and the blood clotting mechanisms are triggered. Such pathology can lead to termination of pregnancy at any time or cause infertility. APS is also considered one of the risk factors for the development of venous thrombosis. Pathology in the hemostasis system may not affect the general condition of a pregnant woman. Many expectant mothers do not even suspect about the problem until dangerous complications develop.

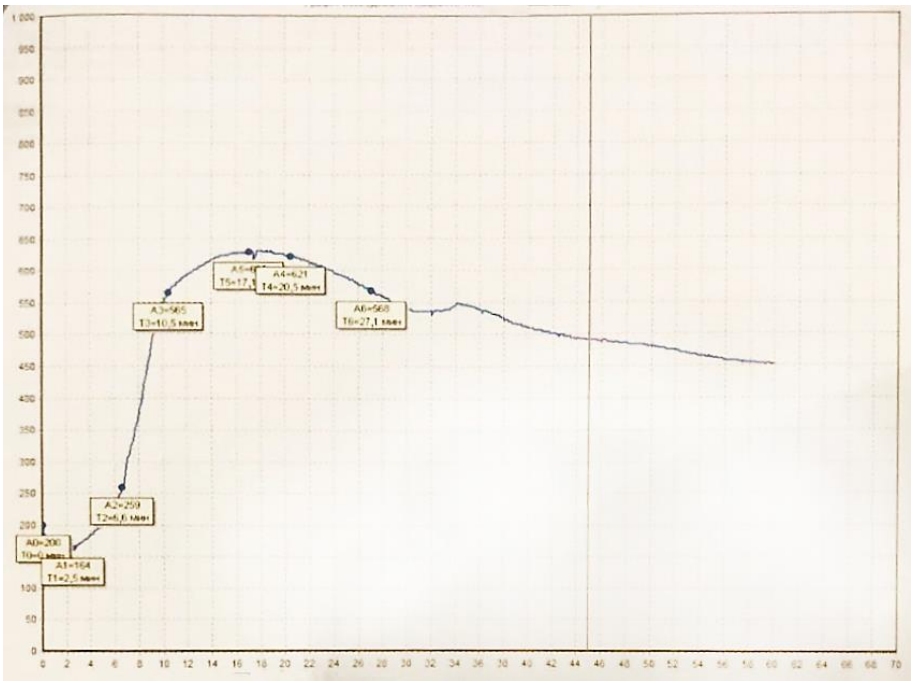
A comprehensive assessment of the pregnant woman's condition is possible using thromboelastography. The analysis is prescribed in the following situations:

- threat of abortion;
- spontaneous miscarriages or regressed pregnancy in the past;
- habitual miscarriage;
- impaired blood flow in the mother-placenta-fetus system;
- fetal growth retardation;
- gestosis;
- other conditions that increase the risk of blood clotting.

When evaluating the results obtained, one should be guided only by the norm for pregnant women. With pronounced changes in the hemostasis system, anticoagulants are prescribed - drugs that reduce the likelihood of blood clots. After the treatment, it is necessary to conduct a study using the NPTEG method again and assess the effectiveness of the therapy. Antiplatelet agents are also used to correct hypercoagulable syndrome. These drugs inhibit platelet aggregation (gluing) and thereby reduce blood viscosity. The dosage and duration of such therapy is determined by the doctor. Let us consider the example of pregnant women (1 trimester) and women at the stage of preparation for pregnancy, NPTEG

indicators that indicate hypercoagulability, and methods of drug correction that can be offered.

3. Woman, 30 years old, pregnancy, two weeks. NPTEG study is of a control nature. At the time of the examination, patient 3 is not taking any medications (Fig. 2.3). The hemostatic potential of patient 3 at the time of the study is characterized by structural normocoagulation (MA = 464 rel. u.) and chronometric hypercoagulation (t5 = 17.1 min) at the stage of formed PFP. The gelation point indicators registered in the range of reference values (t3 = 10.5 min); ICD = 38.19 rel. u. and CTA = 24.39 rel. u. indicate a normocoagulation trend of GP at the proteolytic stage of fibrinogenesis against the background of normal thrombin activity. The process of lateral fibrin folding (IPS = 5.6 rel. u.) is inhibited. The suspension stability of blood is increased (tl = 2.5 min). The aggregation activity of FEC at the initiation stage is normal, ICC = -14.40, the fibrinolytic activity of plasma is enhanced, IRLZ = 12.93% Based on these data, it is recommended to take tranexamic acid 500 mg 2 times a day for 7 days and further monitor the condition.



4. Woman, 43 years old, pregnancy, two weeks. At the time of the examination, she takes aspirin cardio 100 mg, 1 tablet 1 time per day.

Examination (Fig. 2.4) demonstrates that the hemostatic potential is characterized by structural normocoagulation (MA = 473 rel. o.) and chronometric hypercoagulation (t5 = 24.8 min) at the stage of formed PFP. The registered indicators at the gelation point (t3 = 18.9 min); ICD = 22.28 rel. o. and CTA = 22.22 rel. o. indicate a normocoagulation trend against the background of normal thrombin activity.

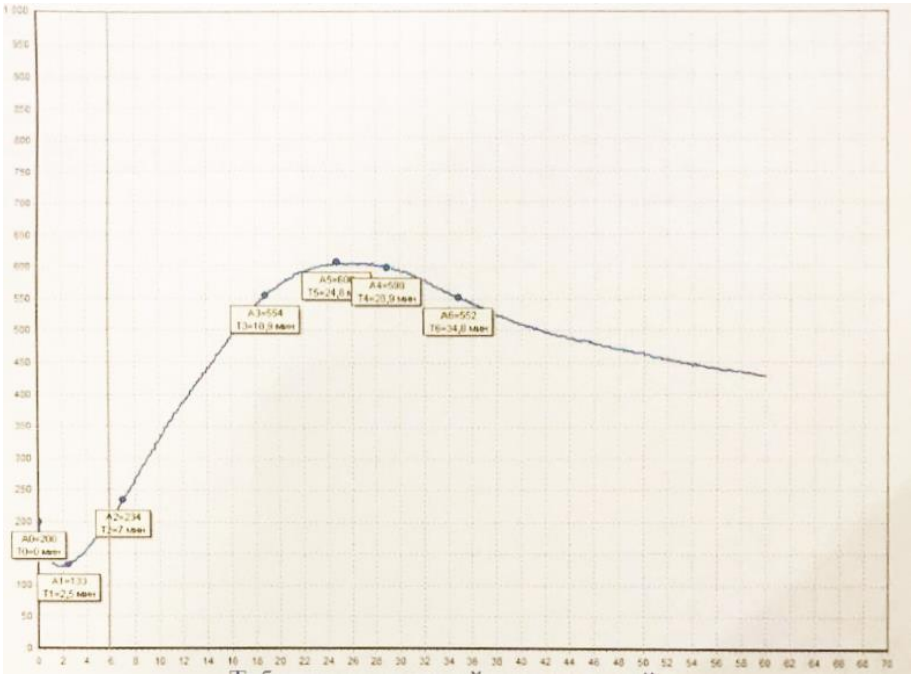


Fig. 2.4. Graphical data of the examination of patient 4.

The process of lateral fibrin folding (IPS = 4.4 rel. o.) is inhibited. The suspension activity of blood is slightly increased (t1 = 2.5 min). The aggregation activity of FEC at the initiation stage is not impaired, ICC = -26.8. The fibrinolytic activity of plasma is increased, IRLZ = 11.42%.

Based on these data, the following recommendations were made: cancel aspirin cardio, prescribe Vit K complex (triple play) 1 tablet 1 time per day -1 month, tranexamic acid 500 mg 1 tablet 2 times per day -10 days. The need for further monitoring.

The presented thromboelastography data show the importance of studying the coagulation properties of blood, hemocoagulation disorders in various pathological conditions, at different stages of physiological pregnancy to resolve further issues of their correction. This sequential process was studied in the dynamic phase, which is what the thromboelastography method allows.

A more complete study of coagulation properties, their impact on reproductive processes in women, is possible, and this was previously determined by us, using the hemostasiogram method - a study of the level of D-dimer, soluble fibrin-monomer complexes, qualitative determination of lupus anticoagulant. It is on the last indicator that I would like to stop. Lupus anticoagulant (LA) is a group of autoantibodies (immunoglobulins) that attack the body's own phospholipids and protein-phospholipid complexes, which interferes with normal blood clotting, increases the risk of blood clots in the body, which is associated with an increased risk of venous and arterial thrombosis, as well as miscarriage. LA is one of the laboratory criteria for diagnosing APS, a syndrome characterized by a tendency to thrombosis and complications during pregnancy, the significance of this syndrome was shown above. The presence of A increases the risk of arterial and venous thrombi, which can lead to heart attack, stroke, pulmonary embolism and other dangerous conditions, and during pregnancy is associated with a high risk of miscarriage, especially in the second and third trimesters, increased in thrombophilia - an autoimmune condition that worsens implantation, gestation, and the course of pregnancy.

We would like to present an analysis of some cases of hemostasis assessment.

1. A 40-year-old patient with habitual miscarriage. The first study revealed an increase in the level of D-dimer (1.19 μg FEU/ml), prothrombin time (12.6 sec), fibrinogen (3.96 g/l), and a decrease in antithrombin activity (79%). This prompted the suspicion of a violation in the hemocoagulation system (hypercoagulation). For correction, Clexane was prescribed subcutaneously for a week, followed by the use

of low doses of acetylsalicylic acid (aspirin cardio 100 mg) for the next 4 weeks. A control study showed normalization of indicators with the recommendation of possible pregnancy planning and waiting for biochemical and ultrasound confirmation of pregnancy.

2. A 33-year-old patient with unsuccessful previous attempts at IVF. Laboratory diagnostics showed a predominant increase in fibrinogen (4.8 g/l). At the same time, an increase in the LA risk index to 1.34 and the homocysteine level to 12.84 μmol/l was detected. Homocysteine is a sulfur-containing amino acid that is formed in the body during methionine metabolism and is normally quickly processed with the help of B vitamins (B6, B12, folic acid). Its increased level (hyperhomocysteinemia) during pregnancy indicates the risk of damage to the placental vascular wall, blood clot formation, impaired fetoplacental blood flow, and miscarriage. The hemostasis specialist diagnosed low-risk congenital thrombophilia, relative hyperfibrinogenemia, and normocoagulation state of hemostasis. It was prescribed: at the stage of pregnancy planning - folic acid 1.5 mg 1 time per day, vitamin B12 500 mcg 1 time per day, meloxicam 15 mg 1 time per day, metipred 4 mg 1 time per day - 1 month; with repeated control of homocysteine and LA. 5-6 days before embryo transfer, drug support with the inclusion of pentoxifylline 100 mg 2 times a day, Clexane subcutaneously 0.4 ml 1 time a day with control of the coagulogram after 3 days, and then repeated consultation when pregnancy is confirmed.

3. A 34-year-old patient with a previous unsuccessful IVF (in vitro fertilization) attempt.

Laboratory diagnostics showed the presence of immunoglobulin M antibodies to beta2 glycoprotein, an increase in the LA index, which allowed us to suspect high-risk acquired thrombophilia, primary APS, normocoagulatory state of hemostasis. Recommended pharmacological support: metipred 4 mg 1 time per day, aspirin cardio 100 mg 1 time per day, clexane 0.4 ml subcutaneously 1 time

per day 5-6 days before embryo transfer, control of the coagulogram on the 3rd day of clexane use, repeated consultation after confirmation of pregnancy.

2. A 37-year-old patient with a history of habitual miscarriage, according to the results of research and anamnesis data - low-risk genetic thrombophilia, hypercoagulable state of hemostasis (increased fibrinogen, prothrombin time, D-dimer, soluble fibrin-monomer complexes). Recommended drug correction: pentoxifylline 100 mg 2 times a day, Clexane 0.4 ml subcutaneously 1 time a day, start administering the drugs 5-6 days before embryo transfer with subsequent control of the coagulogram on the 3rd day of Clexane administration and further consultation after confirmation of pregnancy.

As we can see, the main drugs used to correct hemostasis, improve IVF results, and progress pregnancy were pathogenetic therapy agents metipred (systemic glucocorticoid), meloxicam (selective COX-2 inhibitor of NSAIDs), direct-acting anticoagulant - Clexane (enoxaparin), antiplatelet antiplatelet agent - Aspirin Cardio, antierythrocyte antiplatelet agent - Pentoxifylline. As a result, short- and long-term observations showed an improvement in assisted reproductive technologies, which was accompanied by an increase in their effectiveness by 35-40%.

In addition, we conducted a study of local regional features of reproductive health using the example of Morocco and compared the results obtained with data from Ukraine.

Reproductive Medicine in Morocco: Legal Framework, Clinical Practice, and Socioeconomic Challenges

INTRODUCTION

Infertility affects approximately 15% to 17% of Moroccan couples, yet access to reproductive healthcare remains uneven and limited. Although Law 47-14 legally authorizes medically assisted reproduction, many couples still face serious obstacles—including high treatment costs, lack of insurance coverage, limited availability of services in rural areas, and social stigma. The absence of a national registry, inadequate public awareness, and insufficient support services further complicate the situation. This study addresses these gaps by exploring the legal, clinical, and socio-economic challenges facing reproductive medicine in Morocco.

Research Questions

1. What laws and regulations govern reproductive medicine in Morocco?
2. What are the main medical and financial challenges faced by patients undergoing ART?
3. What are the clinical outcomes and success rates of ART in Moroccan clinics?
4. How does Morocco's approach compare with international standards?
5. What recommendations can be made to improve access and outcomes in reproductive healthcare?

Main Objective:

To examine the current state of reproductive medicine in Morocco and to propose recommendations to improve accessibility, regulation, and clinical outcomes.

- To review and analyze the legal framework (Law 47-14) regulating assisted reproductive technologies.
- To assess the availability, cost, and geographic distribution of ART services.
- To evaluate clinical outcomes and success rates of reproductive technologies.

- To identify socio-cultural and psychological barriers affecting patients.
- To compare Morocco's reproductive healthcare system with international models.
- To suggest policy reforms and public health strategies.

Reproductive Medicine

Reproductive medicine is a branch of medicine that deals with the prevention, diagnosis, and treatment of reproductive problems. It includes a range of services such as fertility diagnostics, hormone therapy, surgical procedures, and assisted reproductive technologies (ART) like in vitro fertilization (IVF) and intracytoplasmic sperm injection (ICSI). Globally, ART has become an essential solution for millions of infertile couples, improving the chances of conception through clinical and laboratory techniques.

Causes and Prevalence of Infertility

According to the World Health Organization (WHO), infertility affects 10–15% of couples worldwide. In Morocco, the prevalence is estimated at 15–17%, with both male and female factors contributing equally. Female infertility is often linked to ovulation disorders, tubal damage, or endometriosis, while male infertility may be caused by low sperm count or varicocele. In some cases, the cause remains unexplained. These conditions can lead to emotional distress, social isolation, and marital strain.

Global Perspectives on Assisted Reproductive Technologies

Many countries have integrated ART into their public healthcare systems. In France and the United Kingdom, ART is partially or fully funded by national health insurance. Tunisia, Morocco's neighbor, also has a well-developed ART infrastructure with around 10,000 cycles annually. These countries also have national ART registries to monitor success rates and ensure transparency. In

contrast, Morocco has limited access, no national registry, and a largely privatized system.

Development of ART in Morocco

Morocco began developing ART in the early 2000s through private initiatives. The adoption of Law 47-14 in 2018 provided a legal basis for ART, but challenges remain. Most ART clinics are located in large cities like Casablanca, Rabat, and Marrakech, leaving rural populations underserved. Approximately 4,000 ART cycles are performed annually, mainly in private clinics, with success rates ranging from 30% to 45%. The lack of public funding and centralized data collection hinders further progress.

Legal and Ethical Considerations

Law 47-14 regulates ART in Morocco, allowing procedures such as IVF only for married heterosexual couples. The law prohibits gamete donation, embryo freezing (except in special cases), surrogacy, and sex selection. Ethical concerns arise regarding equity, access, and the rights of children born through ART. While the law ensures the ethical practice of ART, its restrictions limit access for unmarried couples and marginalized populations.

Research Methodology

This study uses a qualitative and descriptive research design. It combines the analysis of legal documents, national health reports, academic publications, and semi-structured interviews with healthcare professionals. This approach was chosen to capture both the legal and clinical realities of reproductive medicine in Morocco, as well as patients' experiences and challenges.

The research is based on two main types of data:

- **Primary data**, obtained through interviews with gynecologists, clinic staff, and patients (if applicable), and
- **Secondary data**, collected from Moroccan laws (e.g., Law 47-14), Ministry of Health publications, WHO reports, medical journals, and statistical databases on fertility and ART.

Results

Despite the official legalization of assisted reproductive technologies in Morocco through Law 47-14, access to reproductive medicine remains largely limited to urban, affluent populations. Most ART clinics are privately owned and concentrated in major cities such as Casablanca, Rabat, and Marrakech. This creates significant disparities for rural populations who face logistical and financial barriers to care. Moreover, ART procedures such as in vitro fertilization (IVF) remain costly—ranging from 25,000 to 40,000 MAD per cycle—with no insurance reimbursement or state financial support. As a result, many infertile couples either forgo treatment or seek help abroad. The law prohibits gamete donation, surrogacy, and embryo freezing under most circumstances, which further restricts reproductive options. Although the legislation ensures ethical practice and prevents commercialization of reproduction, it also limits solutions for certain medical cases, particularly for women with premature ovarian failure or men with azoospermia.

Clinically, ART success rates in Morocco are comparable to global averages, with IVF success rates ranging between 30% and 45% depending on maternal age and clinic technology. However, the lack of a national ART registry makes it difficult to collect consistent, centralized data on outcomes, complications, or long-term health effects. Interviews with gynecologists indicate that while technical standards have improved, there remains a need for better

training, quality control, and psychological support services for patients. Social stigma surrounding infertility—especially female infertility—also remains a major issue, often deterring women from seeking timely medical help. In summary, while reproductive medicine in Morocco has made important progress, it continues to face legal, economic, and social challenges. Addressing these will require stronger public investment, regulatory reform, and awareness campaigns to normalize infertility care as a legitimate medical need rather than a private burden.

Conclusion

Reproductive medicine in Morocco has witnessed important developments, particularly following the adoption of Law 47-14, which legally regulates assisted reproductive technologies. The availability of ART in private clinics has enabled many couples to access treatment, and success rates are comparable to international standards. However, the sector continues to face major obstacles, including limited geographic access, high treatment costs, and the exclusion of unmarried couples and those requiring donor material due to legal and ethical restrictions. Furthermore, the absence of a national ART registry, limited public funding, and persistent social stigma around infertility undermine the overall impact of current efforts. While progress is evident, the reproductive health system in Morocco must be more inclusive, affordable, and regulated to serve all citizens equally.

The general conclusion confirms the presence of similar problems in Ukraine, Morocco, and throughout the world, which makes it necessary to more widely implement these technologies to improve demography in countries and the world as a whole, to involve and implement methods of medical and instrumental support at different stages of in vitro fertilization.

CONCLUSIONS

1. The demographic situation in many countries of the world is currently experiencing difficult times, the natural population growth is decreasing, there are negative results of fertilization of fertile couples, which is associated with many external and internal factors, including diseases of women of reproductive age in general, and pathology of the hemocoagulation system in particular. This is what was paid attention to in the literature review - the issue of etiology, pathogenesis of thrombophilia - a pathological condition that is considered one of the leading in terms of chronic miscarriage, the development of obstetric and gynecological bleeding, and failures of artificial assisted fertilization.
2. According to the tasks of the work, simultaneously with standard biochemical studies of the level of thyroid hormones, anti-Müllerian hormone, sex hormones, in the complex of reproductive status assessment, studies of blood coagulation properties - thromboelastography, hemostasiogram were conducted and compared. To achieve the productivity and effectiveness of artificial reproductive methods, the level of antithrombin, D-dimer, fibrinogen, thrombin time, prothrombin test, and activated partial thromboplastin time.
3. After the established changes in the hemostasis indicators, antiplatelet (acetylsalicylic acid in low doses), anticoagulant (Clexane), antierythrocyte (pentoxifylline in low doses), anti-inflammatory (methylprednisolone in low doses in the presence of IgM antibodies as an autoimmune marker) therapy was used for pharmacological correction. This improved the level of pre-pregnancy preparation, and in the future, the results of assisted reproductive technologies.
4. The results obtained coincide with the studies conducted in Ukraine and Morocco, which confirms the identity of the problems and the means of their diagnosis and correction.

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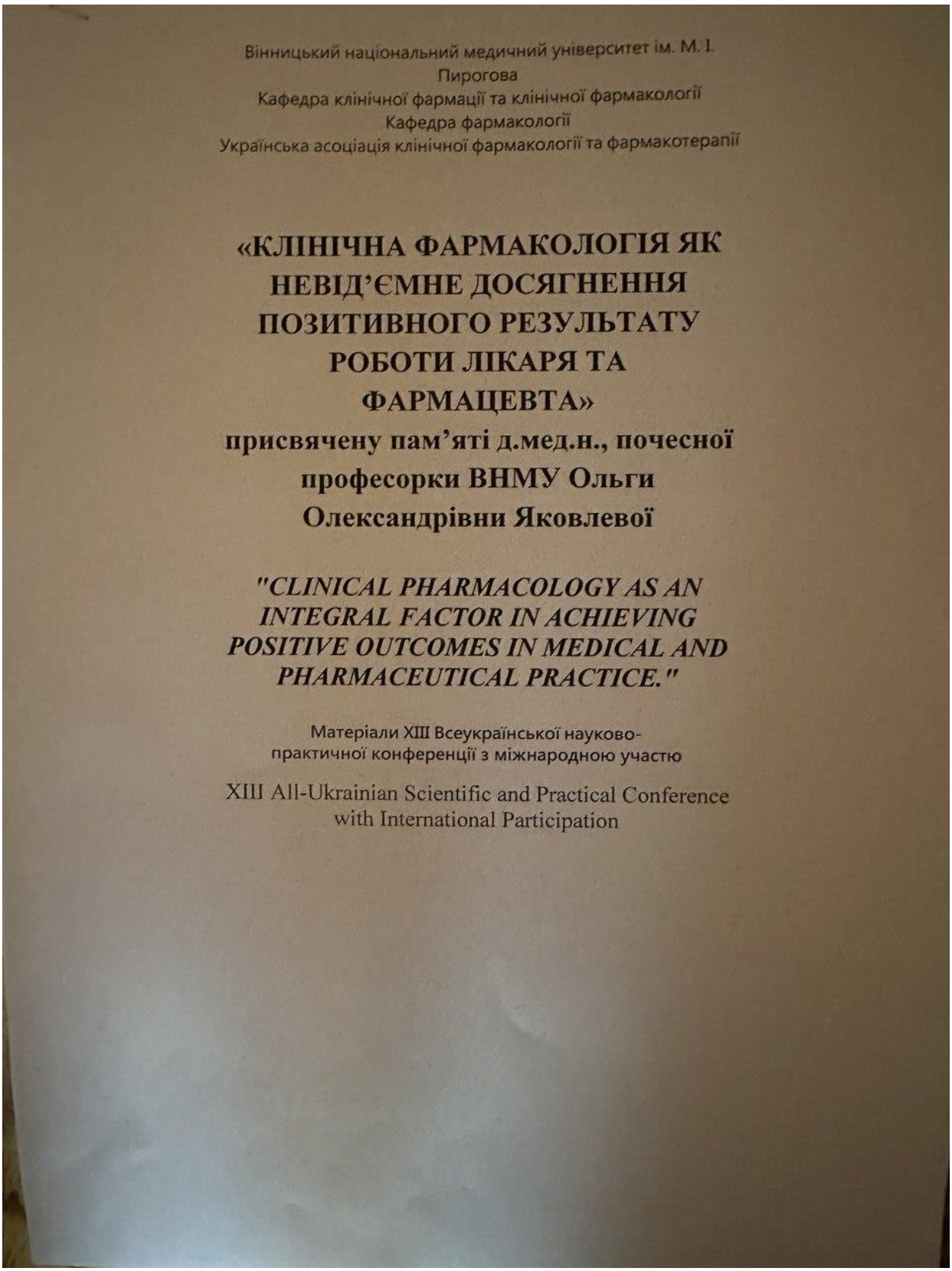
Appendices



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«КЛІНІЧНА ФАРМАКОЛОГІЯ ЯК НЕВІД'ЄМНЕ ДОСЯГНЕННЯ ПОЗИТИВНОГО РЕЗУЛЬТАТУ РОБОТИ ЛІКАРЯ ТА ФАРМАЦЕВТА»

присвячену пам'яті д.мед.н., почесної професорки ВНМУ Ольги Олександрівни Яковлевої

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Вінниця

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ДИФЕРЕНЦІЙНИЙ АНАЛІЗ ЛАБОРАТОРНОГО ДОСЛІДЖЕННЯ ЗГОРТАННЯ КРОВІ ПРИ ДОПОМІЖНИХ РЕПРОДУКТИВНИХ ТЕХНОЛОГІЯХ

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Актуальність. Демографічна ситуація в Україні, як і в усьому світі має негативну тенденцію і супроводжується зниженням результативності природного запліднення, розповсюдженням жіночого чоловічого безпліддя, наявністю захворювань статевої системи у жінок, які потребують відповідної діагностики і лікування. Серед патологічних проблем, які можуть обмежувати ефективність природних циклів запліднення, які можуть зменшувати результативність допоміжних репродуктивних технологій, виділяють порушення в системі про-антикоагуляція, наявність вроджених або набутих станів, які характеризуються тромбоутворенням і тромбоемболією з одного боку, або схильністю до кровотечі з іншого. Саме на визначенні цих змін, а в подальшому на персоніфікованому їх лікуванні були зосереджені наші дії, представлені в роботі.

Мета дослідження. Основною метою роботи було дослідження ролі специфічних лабораторних методів в діагностиці процесів коагуляції, диференційна оцінка їх цінності та використання отриманих результатів в подальшому виборі відповідної корегуючої фармакотерапії та оцінки ефективності та безпеки репродуктивних допоміжних технологій.

Матеріали і методи. В умовах багатопрофільної лабораторної мережі з використанням відповідних біохімічних аналізаторів і діагностикумів проводились біохімічні комплексні дослідження системи згортання крові (коагулограма, тромбоеластограма, гемостазіограма). Забір венозної крові відбувався з урахуванням певних правил підготовки для зменшення впливу зовнішніх і внутренніх факторів на подальші результати: здавати кров натщесерце; за 6-12 годин до здачі необхідно уникати їжі, алкоголю, куріння та обмежити фізичну активність; дозволено пити негазовану воду; не приймати жодних ліків. Дослідження проводились у жінок із не виношуванням вагітності, при попередніх невдалих спробах екстракорпорального запліднення (ЕКЗ) на базі спеціалізованої медичної клініки репродуктивного здоров'я.

Результати. Гемостазіограма – це комплексне багатокомпонентне дослідження, яке дозволяє об'єктивно оцінити стан системи згортання крові. Гемостазіограма є більш інформативною, ніж коагулограма, оскільки включає оцінку D-димеру як індикатора тромбозу та антитромбіну як речовини, що забезпечує нормальну функцію гепарину. Ще одним відомим тестом для вимірювання властивостей згортання крові є тромбоеластографія, але останнім часом гемостазіограма стала частіше використовуватися в

репродуктивній медицині. Гемостазіограма – це комплексний аналіз окремих компонентів системи згортання крові, тоді як тромбоеластограма – це функціональне дослідження всього процесу утворення тромбу. Гемостазіограма оцінює окремі параметри (наприклад, час згортання, рівень фібриногену), тоді як тромбоеластограма показує утворення тромбу та його міцність на графіку, що дозволяє динамічно оцінювати функцію системи гемостазу. Враховуючи існуючі теоретичні дані, саме аналіз згортання крові використовувався для оцінки його стану, підбора відповідних ліків для нормалізації лабораторних показників і, як наслідок, покращення результатів ЕКЗ. Патогенез порушень гемостазу при проблемах з вагітністю, заплідненням, фізіологічним гестаційним перебігом, при тромбофілії, сучасна фармакотерапія та фармакопрофілактика наявних гіпер- або гіпокоагуляційних змін дозволили виділити групи препаратів та безпосередньо препарати вибору: антикоагулянти прямої дії – аналоги низькомолекулярного гепарину (еноксапарин (Клексан)), природні аналоги гепарину (гепарин), антитромбоцитарні антиагреганти – інгібітори циклооксигенази-1 (ацетилсаліцилова кислота (аспірин-кардіо)), антиеритроцитарні антиагреганти, похідні метилксантину з міотропною вазодилататорною активністю – пентоксифілін (Трентал), ефективність яких в подальшому піддавалась ретроспективному аналізу. Слід зазначити певну перспективу визначених схем корекції стану гемостазу, яка виражалась в підвищенні ефективності методів ЕКЗ на 3-5 %, що в абсолютному відношенні має гарний результат.

Висновки. Таким чином, різні лабораторні та інструментальні додаткові дослідження в репродуктивній медицині дозволяють виявити наявні порушення в організмі жінки взагалі, та порушення системи гемостазу зокрема, що в подальшому підвищує результативність різних методів ЕКЗ, забезпечує ефективне та безпечне застосування необхідних лікарських засобів для індивідуалізованої фармакотерапії.