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OBSTETRIC BLEEDING DURING PREMATURE BIRTH

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LIST OF SYMBOLS

AFS	-	Antiphospholipid syndrome
WHO	-	world health organization
NB	-	natural childbirth
BMI	-	body mass index
ELISA	-	enzyme-linked immunosorbent assay
CS	-	C-section
AMF	-	amniotic fluid
PBL	-	pathological blood loss
PB	-	premature birth
PRH	-	Postpartum hemorrhage
PPA		premature placental abruption
SIRSSPMCMCH	-	State institution "Republican Specialized Scientific and Practical Medical Centre for Maternal and Child Health
FGRS	-	Fetal growth restriction syndrome
SR	-	urgent birth
PE	-	preeclampsia
FPN	-	fetoplacental insufficiency
TPB	-	threatened premature birth
APHOO		Postpartum Bleeding of Unknown Origin(Antepartum Hemorrhage Of Unknown Origin)
NO	-	Nitric oxide
sICAM	-	cell adhesion molecule
sVCAM	-	vascular endothelial adhesion molecule
p53	-	Apoptosis protein regulating cell cycle

INTRODUCTION

Premature birth (PB) remains one of the most pressing problems of modern obstetrics. The frequency of PB in the world ranges from about 5% in some European countries to 18% [70, p.27;]. According to the literature, obstetric bleeding complicates 3-10% of births, whereas bleeding among premature births accounts for 5 to 8%. According to WHO, there are 14,000,000 obstetric hemorrhages per year in the world, of which 120,000-140,000 are fatal and 2,000,000 cases result in maternal morbidity [62, p.53;].

According to modern literature databases, there are no multicenter studies to assess the features of pathological blood loss during premature birth, which means the relevance of this study. A change in the hemostasis system is one of the leading factors in the development of pregnancy complications, accompanied by obstetric bleeding and premature birth[1]. Early detection of hemostatic disorders and adequate therapy can help prevent the development of pathological processes and reduce the risk of premature birth. In this regard, the study of the pathogenetic mechanisms of endothelial dysfunction in the context of the development of obstetric bleeding during premature birth is an urgent area of modern obstetric science. Based on the results obtained, it will be possible to develop more effective methods of prevention and treatment of these complications, which will reduce

maternal and child morbidity and mortality, as well as improve the quality of life of women during pregnancy and in the postpartum period.

Currently, preventive measures aimed at reducing obstetric bleeding are being carried out in our country. Along with this, there are a number of unresolved problems in the healthcare system, among which the most important are the prognosis and prevention of obstetric complications in premature births.

[1] Ruzieva N.Kh., Djabbarova L.A., Dj abbarova Yu.K. Causes and ways to reduce preterm birth using international approaches // Re-Health Journal. 2021. No. 1 (9). P. 14-18.

and prevention of obstetric complications in premature births. Comprehensive measures to radically improve the healthcare system will be implemented in the following areas: "... expanding access to quality medical care for mother and child, providing specialized and high-tech medical care and
reducing infant and child mortality." Based on this, it is important to study the causes of premature birth in women, it is relevant to conduct research aimed at improving the quality of life and improving perinatal outcomes, which served as a reason for searching for additional early informative biomarkers of pathological blood loss in premature births and developing principles of early prognosis and prevention of this pathology.

PREMATURE BIRTH AND PATHOLOGICAL BLOOD LOSS: RISK FACTORS, PREDICTION AND PREVENTION

Modern ideas about pathological blood loss during premature birth.

Preterm labor is undoubtedly one of the most urgent and serious problems worldwide. This phenomenon is of great concern to both medical professionals and expectant parents, as it is associated with many risks and complications for both the pregnant woman and the fetus. The incidence of PB in the world ranges from about 5% in some European countries to 18% [9, p.148; 47, p.11; 148, p.46].

According to the literature, obstetric hemorrhages is unfortunately very common in the world before delivery. It is worth noting, however, that the incidence of bleeding in preterm labor varies within a few per cent. These figures emphasis the importance of close monitoring and timely intervention in case of such situations to ensure the safety of both mother and newborn [139, p. 63].

As reflected in the literature, among complications occurring during pregnancy, postpartum hemorrhage (PPH) is the most serious complication and the most critical cause of complications during pregnancy and childbirth. PPH is a multifaceted condition that can result from multiple factors, including uterine atony, retained placenta or membranes, soft tissue trauma of the birth canal, coagulopathy, and uterine inversion [64, p.74;]. Accurate diagnosis of the underlying cause of PPH is essential to implement appropriate treatment strategies and improve patient outcomes. In addition, identification of high-risk features, such as previous PPH, multiple pregnancy, and certain comorbidities, can help in the prevention and timely treatment of PPH. Despite ongoing efforts to reduce the incidence of PPH through preventive measures such as administration of uterotonics and active management of the third stage of labor, PPH remains a significant contributor to maternal morbidity and mortality worldwide [1, p.338; 13, p.45; 43, p.26;].

PPH can cause severe anaemia, acute respiratory distress syndrome (ARDS), acute renal failure (ARF), coma and cardiac arrest. Uterine atony, retained placental

In developing countries, PPH is one of the leading causes of maternal mortality, accounting for 25–43% of maternal deaths (WHO, 2018) [157, p. 53; 160;].

According to the World Health Organization (WHO), approximately 295,000 women died during pregnancy or after childbirth in 2017 [160]. The vast majority of these deaths (94%) occurred in low-resource settings, and most were preventable. Most maternal complications develop during pregnancy, and many are preventable or treatable. Complications such as maternal obesity, curettage during a previous pregnancy, hypertensive disorders, hemoglobin (Hb) levels less than or equal to 10 g/dL may exist prior to pregnancy and may create problems during pregnancy leading to PPH, especially if not treated as part of the woman's antenatal care. The definition of primary postpartum hemorrhage (PPH) as a major cause of maternal mortality and severe morbidity has evolved over time to help identify tissue, soft tissue trauma to the birth canal, coagulation problems and uterine rupture are the most common causes of PPH [36, p. 3-8;].

pregnant women most susceptible to this complication and therefore take timely appropriate measures [157, p.53; 160;]. Despite advances in obstetric care, women with early preterm labor remain at high risk for operative delivery and involuntary obstetric hysterectomy. The severity of this population is reflected in the frequency of these procedures over the years. According to a 2019 study by the Centers for Disease Control and Prevention (CDC), the cesarean section rate for preterm births was 56.7%. This rate was higher than the 31.9% rate for full-term births. Additionally, a review of studies conducted between 1985 and 2013 found that the rate of obstetric hysterectomy in women delivering preterm ranged from 0.12% to 0.48%. This was significantly higher than the hysterectomy rate in women delivering at term, which was 0.04%. The high rate of these procedures highlights the need for improved strategies to prevent and manage preterm birth [143, p.247;].

Preterm birth is the leading cause of neonatal death, accounting for approximately 1 million deaths annually. In addition, children who survive preterm birth are at increased risk of a number of long-term health problems, including developmental delays, cerebral palsy, and chronic lung disease. Effective strategies for the prevention and management of preterm birth are critical to improving the health of not only mothers but also newborns [14, p. 90; 52, p. 103;] According to Rostov scientists (Galushchenko E.M. et al., 2020), women with placental attachment anomalies typically lose 3,000 to 5,000 ml of blood. Placenta previa and accreta increase the risk of major bleeding followed by hysterectomy by up to 51%. The number of abnormal placentation increases by 15.6% annually. The number of cesarean sections is growing every year, and the risk of this complication is increasing accordingly. In addition, the study showed that women with a history of cesarean section have an increased risk of placental abnormalities

According to the Lancet (2021), miscarriage is generally defined as the loss of a non-viable pregnancy. An estimated 23 million miscarriages occur worldwide each year, resulting in 44 pregnancy losses every minute. The pooled risk of miscarriage is 15 3% (95% CI 12 5–18 7%) of all recognized pregnancies. The population prevalence of women experiencing one miscarriage is 10 8% (10 3–11 4%), two miscarriages is 1 9% (1 8–2 1%), and three or more miscarriages is 0 7% (0 5–0 8%). Risk factors for miscarriage include being very young or old in women (under 20 and over 35), older in men (over 40), having a very low or very high body mass index, being black, having had previous miscarriages, smoking, drinking, stress, working night shifts, air pollution, and pesticide exposure. The consequences of miscarriage are both physical, such as bleeding or infection, and psychological. Psychological consequences include an increased risk of anxiety, depression, post-traumatic stress disorder, and suicide [93, p. 1658; 97, p. 2162].

thromboembolism [7; 17, p. 22; 73, p. 74; 93, p. 1658;].

According to Harrison MS, et al. (2021), mothers who had prolonged labor had a 5-fold higher chance of postpartum hemorrhage than those with normal labor duration [119, p. 62;]. A similar conclusion was reached from studies conducted in

China (Liu C-N, Yu F-B, Xu Y-Z 2021), Pakistan (Gani N, Ali TS. 2013) and Cameroon (Halle-Ekane GE, Emade FK 2015). This may be due to the fact that prolonged labor causes uterine atony, which is a leading cause of postpartum hemorrhage. This meta-analysis also showed that the likelihood of developing postpartum hemorrhage among mothers who did not have antenatal care was 9 times higher than those who attended [133, p.1-8; 113, pp.81-85; 118, pp.1-12;]. According to the American College of Obstetricians and Gynecologists, PPH results in cumulative blood loss ≥ 1000 mL or is characterized by symptoms of hypovolemia associated with blood loss within 24 hours after vaginal delivery or cesarean section. First-line treatment for PPH includes pharmacologic measures, intrauterine tamponade, uterine artery ligation, and uterine compression sutures. Uterine artery embolization (UAE) is performed in women with refractory severe PPH [134, p. 363;]. There are additional important secondary consequences of bleeding, which include adult respiratory distress syndrome, shock, disseminated

intravascular coagulation, acute renal failure, infertility, and pituitary necrosis (Sheehan's syndrome). Bleeding that results in the need for blood transfusion is the leading cause of severe maternal morbidity in the United States, followed by disseminated intravascular coagulation. In the United States, the incidence of postpartum hemorrhage increased by 26% between 1994 and 2006, largely due to increases in atony rates. In contrast, maternal mortality from postpartum obstetric hemorrhage has declined since the late 1980s and accounted for just over 10% of maternal mortality (approximately 1.7 deaths per 100,000 live births) in 2009 [99, p. 162; 108, p. 1016; 144, pp. 100-125;].

Thus, the problem of preterm labor requires adequate attention to prevent complications such as hemorrhage, which may have serious consequences.

High risk factors for bleeding in women with preterm labor

The first component of the medical gizmo is the analysis of the course of pathology, which should be provided for before, during and after delivery. This should be done in order to prevent in time anything related to mortality and the course of pregnancy. Thus, a study of interest in these aspects can improve the results as well as the initial reliability [55, p.54;].

Improved strategies for the prevention and management of preterm labor, as well as early detection of abnormal placental attachment, can help reduce the incidence of hemorrhage and associated complications. In addition, measures such as timely administration of uterotonics, active management of the third stage of labor, and judicious use of blood transfusion can help prevent severe maternal morbidity and mortality due to postpartum hemorrhage.

Bazirete O, Nzayirambaho M, Umubyeyi A (2022) Uterine atony remains the leading cause of primary PPH. Large-scale studies are needed to further study potential risk factors for PPH [94; 95, p.678;].

Kljakić D, Milosavljević MZ, Jovanović M. (2020) argue that placental bacterial infection as the first cause of preterm labor and fetal death, when there are

many of them, lead to lung pathology followed by poly organ failure [128, pp. 81-86;].

Infections result in chorioamnionitis and intra-amniotic infection syndrome, which leads to premature placental abruption and spontaneous miscarriage or premature birth.

Russian authors (Kravchenko Yu.D. et al. 2018) analyze the etiological risk factors for massive obstetric hemorrhage. During the study, the scientists mentioned that acute massive blood loss corresponds to one of the risk factors that can be seen in postpartum uterine cartilage tumor and also in the fact that the risk of occurrence after any surgical interventions is very high. Researchers have mentioned and praised these findings in their research [46, pp. 10-11;].

Zaugstad Ola Diedrik (2012), On the other hand, the importance of timely and adequate treatment of hemorrhage is emphasised to prevent severe morbidity and mortality in the pregnant woman. These include measures such as active management of the third stage of labor, use of uterotonics, and prompt recognition and treatment of PPH. Additionally, Zaugstad Ola Diedrik highlights the potential role of new treatments such as recombinant factor VII a and tranexamic acid in the treatment of PPH. He notes that although these treatments appear promising, more research is needed to fully understand their safety and effectiveness in the context of PPH [37, p.190;].

Serova O.F., Sedaya L.V. et al (2018): the placenta accretes in cases where pregnancy occurs in women with a uterine scar, with implantation in the area of the scar after CS. The study highlights a significant risk factor for placenta accreta in pregnancies with implantation in a scarred area following a previous cesarean section. Placenta accreta is a serious complication in which the placenta attaches too deeply to the wall of the uterus and can lead to heavy bleeding during labor. On the other hand, the importance of timely and adequate treatment of haemorrhage is emphasised to prevent severe morbidity and mortality in the pregnant woman. [76, p.28;].

According to the literature, obstetric haemorrhages is unfortunately very common in the world before delivery. It is worth noting, however, that the incidence of bleeding in preterm labour varies within a few per cent. These figures emphasise the importance of close monitoring and timely intervention in case of such situations to ensure the safety of both mother and newborn [139, p. 63].

If placenta previa is suspected or diagnosed, a team of different specialists may be involved in the organisation and management of the birth. This team includes obstetricians, experts in maternal-fetal medicine, as well as anaesthetists and blood bank staff. Depending on the situation, possible treatment approaches may include a planned caesarean section. In this case, the uterus is removed along with the placenta to avoid the risk of significant blood loss [84, p.253;].

Markers of endothelial function and trigger mechanisms leading to pathological blood loss

In the international literature, as well as lines of analyses, endothelial disorder is considered equally as a quasi-condition of midwifery and perinatal pathogenesis: early termination of pregnancy, preeclampsia, fetoplacental insufficiency, as well as the syndrome of increase and suspension of fruit enlargement [6, pp.62-71; 8, pp. 386-390;]. The importance of the endothelium in the creation of fetoplacental pathology, as well as the study of venous pathology in premature pregnancy, are currently one of the more promising difficulties in obstetrics. During the study, the scientists mentioned that acute massive blood loss corresponds to one of the risk factors that can be seen in postpartum uterine cartilage tumour and also in the fact that the risk of occurrence after any surgical interventions is very high. Researchers have mentioned and praised these findings in their research [56, p. 18;].

Physiological features of the female reproductive system create prerequisites for increasing the procoagulant potential of the blood in order to implement key moments of its functioning: ovulation, implantation, pregnancy, childbirth. In some situations, the balance of procoagulant and anticoagulant factors can be disrupted and lead to negative consequences due to the development of thrombosis. Blood is maintained in a liquid state due to the action of several factors. Endothelial cells have a negative charge and contain proteins on their surface that have an anticoagulant effect, and a constant blood flow does not allow a clot to form due to purely mechanical reasons. Therefore, the cause of thrombus formation can be a vascular injury; a change in blood rheology; a slowdown in the blood flow velocity [60, p. 600; 61;].

In the context of these physiological or pathophysiological causes, the importance of the problem of thrombus formation in women becomes obvious. Vascular injury is a natural event of key stages of the reproductive process. Changes in the rheological properties of blood are a consequence of increased synthesis and secretion of estrogens. Slowing of the blood flow rate is an inevitable result of external, lifestyle-related, and endogenous, homeostasis-related causes. Pregnancy virtually erases the line between the physiological and pathophysiological state of blood clotting [8, p. 386; 31, p. 37;] Implantation, trophoblast invasion, development and functioning of the placenta are processes of complex endothelial-hemostasis interaction with multilevel regulation, requiring the restructuring of blood clotting to ensure a cascade of inflammatory reactions that are inevitable in response to damage to maternal tissues. By the time of delivery, the hemostasis system must be ready to quickly stop the bleeding that occurs as a result of placental rejection. For this purpose, during physiological pregnancy, the procoagulant potential begins to increase, and this process continues until delivery [111, p. 7960;].

The microcirculatory bed is a system of small vessels that include arterioles, venules, capillaries and arteriole-venule anastomoses, forming a complex morpho-

physiological complex. They play an important role in the human body, providing tissues with the necessary volume of blood supply and nutrition [106, p. 233;].

One of the main mechanisms of endothelial cell damage is apoptosis - programmed cell death. Anuclear cells are endotheliocytes that have already "died", their nuclei are destroyed, mitosis has ceased. It is important to note that damage to endothelial cells can lead to serious diseases, such as cardiovascular diseases and diabetic retinopathy [11, pp. 214-217;]. The endothelium plays an important role in the body's immune defense by secreting many factors such as angiotensin II, nitric oxide, the endothelial monooxygenase pathway, and factors that regulate blood coagulation. These factors influence the behavior of nearby cells and can trigger inflammatory responses. Not surprisingly, endothelial dysfunction has been associated with diseases such as atherosclerosis, hypertension, Crohn's disease, vascular dementia, and many others. Overall, the endothelium is a critical player in vascular biology and has been the focus of research efforts to understand its role in health and disease [61; 106, p. 233; 112, p. 272;].

Endothelial cell mechanoreceptors are specialized receptors that can respond to physical forces acting on endothelial cells, the cells that form the inner lining of the vascular wall. When endothelial cells experience pressure or tension, mechanoreceptors respond to these changes and transmit information to the nervous system [60, p. 600; 61;].

The three main physical forces that endothelial cell mechanoreceptors respond to are:

1) shear stress is a force that acts on the vessel wall in a direction perpendicular to its axis. For example, when blood flows through a vessel at a speed, a shear occurs that acts on the endothelium. Endothelial cell mechanoreceptors respond to this stress and transmit information to the nervous system;

2) lateral pressure on the vessel wall is a force that acts on the vessel wall in a direction parallel to its axis. When the vessel expands or contracts, the lateral pressure can change. Endothelial cell mechanoreceptors respond to this pressure and transmit information to the nervous system;

3) circumferential stretch between endothelial cells is a force that acts on the endothelium when the vessel wall is stretched or compressed. The mechanoreceptors of endothelial cells react to this stretching and transmit information to the nervous system [115, p.49].

All these physical forces can cause a reaction of the mechanoreceptors of endothelial cells, which transmit information about the state of the vessel wall to the nervous system. This helps to regulate blood pressure and ensure normal blood circulation in the body.

1. Shear stress is the most significant mechanical effect on the vessel walls, which stimulates the release of vasoactive substances [92, pp. 155-164;].

The active substances synthesized by the endothelium are divided into several groups according to their function. However, the main role of the endothelial apparatus is to regulate vascular tone. To do this, the endothelium produces mediators that can be both vasodilators and vasoconstrictors. This mechanism is able to maintain vascular tone and adapt to various environmental conditions. It is important to note that the endothelium also has the ability to produce antagonist mediators, making it a unique organ in the body. Endothelial cells create nitric oxide and prostacyclin to dilate blood vessels. Nitric oxide is synthesized by the enzyme NO synthase. Its action is short-term and leads to vasodilation through the activation of cyclic guanosine monophosphate (cGMP), opening channels and influencing coagulation and cellular immunity.

2. Prostacyclin is a highly active metabolite of arachidonic acid, which is synthesized in the endothelium, activates adenate cyclase and causes vasodilation, and also prevents platelet aggregation. Vasodilators are normally synthesized in the endothelium to maintain the basal level of vascular tone. Vasoconstrictors are normally produced in small amounts, and an increase in their production may indicate endothelial dysfunction [22, p. 19; 34, p. 210; 111, p. 7690;].

Endothelin is a potent vasoconstrictor mediator produced by the endothelium and vascular smooth muscles. It is also a mitogenic factor for some cells. In the blood, endothelin causes vasoconstriction, but its physiological concentrations can

cause vascular relaxation. In addition, endothelin-1 plays an important role in the regulation of calcium and hemostasis in the blood. The vascular intima plays an important role in hemostasis. Von Willebrand factor, plasminogen activator, platelet-derived growth factor, endothelin, and angiotensin are prothrombogenic substances produced by endothelial cells that regulate platelet adhesion to damaged vessels. These substances are activated by damage or stimulation of endothelial cells and platelets. In clinical situations associated with vascular damage or platelet activation, the concentration and activity of these substances may increase [79, p. 60;].

1. PAI-1 is a tissue plasminogen activator inhibitor produced by many cells, including platelets. It prevents premature fibrin lysis. Endothelial cells produce athrombogenic substances, such as nitric oxide, tissue plasminogen activator (tPA), and prostacyclin, which prevent thrombus formation. [112, p. 272-276;].

2. VEGF is the main inducer of angiogenesis. It affects the expression of many factors.

3. TNF is a proinflammatory cytokine that affects the endothelium, lipid metabolism, and coagulation [62, p. 42;]. When exposed to foreign antigens, TNF stimulates the production of IL-1, IL-6, and IL-8. Interleukins activate immune cells, enhance chemotaxis, and act as growth factors [115, p. 49-55;].

The endothelial system secretes NO as the main inhibitor of inflammation. There are basal and stimulated levels of secretion of active substances, including von Willebrand factor, plasminogen activator (tPA), endothelin-1, tumor necrosis factor and interleukins, which can cause endothelial damage and lead to endothelial dysfunction.

4. The endothelial apparatus is a complex system that includes endothelial cells, proteins, enzymes, cell communication molecules and other elements. This is the system responsible for regulating blood flow, controlling the level of metabolic products and gases in the blood and ensuring vascular homeostasis. Under the influence of various internal and external factors, changes in the structure and functions of the endothelial apparatus can occur [22, p. 19;].

This is how endothelial dysfunction develops, which is the cause of many pathological processes in the circulatory system. Endothelial dysfunction can be caused by factors such as atherosclerosis, hypertension, diabetes, inflammatory processes, as well as smoking, alcohol abuse and stress. When endothelial cells begin to function incorrectly, this leads to disturbances in blood flow, the risk of blood clots and damage to the vessel walls [74, p. 14;].

Studying the mechanisms of endothelial dysfunction and endothelial dysfunction development is an important area of prevention and treatment of various pathologies associated with vascular damage. For example, understanding the mechanisms of endothelial dysfunction can help in choosing the best therapy for patients with cardiovascular pathology, such as coronary heart disease and hypertension. In addition, these studies can help determine the most effective strategies for the prevention and treatment of vascular pathologies [87, p. 410;]. To study endothelial dysfunction, it is necessary to understand the mechanisms of its occurrence, which are associated with impaired vascular homeostasis. Endothelial cells have receptors on the membrane surface that respond to chemical and physical damage, leading to secretory activity of the endothelial apparatus. Constant exposure of endothelial cells to agents depletes the production of vasodilatory mediators, which leads to endothelial dysfunction. This condition is characterized by an imbalance of mediators and a disruption of endothelium-dependent processes, as well as a decrease in the ability of endothelial cells to adapt to altered conditions. Endothelial dysfunction can cause intimal destruction and vascular deendothelialization, which increases vasospasm and hypoxia. This dysfunction can also be associated with multiple organ dysfunction and systemic disorders [60, p. 610; 61;].

Factors that activate the endothelium: impaired blood flow velocity, hypoxia and oxidative stress, atherosclerosis, hyperhomocysteinemia, antibodies to phospholipids, inflammatory mediators, viral and bacterial infections. The genetic factor also plays a role. Hormonal fluctuations also affect the functioning of the endothelial apparatus. It is important to suppress the expression of endothelial nitric

oxide synthase and reduce chemoreceptors on the intimal surface [112, pp. 272-276;].

A shift in blood flow voltage in the vessels activates the production of the main vasodilator, NO, which increases blood flow velocity and causes vasodilation. Associated diseases associated with endothelial dysfunction can lead to thickening of the vascular walls and an increase in vascular resistance. Oxidized low-density lipoproteins can stimulate apoptosis of endothelial cells and reduce anti-apoptotic proteins, which leads to vascular deendothelialization and other negative consequences [105, p. 117; 106, p. 235;].

In addition, various risk factors such as smoking, excessive alcohol consumption, diabetes mellitus, hyperlipidemia and others can lead to an increase in the level of oxidative stress and inflammation in the body, which also contributes to the development of endothelial dysfunction. In response to damage caused by these risk factors, endothelial cells can become activated and begin to produce more inflammatory cytokines, which leads to a further increase in inflammatory and oxidative processes. In pregnancy-related endothelial disorders, changes in vascular responses and concentrations of endothelial factors such as NO, endothelin-1, VEGF, and PlGF play a role. Increases in the concentration of thrombotic endothelial factors, including von Willebrand factor and PAI-1, as well as TF, thromboxane, fibronectin, and thrombomodulin are also noted. Moderate activation of blood coagulation during pregnancy is necessary to prevent bleeding. Sufficient levels of procoagulant factors are important to protect against inappropriate trophoblast invasion. Pregnancy-related changes in coagulation factor secretion and vascular regulation may lead to functional vascular disorders [31, p. 37-42;].

The literature describes three stages of altered endothelial function in pregnant women depending on the level of vascular mediator production. The first two stages are physiological adaptation of the vascular system to gestational changes. At the stimulation stage, there is an increase in the production of vasodilatory mediators, such as nitric oxide and prostacyclin. At the activation stage, there is an increase in the synthesis of mediators capable of constricting blood vessels, such as endothelin-

1 and thromboxane A2. These changes allow the body to adapt to changes in metabolism and the needs of the fetus. However, at the third stage - the stage of decompensation or endothelial dysfunction, the compensatory mechanism is disrupted and changes occur that lead to multiple organ dysfunction and the clinical picture of gestational complications. [68, p. 28;] Changes in placental blood flow lead to tissue hypoxia and vascular damage, which increases vascular pathology in complicated pregnancy. Spontaneous abortion is accompanied by a decrease in NO concentration and an increase in the concentration of the vasoconstrictor endothelin-1 in the blood. Threatened spontaneous abortion causes an increase in the expression of VEGF and TNF-α. Thrombin deposition during hemorrhages provokes a violation of vasculo- and angiogenesis, remodeling of blood vessels and endothelium, causing gestational complications. PECAM-1 plays an important role in the trigger of intravascular cytotrophoblast invasion, which can lead to spontaneous abortion in early pregnancy [24; 63, p. 77; 140, p. 610;]. In pregnant women with urogenital infection and a threat of termination of pregnancy, there is a discrepancy between the growth and development of immune cells, which can lead to health problems for the mother and child. Some gestational complications may be associated with increased apoptosis and endothelial cell dysfunction, which may lead to placental insufficiency and other problems. Some factors may help regulate angiogenesis during pregnancy, which may improve the pregnancy and the health of the baby.

In PE, the concentration of nitric oxide degradation products decreases, which is a prognostic factor for the development of the disease [12, p. 27;].

The destruction of the endothelium and the appearance of areas of reendothelialization in the vessels of pregnant women with preeclampsia create conditions for neurohormones, changes in hemostatic properties and activation of the endothelium. This causes the production of cytokines that contribute to the development of PE, as well as inflammatory mediators that can lead to vasculopathy. Disruption of the processes of invasion and angiogenesis in the trophoblast also contributes to the development of PE.

These processes disrupt the functioning of the endothelial apparatus and affect microcirculation. After childbirth, the level of HC remains high for up to 7 days, and the level of desquamated endothelial cells is increased for up to 40 days [34, p. 210-214;].

Apoptosis affects the formation of the placenta, increasing the risk of pregnancy pathology. Impaired NO bioavailability and increased ET-1 and VEGF concentrations are associated with the risk of IUGR.

Endothelial dysfunction is a pathological condition in which endothelial cells do not perform their functions properly. Endothelial cells are an important component of the inner lining of blood vessels, which ensure normal blood circulation in the body. Their dysfunction can lead to various diseases, such as atherosclerosis, hypertension, heart disease and vascular disease, as well as complicate pregnancy or contribute to the development of other complications in obstetrics and perinatology [18, p. 145-150; 60, p. 610;].

Assessing the function of the microcirculatory bed and identifying disorders in the endothelium are important tasks, the solution of which can reduce the overall morbidity in the population. For this purpose, new diagnostic markers are being developed that allow for rapid and accurate determination of disorders in the endothelium [17, pp. 22-29;]. Functional diagnostics is based on measuring blood flow parameters and vascular tone using specialized methods such as cellular technologies, echocardiography, plethysmography, laser Doppler flowmetry, and others.

Such methods provide a detailed picture of the state of microcirculation in tissues and identify disorders in endothelial function. Biochemical diagnostics is based on detecting markers of endothelial dysfunction in biological fluids (blood, urine, and others). For example, angiotensin, which has a vasoconstrictor effect and may indicate a disorder in the endothelium, can be detected in the blood.

Cytological diagnostics allows you to examine endothelial cells, which are the main cells that ensure the functioning of microcirculation. Circulating desquamated endothelial cells may indicate disorders in the endothelium. All these methods have their advantages and disadvantages, and determining their effectiveness depends on the specific situation and indications for diagnostics. Endothelial dysfunction causes problems in microcirculation. There are many instrumental methods for detecting such vascular disorders, such as computer capillaroscopy. They are used in the diagnosis of diabetes mellitus, atherosclerosis, arterial hypertension and other pathologies [18, p.145;].

The effects of factors that increase blood flow, such as stress, papaverine or acetylcholine injections, and atrial stimulation are studied. Invasive methods are used to assess endothelial function, including coronary artery catheterization and angiography. Changes in vessel diameter, blood flow velocity and volume in the area of study are assessed [149, p.81-89;].

Thus, the study of the functional activity of the endothelium is important for the diagnosis and prognosis of various diseases associated with vascular dysfunction. However, existing methods have their limitations associated with expensive equipment, complexity and labor intensity, and limitations in use in obstetrics. Also, physiological changes occurring in the vascular system of pregnant women require special consideration when interpreting the results of the study. However, the development of new technologies and methods may lead to more accurate and accessible diagnostics of the functional activity of the endothelium in the future.

A marker of endothelial dysfunction is nitric oxide, which is synthesized by NOS in the endothelium and promotes vasodilation. Determination of nitric oxide metabolism products (nitrites and/or nitrates) in biological environments is one of the diagnostic methods, but its concentration may depend on other sources of nitrate and nitrite, which reduces the reliability of the method [61, p. 125; 149, p. 81;] Endothelial dysfunction is diagnosed using the concentration of endothelin-1, which is an NO antagonist. High concentrations of ET-1 are observed in ischemic heart

disease, hypertension, after organ transplantation and hemodialysis. However, an increase in this parameter can also be associated with other vascular diseases, which reduces the specificity of the method. Another limitation is that the half-life of ET-1 is about 40 seconds. Modern science studies the function of the endothelium using biochemical methods, but most of them do not reflect the exact state of this apparatus. Evaluation of endothelial dysfunction using markers is difficult due to many reasons, such as instability of the NO molecule, concomitant pathology and changes in physiological conditions. Many synthesized markers are also present in other cells of the body, which reduces their diagnostic value. All the above markers do not provide a direct assessment of the morphofunctional state of the endothelium; their interpretation depends on the concomitant pathology [61, p. 43;].

In this regard, the need to study biochemical markers and easily accessible diagnostic methods for endothelial dysfunction is relevant. The literature provides data on the following dysfunction markers:

Von Willebrand factor (vWF) is a laboratory diagnostic marker that determines blood properties. Its level does not have clear norms and depends on the state of the body. A high level of von Willebrand factor may indicate vascular damage or thrombosis, and a low level - hypothyroidism or systemic lupus erythematosus [43, p. 26;].

Soluble cell adhesion molecules such as sPECAM-1 play an important role in the diagnosis of endothelial dysfunction.

The parameters of the coagulation system are checked for the diagnosis of endothelial dysfunction, including von Willebrand factor, HC, fibronectin, plasminogen activator (tPA), PAI-1, annexin V and thromboxane A2. Determination of the level of LDL and cholesterol is not very informative for assessing endothelial cell damage. In foreign literature, the determination of RNA of damaged endothelial cells is proposed. Inflammatory mediators can also be used as markers of endothelial dysfunction, but the methods for their determination are of scientific interest [112, p. 276;].

Various drugs are used to treat endothelial dysfunction. Their effect is aimed at restoring the functioning of the vascular system, improving vascular tone, reducing coagulation, influencing the cytokine system, etc. However, in obstetrics, the use of drug therapy is limited. Medicines approved for use during pregnancy may not be effective enough in treating endothelial dysfunction.

Introduction of antiplatelet therapy in pregnant women with endothelial dysfunction can reduce the risk of preeclampsia, thrombosis, premature rupture of membranes, and other pregnancy complications [29, p.304;].

Dipyridamole is a drug used to treat endothelial dysfunction in pregnant women. The drug has not only antiplatelet properties, but also angioprotective properties. Dipyridamole stimulates the production of prostacyclin, which is an important factor in improving blood flow and vascular vasodilation, and reduces platelet adhesion to the surface of endothelial cells. In addition, dipyridamole reduces the expression of inflammatory cytokines, which can lead to endothelial dysfunction. The action of dipyridamole is based on its ability to suppress phosphodiesterase activity, which leads to an increase in cAMP and cGMP levels. These substances play an important role in vasodilation under the influence of nitric oxide and prostacyclin [8, pp. 386-390;]. Dipyridamole also increases the level of plasminogen activator (tPA), which activates plasmin and has fibrinolytic properties. The combined effect of the drug on the vascular wall and platelets allows us to consider it as a drug with pathogenetic action in endothelial dysfunction. In addition, dipyridamole has no contraindications for use during pregnancy and can be used at any stage of pregnancy. Thus, it is the drug of choice for the treatment of endothelial dysfunction in pregnant women. Therapy of endothelial dysfunction in pregnant women is a complex task, but modern medicine provides many tools to solve this problem. To treat this condition, drugs are used that have an effect on various links in the pathogenesis of endothelial dysfunction, such as anticoagulants, antiplatelet agents, drugs that affect angiogenesis, etc., [87, p. 410;]. In addition, antioxidants such as vitamins E and C play an important role, improving the condition of endothelial cells by reducing the level of oxidative stress products [149, p. 81;]. It is

necessary to take into account that taking some drugs during pregnancy may be accompanied by negative consequences for the health of the child, therefore the choice of drugs should be made in accordance with their safety and effectiveness. In order to reduce maternal, perinatal and child morbidity, it is necessary to use preventive basic care, not excluding the possibility of pharmacological correction. Thus, further studies of endothelial dysfunction therapy will contribute to the development of more effective and safe methods of prevention and treatment of this condition during pregnancy.

Step-by-step surgical hemostasis is necessary: application of a compression suture according to B-Lynch. High-risk patients should deliver on a planned basis [44, pp. 33-35;].

Prediction and prevention of bleeding in women with preterm labor

Although global efforts are being made to prevent it, obstetric hemorrhage remains a significant risk to the health and lives of mothers and requires the study of more effective measures of prevention and treatment. Bleeding during pregnancy, childbirth and PB continues to be the leading cause of maternal morbidity and mortality worldwide.

Quite often in the practice of obstetrician-gynecologist, bleeding after delivery occurs and is considered as atonic. In developing countries, massive blood loss is dominant in the structure of maternal mortality. There are many conflicting points of view on the genesis of massive obstetric hemorrhage. In modern conditions, organ-preserving technologies have been developed [44, p. 33-35;].

In the structure of obstetric hemorrhage, PPA and atonic hemorrhage dominate. Massive bleeding develops during operative delivery, the presence of a scar on the uterus after CS and pregnancy complications: anemia, large fetus and polyhydramnios. In modern conditions, the introduction of recombinant factor VII is recommended, the effect of which is ahead of the effectiveness of FFP at 30 minutes. Prevention of obstetric hemorrhage in the high-risk group (RCOG, 2009) consists of intraoperative administration of carbetocin in the presence of a uterine scar, placenta previa, placental abruption, large fetus, uterine fibroids [54, p. 210;].

Delivery should be accompanied by intraoperative reinfusion of autohomologous erythrocytes in case of placenta previa and detachment of a normally located placenta, a scar on the uterus and expansion of the scope of surgical intervention, this is the conclusion reached by scientists N.I. Kan, A.S. Lillepeo, N.G. Teterina (2017). The authors conducted a prospective expert analysis of 33 cases of massive obstetric hemorrhage with blood loss of more than 1.5% of body weight in 2016, registered at the maternity hospital of the State Healthcare Institution Central Clinical Medical and Sanitary Department of the City of Ulyanovsk [44, p. 33-35;].

The structure of massive obstetric hemorrhage is represented by placenta previa in 12.1% of cases; PPA- 30.3%, hypotonic bleeding in 51.5% of cases. Each patient had from 2 to 4 extragenital diseases: anemia - 51.5% of women, obesity - 18.2%, gastrointestinal pathology - 18.2%, kidney disease - 15.1%, arterial hypertension - 12.1%.

In 50.0% of pregnant women, the obstetric history is burdened by medical abortions, the presence of a scar on the uterus after a previous cesarean section - 27.3%, gynecological infectious and inflammatory diseases - in 45.4%, cervical pathology - 39.4%, uterine leiomyoma - 6.1% of cases [44, p. 33-35;].

Vaught A.J. (2016) Argued that extragenital diseases and obstetric history factors can significantly increase the risk of obstetric bleeding. Therefore, it is important to carefully monitor and manage these conditions during pregnancy and labor. In addition, health care providers should be trained in the identification and treatment of obstetric hemorrhage, including the use of appropriate interventions such as uterine massage, oxytocin administration, and, when necessary, surgical interventions such as hysterectomy. Implementation of evidence-based protocols and training programs can help improve outcomes for mothers and babies affected by obstetric hemorrhage [153, p.611;].

Romagano MP, Fofah O, Apuzzio JJ (2020) The authors' study aimed to determine whether early preterm birth leads to increased maternal morbidity. Those included were between 23 0/7 and 28 6/7 weeks of gestation and their newborns

were admitted to the neonatal intensive care unit. The prevalence of maternal morbidity, including blood transfusion, infection, placental abruption, postpartum depression, hemorrhage, and prolonged postpartum maternal hospitalization, was assessed. A composite analysis was developed that included blood transfusion, maternal infection, placental abruption, and postpartum depression. Outcomes were compared for women who delivered between 23 0/7 and 25 6/7 weeks of gestation (early group) and 26 0/7 and 28 6/7 weeks of gestation (late group). Multivariate logistic regression analysis was performed to assess factors contributing to cumulative morbidity [144, p. 125;].

The data suggest that maternal morbidity is higher in the former group of deliveries. Cumulative morbidity and maternal infection were more common in women who delivered earlier than 26 weeks of gestation. Management of women at risk for early gestational birth should include discussion of increased maternal complications.

Watad H, Amsalem H. (2020): The aim of the study is to determine whether a single episode of vaginal bleeding occurring between 24 and 34 weeks of gestation is associated with preterm birth and other adverse maternal and neonatal outcomes. The authors conducted a retrospective cohort study in the maternal-fetal medicine unit of two campuses of a large tertiary medical center with approximately 12,000 deliveries per year. The study population consisted of all women with a singleton pregnancy between 24 + 0/7 and 33 + 6/7 weeks of gestation admitted to the high-risk antenatal unit due to a single episode of vaginal bleeding of unknown origin between May 2003 and December 2014. Maternal and neonatal parameters of the study group were compared with maternal and neonatal parameters of the remaining singleton births occurring at the institution during the study period [156, p.1656-1663;].

The primary outcome was the preterm birth rate, while secondary outcomes were other adverse maternal and neonatal outcomes. Multivariate logistic regression was performed to identify risk factors for preterm birth in the study group. Two hundred thirty women met the inclusion criteria, and 51,468 women were in the

comparison group. Preterm birth rates were 20% and 5.5% in the study and comparison group, respectively, RR = 3.55 [2.63-4.78] ($p < .001$). The AOR for preterm birth among the study group for women with a previous preterm birth was 4.62 [1.17-18.20] ($p = 0.029$) and for women with a short cervix was 9.35 [2.30-37.95] ($p = 0.002$). One episode of third trimester vaginal bleeding is an independent risk factor for spontaneous preterm birth.

Having a short cervix or a history of previous spontaneous preterm birth significantly increases this risk. Third trimester vaginal bleeding is strongly associated with preterm birth. Knowledge of this association has valuable clinical implications for obstetric practitioners.

Yeung SW, Tam WH, Cheung RY. (2012): examine the risk of preterm birth before 34 weeks in women with antepartum hemorrhage of unknown origin, and determine the incidence and risk factors in predicting preterm birth among women taking APHUO before 34 weeks of gestation. The predictability of risk factors was assessed by both univariate and multivariate analyses [162, p.167;].

Cumulative rates of preterm birth before 34 weeks were compared using Kaplan-Meier survival analysis and the log-rank test between individuals with and without risk factors. Rates of preterm birth before 34 and 37 weeks of gestation were 7.3% and 17%, respectively. Uterine contractions, persistent bleeding, two or more episodes of APHUO, and history of spontaneous preterm birth were significant risk factors for preterm birth before 34 weeks in multivariate logistic regression. Women with one risk factor had a hazard ratio of 5.5 (95% CI: 3.2-9.6) for preterm birth before 34 weeks compared with women with no risk factors, whereas women with any two risk factors had a hazard ratio of 5.2 (95% CI: 2.1-12.9) compared with women with one risk factor [77, p.81-87;]. APHUO before 34 weeks of gestation is associated with a three- to five-fold increase in the risk of preterm birth. Identification of multiple risk factors may also help in predicting early preterm birth and appropriate management of these patients.

Serova O. F., Sedaya L. V. et al (2018) When assessing the location of the placenta relative to the internal os using ultrasound, the researchers found that

women with complete placenta previa had a 3.9-fold higher risk of preterm birth before 34 weeks compared to women without placenta previa (95% CI: 1.3-11.8). In addition, other risk factors, such as cervical length <25 mm and previous preterm births, may increase the risk of preterm birth before 34 weeks. Thus, identifying these risk factors through prenatal care and appropriate management may help reduce the incidence of preterm birth and improve maternal and neonatal outcomes [76, p.28-33;]. For prophylaxis, three options were found to be more effective than oxytocin alone in preventing postpartum haemorrhage (PPH) greater than 500 ml: the combination of ergometrine and oxytocin, carbetocin, and the combination of misoprostol and oxytocin. These three options were found to be more effective in preventing PPH greater than 500 ml than oxytocin alone. The combination of ergometrine and oxytocin was shown to be particularly effective in preventing uterine atony, a common cause of PPH. Carbetocin, a longer-acting oxytocin analogue, was also found to be effective in preventing PPH by stimulating uterine contractions. Additionally, the combination of misoprostol and oxytocin was shown to be effective in preventing PPH in resource-limited settings where access to medical interventions is limited. Overall, the use of these interventions to prevent PPH can significantly reduce the incidence of severe maternal morbidity and mortality [77, p.81-87; 83, p.49;].

The use of tranexamic acid may also be effective in reducing maternal mortality due to postpartum hemorrhage. Tranexamic acid is a drug that helps prevent the breakdown of blood clots, which can reduce excessive bleeding in cases of postpartum hemorrhage. Numerous studies have shown that the use of tranexamic acid can significantly reduce the risk of maternal mortality due to PPH. However, it is important for healthcare providers to carefully consider the risks and benefits of using tranexamic acid, especially in patients with a history of thrombosis or other conditions that affect blood clotting. As with any drug, close monitoring and careful management are necessary to ensure the best possible outcomes for both mother and baby [59, p.83;].

The role of 4-factor PCC (prothrombin complex concentrate) in obstetric hemorrhage is currently being studied. Features of the pharmacological action of this drug: 4-factor PCC (prothrombin complex concentrate) is able to quickly replenish the deficiency of a number of plasma factors of the hemostasis system. In addition, 4-factor PCC (prothrombin complex concentrate), integrating into the lysosome membrane, changes its structure and functions, thereby regulating the proteolytic balance of cells, prevents spontaneous autolysis and normalizes the process of limited proteolysis [103, p. 205]. Remneva O.V., and co-authors (2019) showed how obstetric and telemedicine technologies can be used to improve the effectiveness of care for women in the Altai Territory with massive obstetric bleeding. A clinical and statistical analysis of the case histories of 54 women who suffered massive obstetric bleeding was carried out before and after the implementation of the risk strategy using the telemedicine technology "Pregnancy Register". The study included patients who had massive obstetric bleeding before (Group I) and after (Group II) the implementation of the risk strategy [71, p. 41-47;].

The results of the study showed that the use of the risk strategy and telemedicine technologies significantly reduced the incidence of massive obstetric hemorrhage in women. In particular, the incidence of massive obstetric hemorrhage decreased from 5.5% in Group I to 1.8% in Group II. In addition, the use of telemedicine technologies allowed for timely and accurate monitoring of the health status of pregnant women and allowed health workers to quickly intervene in cases of complications.

The study also emphasizes the importance of early detection and treatment of risk factors for massive obstetric hemorrhage, such as placenta previa, placenta accreta, and uterine fibroids. The risk strategy implemented in the study included regular ultrasound examinations to identify these risk factors, as well as timely referral to specialized medical centers in high-risk pregnancies.

Overall, the study demonstrated the effectiveness of the risk management strategy combining telemedicine technologies and obstetric care in reducing the incidence of massive obstetric hemorrhage in women. The authors recommended

that this approach be more widely used to improve maternal health outcomes and reduce maternal mortality rates in similar regions with limited access to obstetric care [40, p. 148; 46, p. 10;].

Barinov S.V. et al. (2018) conducted a study to evaluate the effectiveness of Dr. Arabin's obstetric pessary in improving pregnancy and birth outcomes in women at high risk of miscarriage. The study involved 125 pregnant women at high risk of miscarriage due to a short cervix or previous preterm birth. The women were randomly assigned to either an intervention group where they received Dr. Arabin's obstetric pessary or a control group where they received standard care [15, p. 37;].

The study found that the use of Dr. Arabin's obstetric pessary significantly reduced the incidence of preterm birth in the intervention group compared to the control group. In particular, the rate of preterm birth before 34 weeks of gestation was 6.5% in the intervention group compared to 22.2% in the control group. In addition, the use of the obstetric pessary was associated with a significant reduction in the incidence of low birth weight infants and neonatal intensive care unit admissions.

The authors concluded that the Dr. Arabin obstetric pessary is a safe and effective method for preventing preterm birth in women at high risk of miscarriage. They recommended that this intervention be considered as part of routine care for pregnant women at high risk of preterm birth [15, p. 37;].

The Dr. Arabin obstetric pessary is an innovative intervention that can significantly improve pregnancy and birth outcomes in women at high risk of miscarriage. Using this intervention in combination with other obstetric care strategies can help reduce the incidence of preterm birth, which is a leading cause of infant morbidity and mortality [15, p. 37;]. Researchers of the Republican Perinatal Center of the Ministry of Health of the Republic of Uzbekistan Babadjanova Sh.D., Asadov D. (2020) developed a technology for preventive ligation of uterine vessels during cesarean section for the prevention of postpartum hemorrhage. Postpartum hemorrhage is a leading cause of maternal mortality and morbidity worldwide and is especially common in developing countries such as Uzbekistan. In an effort to

prevent postpartum hemorrhage, Babadjanova Sh.D., Asadov D. (2020) developed a new technology for preventive ligation of uterine vessels during cesarean section [13, p.45-46;].

The technology involves the use of a specialized instrument that allows identifying and ligating the uterine vessels before childbirth. This method ensures that the uterine vessels are already ligated before manipulation of the uterus, which reduces the risk of vascular damage during childbirth. The use of this technology can also help reduce the need for blood transfusions and other interventions that may be required in cases of postpartum hemorrhage.

Babadzhanova Sh.D., Asadov D. (2020) conducted a pilot study to evaluate the effectiveness of this technology in the prevention of postpartum hemorrhage in women during cesarean section. The study involved 50 women who underwent cesarean section using the preventive ligation technique, and the results were compared with a historical control group of 50 women who underwent cesarean section using the standard technique [13, p.45-46;].

The study found that the use of the preventive ligation technique is associated with a significant decrease in the incidence of postpartum hemorrhage. In particular, the incidence of postpartum hemorrhage in the intervention group was 2% compared with 16% in the historical control group. The use of the preventive ligation technique was also associated with a significant reduction in the need for blood transfusions and other interventions for postpartum hemorrhage.

The authors concluded that the use of the preventive ligation technique is a safe and effective strategy for the prevention of postpartum hemorrhage in women who have undergone cesarean section. They recommended considering this method as part of the routine care of women who have undergone cesarean section, especially in settings where the risk of postpartum hemorrhage is high [35, p. 28-39; 57, p. 35; 83, p. 49;].

French scientists Voillequin S., et al. (2022) consider the urgent administration of oxytocin for the first-line treatment of postpartum hemorrhage: based on a vignette among midwives. The World Health Organization (WHO)

recommends the use of uterotonics for the prevention of PPH in the third stage of labour in all deliveries. Oxytocin given prophylactically in the third stage of labour is effective in reducing PPH and is therefore considered a component of active management of the third stage of labour. For this reason, prophylactic oxytocin injection is routinely recommended internationally and is part of the French guidelines. This prophylaxis aims to prevent uterine atony, which is responsible for 70–80% of DPHs and remains their single most common cause [154, p.353;]. However, guidelines for the management of PPH are not consistent or standardised.

Uterotonics are the mainstay of treatment when prophylaxis fails and excessive bleeding occurs. Based on moderate-quality evidence, WHO recommends oxytocin as a first-line uterotonic for the treatment of PPH, including for women who have already received it for PPH prophylaxis. Sometimes, however, guidelines prescribe a two-stage administration, alone or in combination with another uterotonic if needed, and sometimes without a specific timing sequence of administration.

These recommendations, which also vary in doses, routes of administration, and schedules of oxytocin treatment, are largely based on expert consensus. However, all guidelines agree that oxytocin should be used prophylactically in the third stage of labor and therapeutically immediately after diagnosis of PPH, since the timing of its administration may influence the amount of maternal blood loss.

A French population-based cohort study confirmed that the risk of morbidity increases when initial care is delayed. In particular, delayed oxytocin administration was associated with higher rates of severe PPH. In addition, several studies consider rapid administration of oxytocin (<15 min) as a criterion for quality of care [98, p.701;].

Sentilhes L, Goffinet F, Vayssière C, Deneux-Tharaux C. (2017) French national guidelines state that if PPH occurs, the first obstetric procedure to be performed is manual removal of the placenta or, if it has already been removed, manual exploration of the uterus (to remove clots). This procedure should be followed by an injection of 5 to 10 IU oxytocin, even if a prophylactic injection has

been given. Persistent bleeding within 15 to 30 min after diagnosis and initial treatment of PPH should lead to second-line management. These guidelines are applicable nationwide and the initial management does not differ between maternity units [147, p.12-21;]. Marshall NE, Vanderhoeven J, Eden KB (2015) showed in a multicenter longitudinal intervention study in Oregon (USA) that regular simulation-based team training reduced delays in oxytocin administration in non-academic centers. The team began using oxytocin 48 s earlier (SD 66, p = 0.003) compared with their pre-training data. A prospective observational study at an academic medical center reported a significant reduction in the time difference between uterotonic drug administration and blood transfusion after implementation of a simulation program (p = 0.035) [136, p.495;]. Nelissen et al. (2015) conducted a half-day obstetric simulation training in a rural hospital in Tanzania as part of a prospective intervention study and found that the proportion of women receiving oxytocin as part of PPH treatment significantly increased from 43.0% before training to 61.2% after (p = 0.04). [137, p.46-53;]

With the liberalization of China's fertility policy, there are an increasing number of older pregnant women, and their risk of postpartum hemorrhage increases accordingly. The key to successful rescue is immediate and rapid blood transfusion; however, traditional allogeneic blood transfusion is associated with safety issues including blood shortage, transfusion-associated infection, and immune suppression, which poses great risks to mother and infants. In recent years, with the development of blood transfusion concept and the maturity of blood transfusion technology, autotransfusion has become an integral part of clinical blood transfusion. In addition, it has attracted considerable attention due to its ability to effectively relieve the increasingly strained blood supply and prevent the occurrence of homoimmune reactions and the transmission of diseases [121;]. According to various sources, autologous blood transfusion is divided into the accumulative type of autologous blood transfusion, which was to store one's own blood in advance for use when you need it in the future, diluted autotransfusion, which was collected and stored before surgery and diluted with plasma substitutes, and intraoperative cell-salvaged

(IOCS), the latter being the most widely used. In IOCS (intraoperative cell-salvaged), a device is used to restore, anticoagulate and filter intraoperative blood loss and postoperative bleeding. The blood is then re-circulated to the patient. In patients who have undergone cesarean section, intraoperative initiation of prophylaxis has minimal effects on hemorheology and coagulation function and does not increase the risk of amniotic fluid embolism. A total of 87 patients who underwent cesarean section and blood transfusion from March 2015 to June 2020 were included in this prospective controlled study. They were divided into observational (43 cases) and control (44 cases) groups using the random number table method. Patients in both groups were delivered by lower segment cesarean section. Hemorheology [red blood cell count, platelet volume, and fibrinogen] and coagulation function (partial prothrombin time, prothrombin time, platelet count, and activated coagulation time) were measured before and 24 h after transfusion [98, p.701-713;].

About 24 hours after transfusion, the red blood cell count, platelet ratio, and fibrinogen value decreased significantly in the two groups ($P < 0.05$); platelet count decreased significantly in these two groups; activated partial thromboplastin time, prothrombin and activated recalcification time were significantly increased in the two groups ($P < 0.05$); and no statistical differences were observed in hemorheology and coagulation function scores between the two groups ($P > 0.05$). In addition, there was no significant difference in the incidence of adverse reactions between the two groups ($P > 0.05$).

Conclusion on Chapter 1

Despite advances in obstetric care, obstetric hemorrhage continues to be a significant cause of maternal morbidity and mortality worldwide. To address this persistent problem, further research is needed to advance our understanding of the etiopathogenesis of obstetric hemorrhage, as well as opportunities to improve prognosis, prevention, and treatment.

Research efforts should focus on identifying risk factors for obstetric hemorrhage, including maternal and fetal conditions, obstetric procedures, and

socioeconomic factors. Early identification and management of these risk factors through regular antenatal care and appropriate interventions can help prevent obstetric hemorrhage. In addition, there is a need to develop and evaluate new technologies and interventions to prevent and treat obstetric hemorrhage. These may include innovative surgical techniques, medical treatments, and the use of telemedicine technologies to improve access to high-quality obstetric care.

In addition, there is an urgent need to improve the training and education of health care providers in the management of obstetric hemorrhage. This includes the development of standardized protocols and guidelines for the prevention and management of obstetric hemorrhage, as well as ongoing training and simulation exercises to improve health care providers' competence and confidence in the management of obstetric emergencies. Obstetric hemorrhage remains a major challenge in obstetrics and further research is needed to expand our understanding of this complex issue. Through a multidisciplinary approach that includes research, education and innovation, we can improve maternal and child health outcomes and reduce the burden of obstetric hemorrhage worldwide.A review on the topic: "Prediction and prevention of obstetric hemorrhage during premature birth" was prepared based on the databases: EBSCOhost, Springer NATURE, Scopus, PubMed, Google Scholar, eLibrary for the period from 2012-2022.

RESEARCH METHODS INCLUDED IN THIS MONOGRAPH

The study was carried out in the period 2021-2023. in the branch of Samarkand SIRSSPMCMCH, (chief doctor – Khamraeva L.K., Samarkand).

This study used a comprehensive approach that included various methods of clinical, laboratory, ultrasound and statistical research.

The retrospective study consisted of studying the birth histories of patients with preterm birth complicated by obstetric hemorrhage. We studied 171 cases of childbirth complicated by pathological bleeding for the period 2016-2021.

Pregnant women were included in the study as requested.

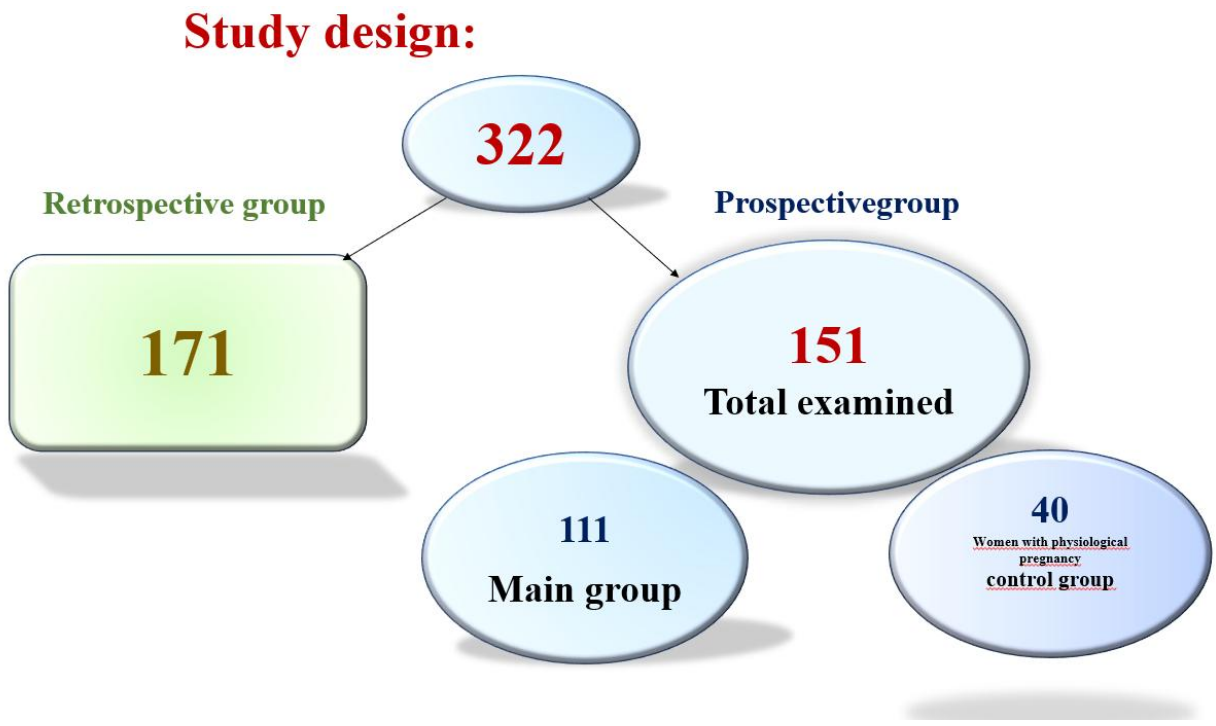

Figure 2.1.– Principles of forming clinical groups

According to the set goals and objectives, a cohort controlled study was conducted, based on the data of which the following clinical groups were formed:

We examined 151 pregnant women with TPB and the risk of developing obstetric hemorrhages during childbirth, who were divided into three clinical groups: I - main group consisted of (n = 55) women with TPB, II - comparison group - (n =

56) women with TPB. The control group consisted of (n=40) women with physiological symptoms during pregnancy and childbirth.[155, c.2-3;]

In accordance with the planned clinical and laboratory examination, diagnosis and developed methods, criteria for inclusion in the study were drawn up.

Criteria for inclusion in the study.[155, c.2-3;]:

Women with a history of premature birth and rupture of amniotic fluid.

History of obstetric bleeding.

Exclusion criteria:

1. Isthmic cervical insufficiency.
2. Multiple pregnancy.
3. Preeclampsia/Eclampsia.
4. Anomaly of fetal development.
5. Anomalies and tumors of the uterus and ovaries.
6. Severe somatic pathology.
7. Pregnancy after IVF.
8. Women with hereditary and congenital blood diseases

To obtain written consent to participate in the research study, all pregnant women were informed of the purpose and methods of the study.

During the work, general clinical and special research methods were used: laboratory, instrumental .[155, c.3;].

Individual questionnaires that documented the anamnesis characteristics, women's health status, and the course of pregnancy and childbirth had to be filled out for the clinical study carried out.

A case-control cohort study was followed prospectively, with all participants admitted to a pregnancy care unit [159, c.45;].

When studying the anamnesis, lifestyle, previous diseases, bad habits, personal and family history were taken into account. The state of menstrual function and gynecological history were studied, as well as a general examination and analysis of the condition of the body.

All pregnant women with TPB underwent all regulated laboratory tests.

- The typical flow-through hematological analyzers used in laboratories were used to perform a general blood test. Ethylenediaminetetraacetic acid, or EDTA, was sprayed into plastic tubes during the morning blood sample procedure.

- Group membership, the presence of the Rh factor, and the presence and titer of Rh antibodies using standardized sera when the Rh factor is absent [159, c.85;].

- The following indicators were examined as part of the coagulation system study.

- partial thromboplastin time activated (aPTT). Method: Plasma clotting time was measured using phospholipid activation (with cephalin) and standardized contact (with kaolin).

- Prothrombin index (PTI): a percentage representation of the difference between the patient's plasma clotting time and that of a healthy individual. Method: measuring the amount of time that fibrin forms in blood plasma when tissue thromboplastin and calcium ions are present.

- One of the characteristics of the prothrombin complex's (factors II, VII, V, and X) properties is prothrombin time. Method: measuring the amount of time that fibrin forms in citrated plasma with tissue-standardized thromboplastin and a calcium chloride solution present.

- fibrinogen. Method: measuring the amount of time that diluted citrated blood plasma takes to clot in the presence of excess thrombin in relation to fibrinogen concentration [159, c.76;].

- International Normalized Ratio (MHO): this is the prothrombin time to ero standard value ratio, calculated and reported.

- D-dimer is a protein, a product of the destruction of the fibrin molecule. Method: quantitative latex agglutination.

During the study, all women underwent all regulated laboratory and instrumental studies. Additionally, to assess the condition of the endothelium, a number of blood serum parameters were studied:

- Content of markers of endothelial dysfunction in the blood (thrombomodulin, soluble adhesion molecules - ICAM-1 and VCAM-1).In all

patients, the level of ICAM-1 (intercellular adhesion molecule), VCAM-1 (vascular cell adhesion molecule) was determined in the blood serum using a quantitative enzyme-linked immunosorbent assay (ELISA) using the Human sVCAM-1 BMS232TEN test system ("Bender MedSystems") using the Mindray BC-499 analyzer. Values of 400.6–1340.8 ng/ml were taken as normal. In the morning on an empty stomach, venous blood was collected into vacutainers, then the resulting biosamples were cooled at a temperature of –20°C and centrifuged at a speed of 1000 rpm before analysis [159, c.76;].

- Von Willebrand factor (vWf) is a glycoprotein synthesized by endothelial cells. The level of von Willebrand factor indicates the state of the rheological properties of the blood. An increase in the concentration of von Willebrand factor in the blood plasma is detected when endothelial cells are stimulated or damaged, platelet aggregation, etc. [60, p.610;].Study Factor von Willebrand was carried out using the TECHOZYM von Willebrand factor ELISA test system (Technoclone) using the ELISA method. Normal values were taken to be in the range from 0.5 to 1.5 units/ml/

- One transcription factor that is involved in controlling the cell cycle is the p53 protein. The primary process by which endothelial cells are destroyed is apoptosis. When DNA fragments are found, the p53 protein becomes more active, which starts the process of destroying cells. The activity of apoptosis in tissues is indicated by the level of p53 protein in peripheral blood. Enzyme immunoassay was used to determine the protein p53 using the relevant reagents from Vector-Best CJSC (Russia) in accordance with the manufacturer's protocol.

- General urine analysis. Method: macroscopic evaluation with description of physical properties, chemical studies and microscopic examination of urine sediment.

- Microbiological examination of vaginal discharge and cervical canal.

All studies were carried out on the basis of the laboratory of the branch of the Russian Scientific and Medical Center for Medical Research and the private medical center "MedSI"

The use of ultrasonography is widespread. Through ultrasound, the condition of their cervix was evaluated along with dynamics of changes in cervix length and width as well as the condition of placenta blood circulation. The placenta's thickness, maturity, localization, and structure, as well as the presence and quantity of amniotic fluid, were also taken into account. This was done with the apparatus “Aloka500” (Japan) and “Mindray”(China).

Statistical processing of the results was carried out using Statistica 12.0 and Microsoft Excel 2007. Numerical characteristics were calculated based on modern approaches to medical-statistical analysis. Parametric tests (such as Student's and Fisher's t tests) were used to assess the significance of differences in values for normally distributed data, and nonparametric tests (including Kolmogorov-Smirnov, Wilcoxon, and Mann-Whitney) were used for abnormally distributed data.

RISK FACTORS FOR PATHOLOGICAL BLOOD LOSS DURING PREMERATE BIRTH.

Retrospective analysis of medical records of women with PR

The criteria for identifying risk factors for preterm birth based on birth histories were the birth outcomes of a retrospective group, the analysis of which was carried out by us in the branch of the Republican Specialized Scientific and Practical Medical Center for Maternal and Child Health in Samarkand (chief physician - Khamraeva L.K., Samarkand) for 2016-2020 [157, c.7;].

When choosing birth stories, attention was paid to the outcome of birth (complications such as bleeding). We studied 171 cases of premature birth, which were complicated by pathological blood loss in the gestational age of 28-34 weeks of pregnancy.

The average age of women ranged from 17 to 37 years (Figure 3.1).

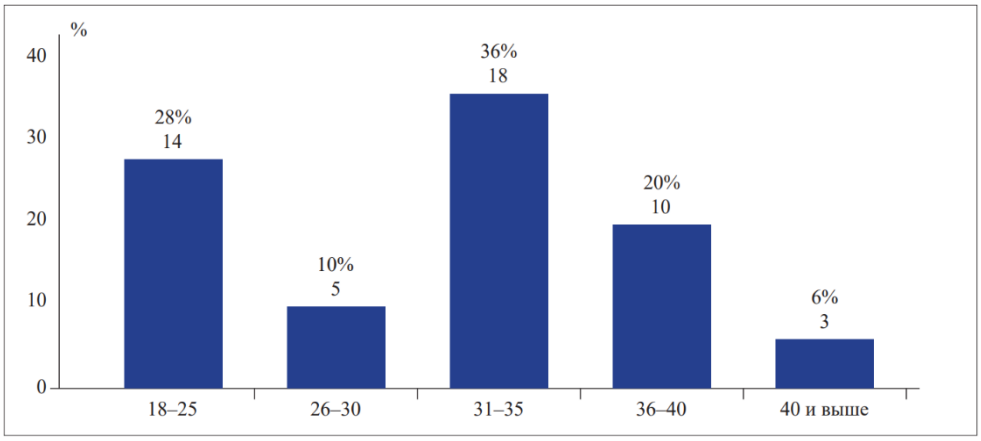

Figure 3.1 Age of women in the retrospective group.

The age of the women was: 18–25 years — in 14 women (28%), 26–30 years — in 5 women (10%), 31–35 years — in 18 women (36%), 36–40 years — in 10 women (20%), 40 or more - in 3 women (6%).

In terms of social status, housewives prevailed (46.0%), working women (39.4%), and students (14.5%).

When studying the nature of menstrual function, it was found that the average age of menarche was 12±3 years, the duration of menstruation was 5.07±2.1 days, the onset of sexual activity was on average 18±3.1 years.

Menstrual function of pregnant women was assessed by age at menarche, duration of menstruation, amount of blood lost, and complaints of pain (Fig. 3.2).

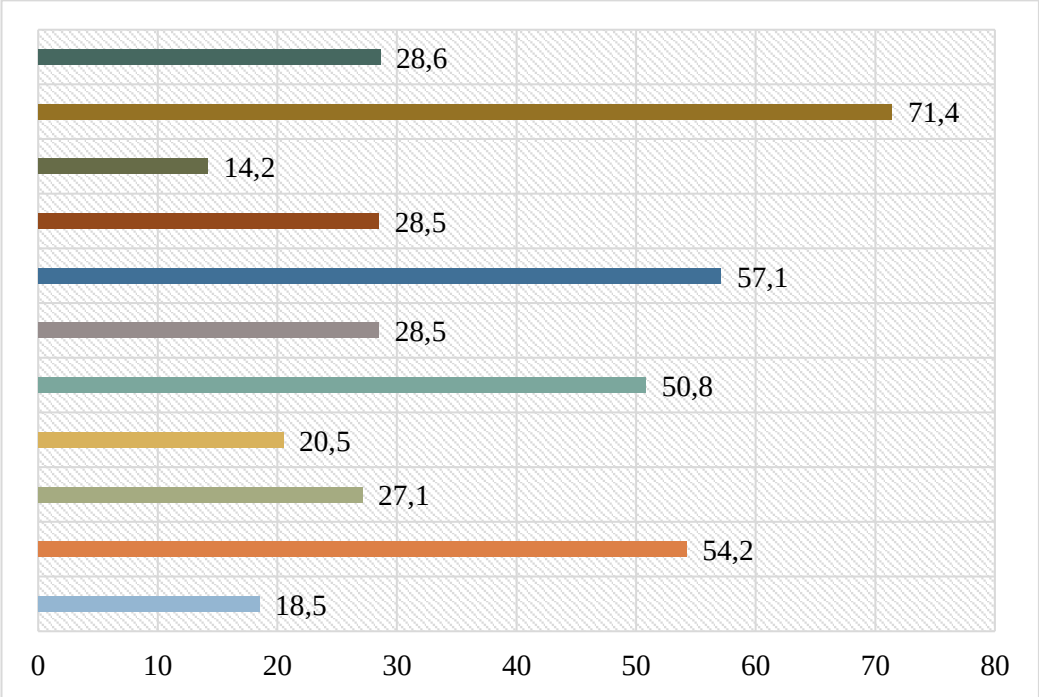

Figure 3.2. Characteristics of menstrual function.

Note. AM – age of menarche, DM – duration of menstruation, NMF – nature of menstrual flow, NC – nature of the cycle

It was found that more in pregnant women reported complaints about the following: frequent stress, bad habits, occupational hazards, a history of threatened miscarriage, a history of preeclampsia, a history of eclampsia, oligohydramnios, polyhydramnios, and somatic pathology (Fig. 3.3). The presence and frequency of extra genital pathology in the women examined played an important role in the development of complications. Thus, 61% of women had a history of inflammatory diseases in childhood, fluid (98%), diseases of the respiratory system, ear, nose and throat (85%), kidney diseases (56%), anemia (61.4%) which could have a negative impact on the condition of various organs

and systems during the formation of the reproductive function of the future woman.

When collecting a gynecological history, the main pathology was identified - inflammatory diseases of the reproductive tract, among them colpitis (61.4%), inflammatory diseases of the uterus (39.3%), and menstrual dysfunction (16.2%) predominated.

The outcomes of previous pregnancies were of no small importance for the current pregnancy.

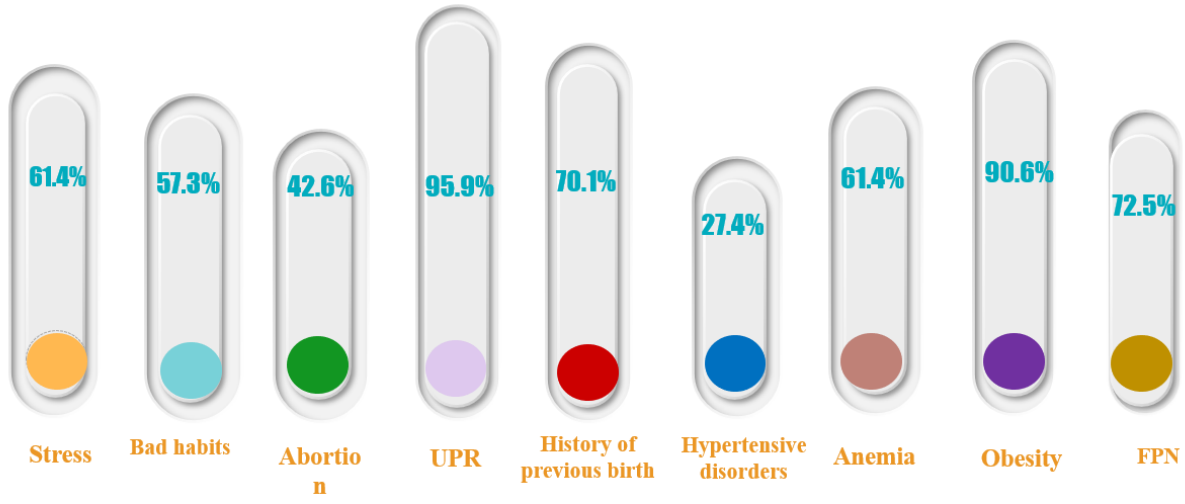

Figure 3.3. Analysis of risk factors of a retrospective group.

A distinctive feature of the obstetric history of pregnant women with PB is a high frequency of abortions (42.6%), threatening premature birth (95.9%), abruption of a normally located placenta (2.9%), hypertensive disorders (19.3%) (Fig. .3.3).

According to parity, among the examined primiparous women, 30% were multiparous and 70% were multiparous (Fig. 3.4). When studying the parity of women, it was revealed:

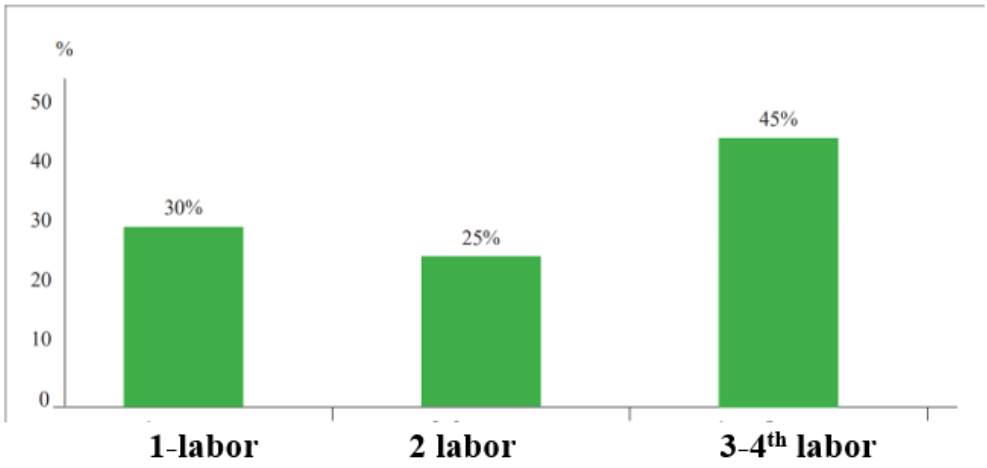

Figure 3.4. Parity of women with PB **complicated by atonic bleeding.**

1st birth - (30%), 2nd-3rd birth - (25%), 4th or more births - (45%). The majority of women with birth defects complicated by bleeding were multiparous (63.1%), primiparas accounted for 36.9% (Fig. 3.5).

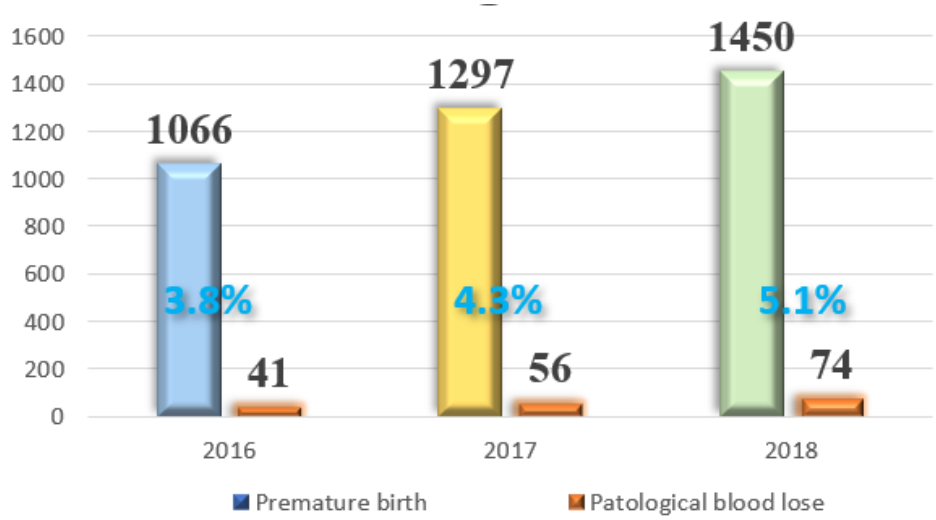

Figure 3.5. Number of PB and atonic bleeding during PR

In the Samarkand region, according to data, for the period from 2016 to 2018, as well as throughout the country as a whole, the general trend toward an increase in the frequency of premature births and atonic bleeding during pregnancy remains. According to the data presented in Figure 3.5, it is clear that the frequency of atonic bleeding during childbirth and in the postpartum period with premature birth increases from year to year. This undoubtedly leads to an increase in social problems and obstetric complications.

Analyzing the outcome of the births of the retrospective group, it was revealed that the birth ended through the vaginal birth canal in 74% (127) of cases and through cesarean section in 26% (44) (Fig. 3.6).

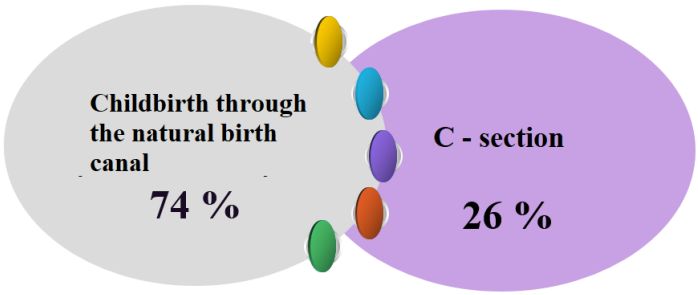

Figure 3.6. Methods of delivery in a retrospective group.

According to the literature, it has been established thatPhysiological blood loss is considered to be blood loss up to 10% of the volume of blood volume (up to 500 ml) during vaginal delivery, and up to 1000 ml - during cesarean section, pathological - 10-30% of the volume of blood volume (>500 ml) - DNB, >1000 ml of CS, massive more than - 30 % bcc.

It was found that pathological blood loss occurred in 100% of cases, given the special selection of stories.

The volume of blood loss in the retrospective group, with NB was 1223.04±43.2 ml, with CS was on average 1199.12±52.1 ml. (Fig. 3.7).

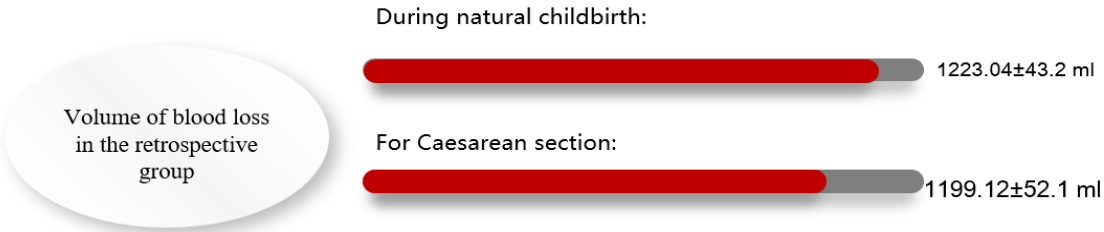

Figure 3.7. Volume of blood loss in the retrospective group

When analyzing the causes of bleeding, it was found that common causes of bleeding were: PPA 3.3%, uterine atony 28.9%, placenta defects 9.5%, trauma 11.4%, changes in the hemostatic system 54.7%. In some cases, combined causes of PBL were noted.

To treat PC, drug and surgical interventions were performed (Table 3.1).

Table 3.1

Methods for stopping bleeding (according to a retrospective group)

Number of patients	Conservative stopping of PC		Surgical **PBL** stop	
171 – 100%	158	92.4%	13	7.6%

As can be seen from the table, conservative stopping of PBL was 92.4%, surgical stopping 7.6% of cases.

We were faced with the question: What additional measures could prevent PBL during childbirth and the postpartum period? "To answer the question, we carried out additional research methods. Considering that one of the causes of PBL is impaired hemostasis in 54.7% of cases, we studied hemostasiological indicators as a trigger mechanism for PBL (Table 3.2).

Coagulogram analysis of the retrospective group (before birth)

Table 3.2.

Index (n=171)	**Meaning**	**%**
APTT (sec.)	**38.12±4.41**	59.1%
Prothrombin index (%)	**90.6±7.47**	62.5%
Fibrinogen (g/l)	**4.1±0.91**	57.3%
Prothrombin time (sec.)	**14±0.2**	53.8%
INR	**1.83±0.1**	67.2%

As can be seen from the table, changes in the hemostatic system in the form of coagulation disorders were observed in almost 50% of cases, which in turn proves the above opinions.

In pregnant women with preterm labor, there is an increase in prothrombin levels, which indicates excessive activation of the extrinsic coagulation pathway. A shortened APTT indicates increased activity of the intrinsic coagulation pathway. An increase in fibrinogen levels in combination with the above-mentioned activity of coagulation processes leads to the development of

hypercoagulation syndrome in pregnant women, which contributes to premature birth, which is consistent with literature data [59, p. 83;].

According to the data of the hemostatic system in pathological blood loss of women who gave birth prematurely, we can conclude that there is insufficient study of biochemical markers of the hemostatic system, as well as the possible role of endothelial dysfunction in the development of blood lose in PB. In addition, the development of effective methods for treating hypercoagulability syndrome in pregnant women in the early stages will make it possible to prevent premature birth.

Clinical characteristics of the condition of pregnant women at risk for PBL during preterm birth (prospective analysis)

This monography work was carried out at the branch of the Russian National Research Medical Center for Medical Research in Samarkand in the Department of Pathology of Pregnant Women for 2021-2023.

For definition the stage of the clinical study, 151 pregnant women were examined and divided into three groups (Fig. 3.8).

Figure 3.8. Group distribution design

The study included women aged 18 to 36 years, the majority of them were aged 25 to 30 years (45%), 31-36 years (30%) and 18-25 years (25%) (Fig. 3.9), the average age was 27±2.1 years.

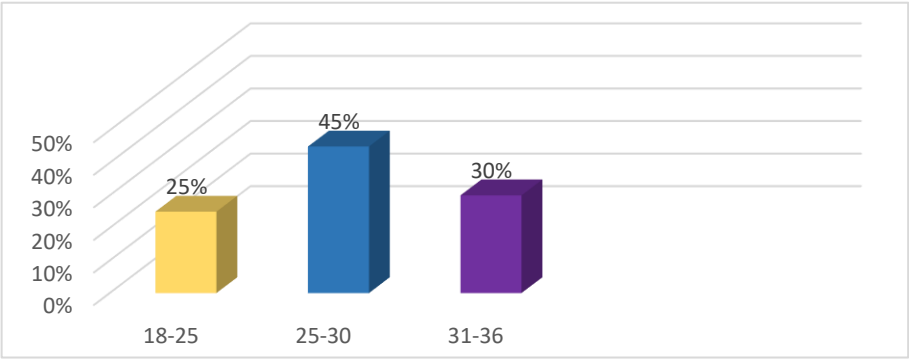

Figure 3.9. –Age range of women examined

By social status: 28% were housewives, 27% were students, 45% were employed (Figure 3.10).

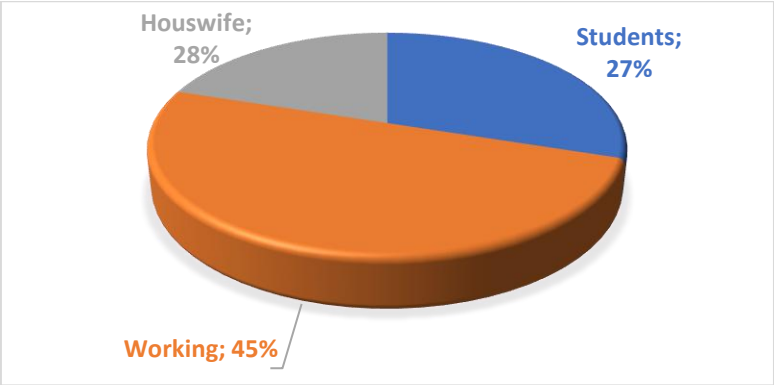

Figure 3.10.– Distribution of women by social status.

The distribution of women by place of residence is presented in Figure 3.8, with 52% of women living in the city and 48% in the regions. Notably, half of the women who bled during preterm labor were from rural areas (Figure 3.11) [155,c.2;].

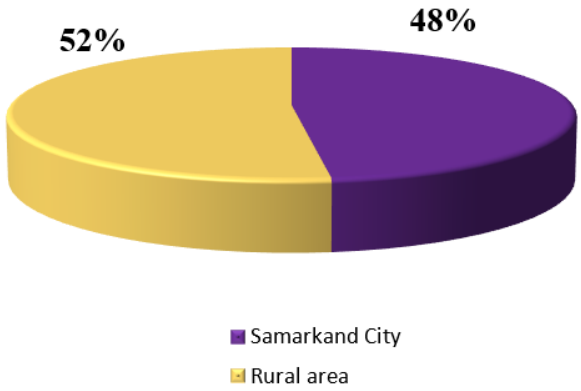

Figure 3.11– Place of residence of women included in the study.

To identify a risk group based on anamnesis, we used the “Prognostic matrix for identifying risk factors” (Computer program: 03.13.2022 (Intellectual Property Agency under the Ministry of Justice of the Republic of Uzbekistan No. DGU 2022 1122)) (Fig. 3.12.)

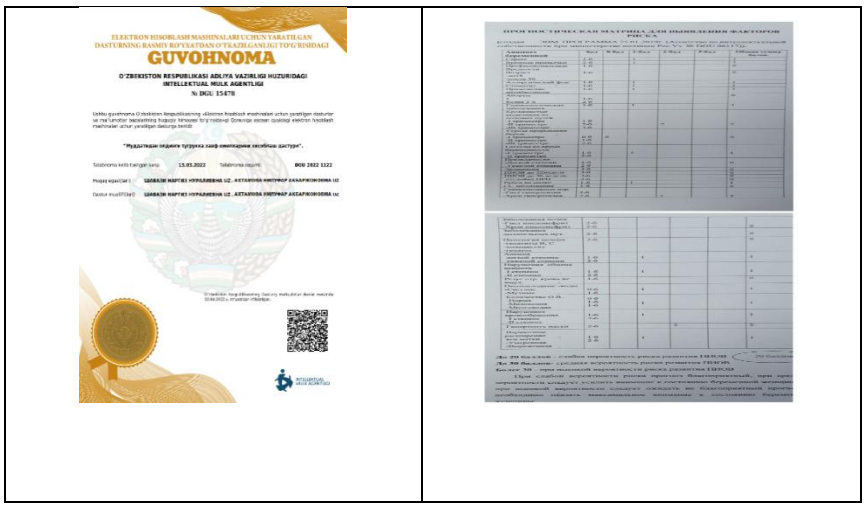

Figure 3.12. Prognostic matrix for identifying risk factors blood lose in PB.

Based on the results of the pathological condition in matrix, pregnant women can be divided into 3 groups

- ✓ Group 1 – low probability of developing PB (up to 5);
- ✓ Group 2 - average, probability of developing PB (from 6 to 20):
- ✓ Group 3 - high probability of developing PB (more than 20)

The assessment of BMI was of significant interest in terms of assessing the volume of blood loss, which is presented in Table 3.3.

Table 3.3.

BMI of women in study groups

Index	Groups		
	1 (n=55)	2 (n=56)	3 (n=40)
Height, cm	164.5±6.8	165.4±5.9	167.2±7.6
Body weight, kg	71.2±11.5	68.8±10.2	63.4±5.8
BMI	32.87±4.68	33.00±4.66	26.49±4.27

BMI analysis showed that in group I the average BMI was 32.87±4.68; in group II 33.00±4.66.

The analysis was conducted to predict the risk of pathological blood loss in premature birth. For this purpose, various features of the anamnesis were studied, including reproductive, gynecological, somatic, infectious, as well as the course of the current pregnancy, causes of bleeding and the postpartum period.

When analyzing the reproductive history in the compared groups, the

following results were obtained (Table 3.4). The average age at menarche was 13.1±1.21 years in the first group, 14.3±1.43 in the second study group and 12.4±1.08 in the control group. As can be seen from the presented data, the age of menarche and the duration of menstruation were statistically comparable in the study groups.

Table 3.4.

Reproductive history of women in the study groups

Index	Groups, n (%)		
	1 (n=55)	2 (n=56)	3 (n=40)
Age at menarche, years	13.1±1.21	14.3±1.43	12.4±1.08
Duration of menstruation, days	5.10±0.5	6.01±0.8	5.04±1.01

A distinctive feature of the obstetric history of pregnant women with TPB is the high frequency of spontaneous abortions in group I (70.7%); in group II (67.6%), threat of premature birth in group I (57.8%); in group II (78.6%), history of premature birth in group I (62.4%); in group II (61.3%) (Fig. 3.13) [155,c.2;].

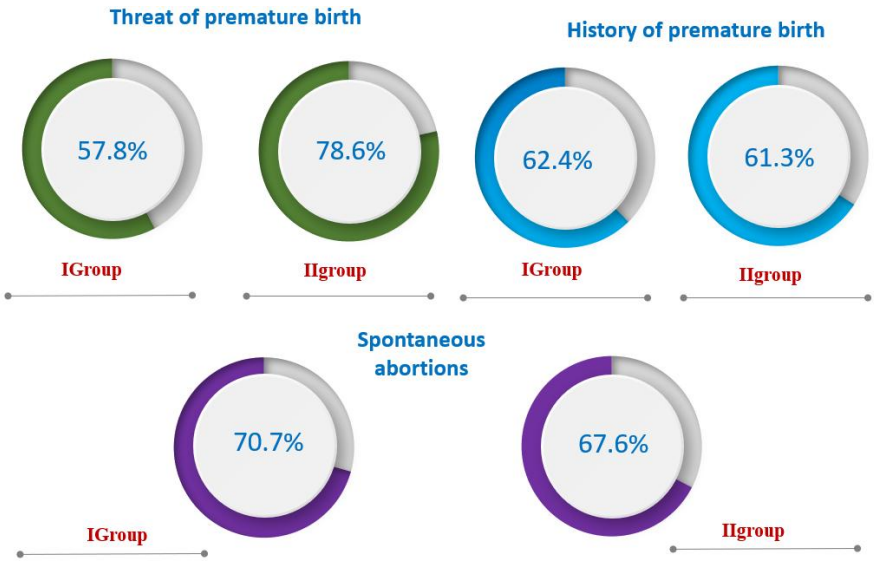

Figure 3.13. Obstetric history of women in the studied groups

A study of the parity of women showed that 45% of them were primiparous, and 55% were multiparous (Fig. 3.14.).

This indicates that women had social, clinical and anamnestic features associated with known risk factors for preterm birth and pathological blood loss.

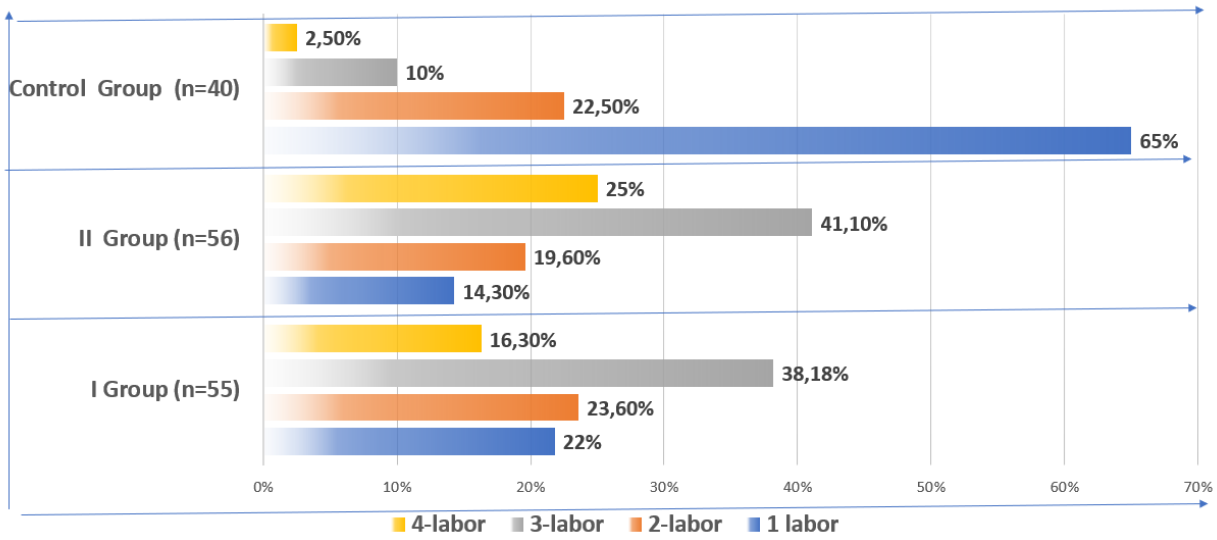

Figure 3.14. – Pregnancy parity among women in the study groups

When studying the parity of women in the first group, 12 women (22%) had the 1st birth, 13 women (23.6%) had the 2nd birth, 21 (38.1%) had the 3rd birth 4 9 women (16.3%) had 1st or more births; in the second group, 8 women (14.3%) had 1st births; 11 women (19.6%) had 2nd births. 3rd birth - in 23 (41.1%) 4th or more births - in 14 women (25%) in the control group; 1st birth was in 26 women (65%), 2nd birth - in 9 women (22.5%), 3rd birth - in 4 (10%) 4th - in 1 woman (2.5%) (Fig. 3.11.) [155,c.2;].

The gestational age of women in the main 2 groups was from 28 to 34 weeks. (Table 3.5.).

Table 3.5.

Gestational age in women in the study groups

Group	M	SD	Me	Q25	Q75	Min	Max
Group I	32.95	2.82	34	31	35	28	**34**
Group II	28.66	4.76	28	24	34	28	**34**
Control group	**38.82**	**2.05**	**39**	**38**	**40**	**37**	**41**

Note: **M** (mean) is the arithmetic mean, or the average sum of all values divided by their number; **SD** is the standard deviation; **Me** (median) is the median value located in the middle of the variation series;

Q25, Q75 are the interquartile range, the difference between the upper and lower quartiles (or 75% and 25% percentiles); Min is the minimum, the smallest value of the variable; Max is the maximum, the largest value of the variable.

The table shows the overall gestational age of women in the study groups. The average gestational age of pregnancy in the main groups was on equal 28.66±4.76 weeks, in the control group approximatly 38.82±2.05 weeks.

Pregnant women in the first group had a significantly most of vaginitis 48 (87.2%), indicating that vaginitis may play a significant role in the development of pathological blood loss during preterm birth (injuries). In addition, in women, cervical pathologies were more often detected 49 (89.1%) in the first group and 51 (92.7%) in the second group, abortions and miscarriages were most common in the first group 44 (80%), which may be associated with the risk of developing obstetric complications during childbirth (Fig. 3.15).

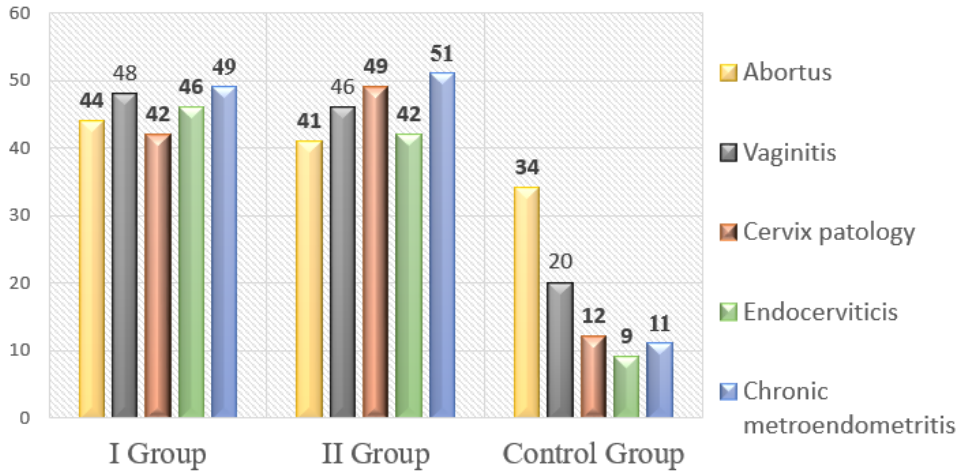

Figure 3.15. Gynecological history

That show the presence of gynecological diseases can significantly increase the risk of developing pathological blood loss during premature birth, and requires more careful monitoring and treatment by doctors. Actualy care emphasizes the importance of pre-screening women at high risk of preterm birth [157].

When analyzing somatic diseases, it was revealed that women in clinical groups had a comparable frequency of a history of obesity of varying degrees, myopia and varicose veins (VV) of the lower extremities (Fig. 3.16)

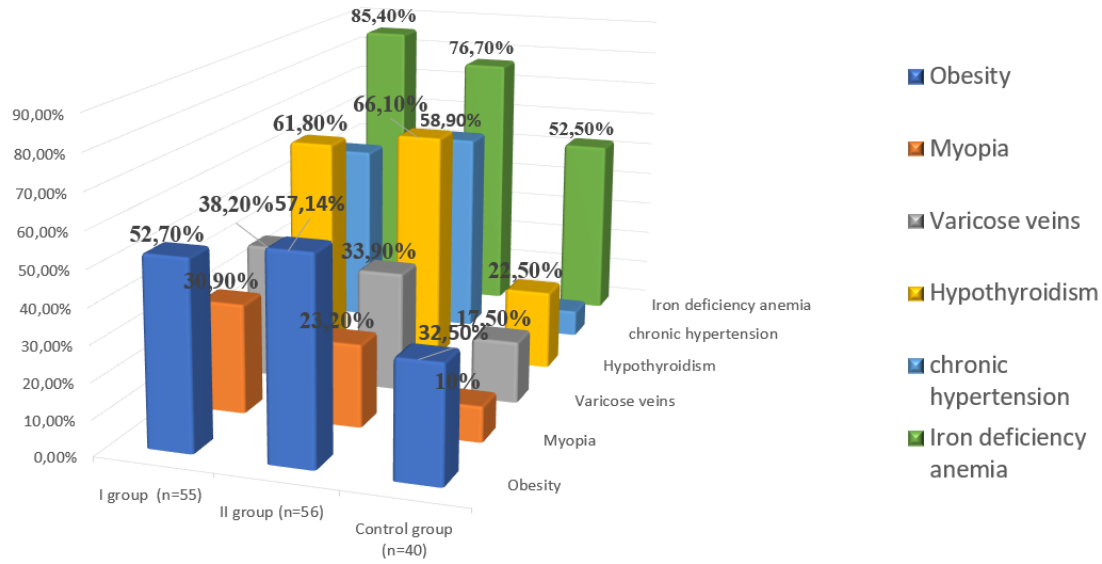

Figure 3.16. Analysis of somatic pathology among the study groups.

Chronic arterial hypertension and iron deficiency anemia were more often diagnosed in women from the first group 30- 60%; 47 (85.4%), and the second group 33 (58.9%); 43 (76.7%) (p=0.0125).

Chronic pyelonephritis and frequent acute respiratory viral infections are not associated with bleeding during premature birth. A history of somatic pathology may increase the risk of pathological blood loss during childbirth, regardless of gestational age. An assessment of the medical history is necessary to prevent abnormal bleeding during preterm birth.

It must be recognize that these results may be limited and cannot be generalized to the entire female population, since the study was conducted only on a group of women with PBL and preterm birth. To fully understand the impact of infectious and inflammatory diseases on the likelihood of early pregnancy, additional research is needed that takes into account a wider range of factors.

Thus, the analysis showed that women with pathological blood loss during premature and term labor were more likely to have IDA.

As part of the study, all the examined women underwent radiological examination and Dopplerography, which revealed the presence of pathology and blood circulation disorders. This stage of diagnosis turned out to be key for understanding the state of pregnancy and possible risks.

During the study, parameters such as muscle tone, the amount of amniotic fluid, the condition of the placenta and the length of the cervix in millimeters were carefully examined. It should be noted that muscle hypertonicity was detected in the first group in 89% of cases, while in the second group this indicator was 90%. These results highlight the high prevalence of this condition among the examined women and confirm the need for further monitoring and correction of pregnancies with similar abnormalities (Fig. 3.17).

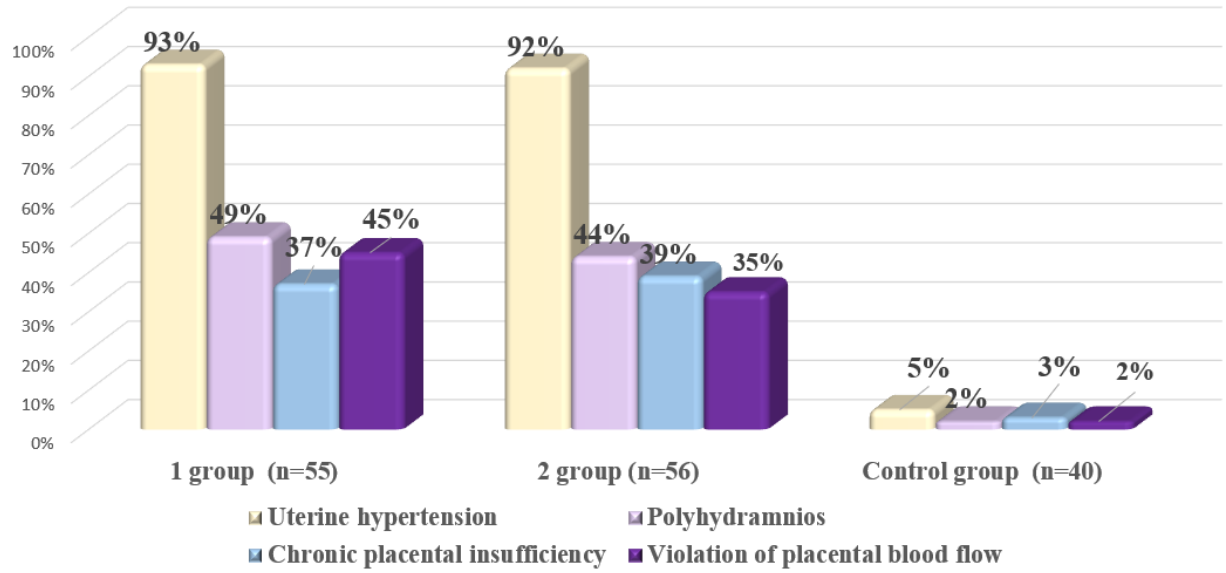

Figure 3.17. Sonographic signs of chronic placental insufficiency

Women in the first group had a higher proportion of uteroplacental blood flow disorders than in the control group. Chronic placental insufficiency was detected only in women with premature birth. The frequency of uteroplacental blood flow disorders was higher in the second group (35%) than in the first group (45%) and the control group (2%).

Conclusions for the chapter:

Thus, it was revealed that the causes of pathological blood loss in premature birth can be anamnestic data of the retrospective and prospective group (interruption of pregnancy and premature birth are, miscarriage, various types of abortions (spontaneous, medical)), EGP and ultrasound data.

To fully understand the impact of the above reasons for the likelihood of PBL occurring during premature birth, additional studies are needed to predict this pathology.

LABORATORY STUDIES OF WOMEN WITH PREMATURE BIRTH.

Features of the hemostasis system indicators

The course of pregnancy is accompanied by adaptive changes in the hemostasis system, which plays an important role in the gestation process. The results of the study of the plasma link of the hemostasis system are presented in Table 4.1.

Table 4.1.

Parameters of the plasma link of the system hemostasis (n=151).

Index	APTT, sec.	Prothrombin index, %	Fibrinogen, g/l	INR
Group I, n=55	37.1±3.52	91.2±9.23 %	4.0±0.89	1.9±0.08
Group II, n=56	35.44±2.41	93.4±14.23%	3.9±0.93	1.4±0.12
Control group, n=40	29.4±3.24	86.4±10.21	3.8±0.84	1.1±0.04

The APTT index in the study groups with TPB was 1.3 times higher than in the control group ($p<0.05$). PTI: in the study groups it was 1.1 times higher than in the control group ($p<0.05$). Fibrinogen: 1.1 times higher than in the control group ($p<0.05$). INR: in the study groups it was 1.7 times higher than in the control group. ($p<0.05$). The study of the coagulation system in pregnant women also includes the analysis of the cellular component of hemostasis. The scientific literature has demonstrated the role of platelets in ensuring trophism of the vascular intima: electron microscopy confirmed the angiotrophic function of platelets [6, p.62;]. This additionally justifies the inclusion in our study of the analysis of the state of the cellular component of the hemostasis system, which ensures a more complete study of the factors influencing the morphofunctional state of the endothelium. The results obtained are presented in Table 4.2.

Table 4.2.

Platelet component of the hemostasis system in the study groups (n=151).

Index	Group I, n=55	Group II, n=56	Control group, n=40
Mean platelet count (PLT), ×109/l	343.5±69.12*	334.2±69.11*	154.2±69.11
Mean platelet volume (MPV), fl	11.7±0.93*	12.9±0.87*	9.1±1.32

- significance of differences P <0.05

Note: PLT - platelet count; MPV is the mean platelet volume.

The platelet count in patients in the first group and the second group was 1.4 times higher than in the control group. The determination of the average platelet volume in the first group and in the second group was 1.3 times higher than in the control group (p <0.05).

Thus, when analyzing some parameters of hemostasis, no significant differences were found in the groups of participants.

Results of analysis of markers of endothelial dysfunction

This study also identified biochemical markers of endothelial dysfunction. These indicators are available for laboratory analysis and objectively reflect changes in the functional state of an endothelium. Highly sensitive von Willebrand factor (vWf) and apoptosis protein p53 in blood serum are the most reliable laboratory markers for the pathology being studied [159].

Table 4.3.

Markers of endothelial function in pregnant women in the study groups.

Index	Group I (n=55)	Group II (n=56)	Control (n=40)
Von Willebranade factor,%	120.0±20.18*	128.0±19.05*	101.6±9.47
D-dimer	318.05±5.62 *	321.03±4.6*	179.25±4.76
Protein p53, U/ml	0.01±0.011*	0.01±0.009*	0.003±0.0013

Note: *reliability of differences between groups I and II
****reliability of differences by control group**

The concentration of Von Willebrand factor averaged 101.6%, with a standard deviation of ±9.47% in the control group. It was revealed that the average level of von Willebrand factor was 120.0%, and the standard deviation was ±20.18% in the first group in women with TPB, its concentration in group II in women with TPB was 128.0±19.05, and in in the control group in women with a physiological course of pregnancy was 101.6±9.47.

The concentration of apoptosis protein p53 in peripheral blood plasma in women with TPB was 3.33 times higher than in women with a physiological pregnancy (control group).

D-dimer is a protein, a product of the destruction of the fibrin molecule, which indicates a disorder in the coagulation system. Thus, in women with TPB in the first and second groups, its value was 1.78 higher than in the control group.

Endothelial dysfunction was found in women of groups I and II; they were increased in the blood serum compared to the control group. To assess the significance of differences in the studied characteristics, the Mann-Whitney test was used. In summary, this study shows that women with threatened preterm labor experience endothelial dysfunction, which is manifested by elevated serum

biochemical markers. This may be one of the reasons for gestational disorders and requires further study to develop promising methods for the treatment and prevention of this pathology.

An important component of health care is the assessment of the risk of pregnancy pathology, which should be carried out both antenatally, during and postnatally. This is essential for the timely prevention of morbidity and mortality associated with pregnancy pathology. Thus, careful attention to these aspects can improve outcomes and maternal safety [55, p.54;].

Bazirete O, Nzayirambaho M, Umubyeyi A (2022) Uterine atony remains the leading cause of primary PPH. Large-scale studies are needed to further study potential risk factors for PPH [94; 95, p.678;].

Kljakić D, Milosavljević MZ, Jovanović M. (2020) argue that placental bacterial infection as the first cause of preterm labour and fetal death, when there are many of them, lead to lung pathology followed by poly organ failure [128, pp. 81-86;].

The average values of markers - von Willebrand factor and apoptosis marker protein p53 were compared between groups of women - with TPB (group I) (group II), and women with a physiological course of pregnancy (control group).

The significance of Icam and Vcam markers in the genesis of obstetric hemorrhage during preterm birth.

In recent years, scientists have increasingly focused on the role of functional endothelial indicators in the pathogenesis of uterine bleeding, especially in premature birth. As is known, endothelial cells lining the blood walls of the placenta and uterus perform an important function in regulating tone, nutrition and platelet composition. In particular, endothelial dysfunction is characterized by impaired decreased tone, increased vascular permeability, as well as impaired dissolution of fibrin fibers. It should be noted that such pathology can lead to various complications during childbirth, including bleeding. Thus, the study of these processes is extremely important for understanding the mechanisms of development of pathologies of

pregnant women and the development of effective methods of treatment and prevention.

Functional endothelial markers such as von Willebrand factor, soluble vascular cell adhesion molecule-1, soluble intercellular adhesion molecule-1 are commonly used as indicators of endothelial dysfunction.

sICAM (intercellular adhesion molecule) and sVCAM (vascular cell adhesion molecule) are functional endothelial markers that play an important role in the pathophysiology of obstetric hemorrhage in preterm birth. These markers are expressed on the surface of endothelial cells and mediate adhesion, migration, and transendothelial migration of leukocytes.

These markers have been shown to be elevated in various obstetric complications, including preterm birth with PC. Moreover, their levels have been shown to correlate with the severity of bleeding and adverse pregnancy outcomes such as preterm birth, intrauterine growth restriction, and fetal death.

The precise mechanisms underlying the association between endothelial dysfunction and obstetric hemorrhage during preterm labor are not fully understood. However, it is believed that endothelial dysfunction may lead to impaired placental blood flow and abnormal uterine contractions, which are known risk factors for obstetric hemorrhage. In addition, impaired coagulation and fibrinolysis, which are also associated with endothelial dysfunction, may contribute to the development of bleeding during preterm labor.

Table 4.4.

Content of markers of endothelial dysfunction in the blood

Indicators	Group of examined pregnant women		
	Control group, n= 40	I group, n=55	II group, n=56
sICAM-1, ng/ml	998.88±15.0*	1307.11±26.14*	1297.1±49.1**
sVCAM-1, ng/ml	642.30±9.86*	798.97±8.70	802.43±3.8**

Note: *reliability of differences between groups I and II
****reliability of differences by control group**

Activation was detectedsICAM-1 by 1.3 times and sVCAM-1 by 1.1 times, on average in both groups,which was confirmed by a significant increase in blood serum levels in pregnant women compared to similar indicators in healthy pregnant women.

Thus, functional endothelial markers are valuable tools for assessing endothelial dysfunction in pregnant women and can provide important insights into the pathogenesis of obstetric hemorrhage during preterm labor. Further research is needed to fully understand the mechanisms underlying the association between endothelial dysfunction and obstetric hemorrhage and to develop effective interventions to prevent or treat this serious complication of pregnancy.

Increased expression is observed during preterm birthsICAM-1AndsVCAM-1, which is associated with increased recruitment and infiltration of leukocytes into the placenta and decidua. This infiltration is thought to contribute to inflammation, oxidative stress, and vascular damage, which may precipitate obstetric hemorrhage.

In addition to their role in attracting leukocytes, sICAM-1AndsVCAM-1also participate in the regulation of vascular tone and permeability.

These markers may serve as potential targets for the development of new therapeutic strategies aimed at reducing the risk of obstetric hemorrhage and improving maternal and fetal outcomes in preterm birth.

There have been several studies examining the rolesICAM-1and VCAM in obstetric hemorrhage during preterm labor. One study published in the Journal of Obstetrics and Gynecology Research in 2018 found that levelssICAM-1AndsVCAM-1were significantly increased in women with preterm labor complicated by bleeding compared with women without bleeding ($p<0.001$). The study also showed that the levels of these markers were positively correlated with the severity of bleeding ($p<0.001$) [130, p.516;].

Another study published in the American Journal of Reproductive Immunology in 2017 found that women with preterm birth who experienced obstetric hemorrhage had significantly higher levelssICAM-1AndsVCAM-

1compared with women without bleeding (p <0.05). The study also found that the levels of these markers were positively correlated with the degree of leukocyte infiltration in the placenta (p < 0.05) [149, p.68;].

women with threatened preterm labor have higher values of markers (von Willebrand factor, apoptosis marker protein p53, D-dimer and sICAM-1 and sVCAM-1 levels) than women with a physiological pregnancy. This confirms the involvement of endothelial dysfunction and apoptosis in the possible development of pathological bleeding in preterm labor and in the postpartum period.

These data suggest that endothelial dysfunction and leukocyte infiltration play an important role in the pathogenesis of obstetric hemorrhage in preterm birth. Focus onsICAM-1AndsVCAM-1may be a potential therapeutic strategy to reduce the risk of obstetric hemorrhage and improve maternal and fetal outcomes in preterm birth. However, further research is needed to confirm these findings and develop effective interventions.

Conclusion on the chapter: Recently, vascular and hemodynamic disorders in pregnant women, which are observed in various somatic diseases, have traditionally been considered risk factors for PTB. The basis for hemodynamic and microcirculation disorders, including in the uteroplacental pool, developing in various somatic pathologies, is generalized endothelial dysfunction. There are several hypotheses explaining the development of endothelial dysfunction in PTB.

These changes are associated with the intensification of intravascular blood coagulation processes, including in the uteroplacental blood flow. The severity of shifts in the vascular-platelet, coagulation, fibrinolytic and anticoagulant links of hemostasis is determined by the characteristics of the course of pregnancy and the initial state of the coagulation system. Thus, the results of the study show that

PREDICTION AND PREVENTION OF BLEEDING DURING PREMATURE BIRTH

The influence of the proposed therapy on the outcome of pregnancy and childbirth in women with TPB in the study groups

Changes in placental blood flow lead to tissue hypoxia and vascular damage, which increases vascular pathology during complicated pregnancy. Spontaneous abortion is accompanied by a decrease concentration and an increase in the concentration of the vasoconstrictor endothelin-1 in the blood. Threatening spontaneous miscarriage causes an increase in the expression of VEGF and TNF-α. Thrombin deposition during hemorrhages provokes disruption of vasculo- and angiogenesis, vascular and endothelial remodeling, causing gestational complications [24; 63, p.77; 140, p.610;].

To identify risk factors for PBL in PR, we carried out a number of laboratory research methods, such as determining endothelial dysfunction and the activity of the hemostatic system in the study groups.

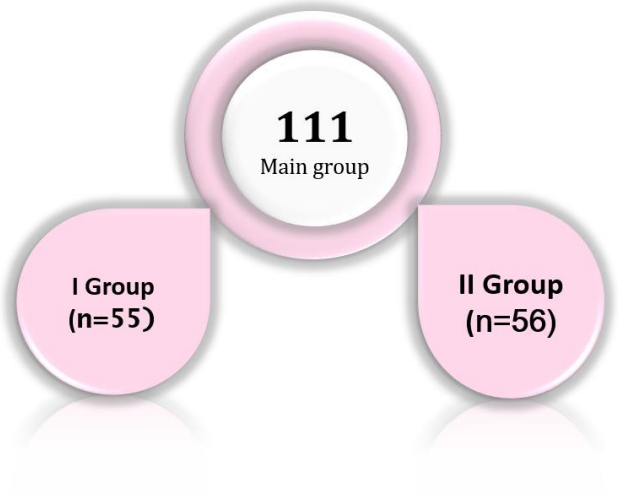

Figure 5.1 Distribution of groups depending on the therapy received.

The study included 111 pregnant women with TPB (main 2 groups) to assess the effect of antiplatelet therapy on the functional state of the endothelium during pregnancy. All pregnant women of group I (n=55) with TPB receive the proposed therapy in addition to pregnancy-preserving therapy, group II (n=56), pregnant women with TPB received traditional therapy (Fig. 5.1).

After laboratory tests and identification of changes in the hemostatic system (Tables 4.1; 4.2; 4.3; 4.4;), all women of group I were prescribed Dipyridamole (4,8-Di-1-piperidinylpyrimidol pyrimidin-2,6-diyl) under the control of the coagulation system .

Dipyridamole was prescribed at a dosage of 75 mg/day, 1 tablet x 2 times a day for 14 or more days under the control of the coagulation system.

With the onset of labor, the prescription of Dipyridamole was immediately stopped; in the normal course of pregnancy, therapy continued until the end of the prescribed period. The prescription of Dipyridamole did not exceed 34 weeks.

Women of the second group took traditional therapy.

Traditional therapy included tocolytic, hormonal therapy and RDS prevention.

After the prescribed therapy, the following coagulogram parameters were studied: activated partial thromboplastin time, prothrombin index, fibrinogen, international normalized ratio, mean platelet count, and mean platelet volume (section 5.3).

To assess the risk of bleeding in preterm birth, the mode of delivery and the outcome of labor, the causes of bleeding, the correlation between gestational age and blood loss, the analysis of blood parameters and the characteristics of the course of labor were studied.

Analyzing the outcome of birth among the study groups, early birth defects in group I occurred in 10.9% of cases, in group II in 23.2% of cases, late birth defects in group I occurred in 27.2% of cases, in group II in 33.9% of cases. cases, Urgent births in group I were observed in 61.8% of cases, in group II in 42.9% of cases (Fig. 5.2).

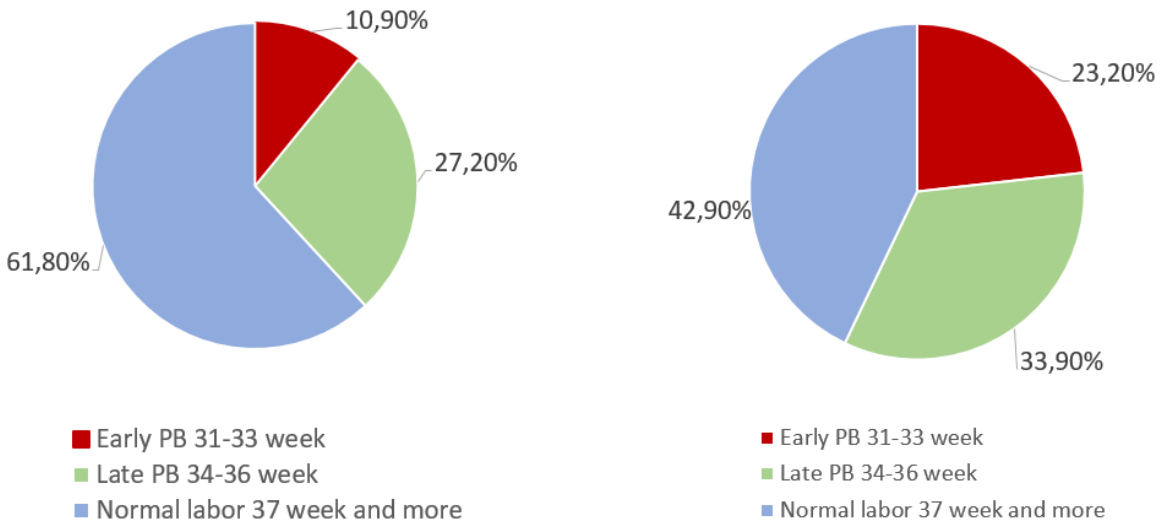

Figure 5.2. Dates of delivery in study groups

Methods of delivery of women are presented in Table 5.1.

Table 5.1.

Statistical data on modes of delivery for the study groups

Groups	(n=151)				
	Group I (n=55)		Group II (n=56)		p
Childbirth through ERP	39	70.9%	15	26.7%	p<0.001
Childbirth by intracranial surgery	16	29.1%	41	73.1%	p<0.001

Note: p-significance of results between the first and second groups.

When analyzing the outcome of childbirth, it was revealed that 70.9% of births occurred through the ERP in the first group and 26.7% in the second group.

The frequency of cesarean section (CS) was significantly higher in the second group (73.1% of cases) (p<0.001), while in the first group cesarean section occurred in 29.1% of cases.

The most common indications for cesarean section were inconclusive fetal condition (23.9%), PPA (2.1%), PROM (22.1%).

Assessment of laboratory parameters after therapy among the studied groups.

This study used the results of biochemical studies to evaluate the effect of therapy Dipyridamole on the functional state of the endothelium in pregnant women diagnosed with TPB.

At the same time, no significant differences were found between the groups in age, lifestyle, anthropometric indicators and chronic pathology.

After the proposed and traditional therapy, laboratory parameters were re-evaluated.

Table 5.2.

Laboratory parameters among the study groups before and after therapy

Parameter	Group I (n=55)		Group II (n=56)		p
	Before treatment	After treatment	Before treatment	After treatment	
sICAM-1	1307±26.14	1003±25.38	1297±26.09	1301±25.38	P1 <0.048 P2<0.001
sVCAM-1	798.97±8.70	545.4±8.92	791.3±8.92	795.3±8.92	P1 <0.030 P2<0.001
F. Willebrand (%)	120.0±20.18	99.5±7.43	124.2±20.52	127.2±7.43	P1 <0.028 P2<0.001
p53 protein, U/ml	0.02±0.009	0.01±0.008	0.02±0.007	0.02±0.002	P < 0.001 P<0.001
D-dimer	318.05±5.62	202.41±12.1	321.05±4.22	328.31±6.21	P < 0.025 P<0.001

Note: p1-reliability of results between the first and second groups before treatment. P2-reliability of the results between the first and second groups after treatment.

An analysis of the laboratory tests obtained showed that after the prescribed therapy there was a significant improvement in vascular endothelial markers.

The content of sICAM-1 after therapy improved by 76.7%,sVCAM-1 – 68.3%,F. von Willebrand in 82.9%, p53 protein in 40.0% and D-dimer in 63.5% of cases($p<0.05$). Whereas in the second group, laboratory parameters remained unchanged and were not observed with statistically significant differences.

A coagulogram study was carried out on all pregnant women before treatment, after treatment, during childbirth and in the postpartum period before discharge.

Table 5.3

Coagulogram results after therapy.

Parameter	Group I		Group II		p
	Before treatment	After treatment	Before treatment	After treatment	
APTT (sec)	30.1±2.3	33.4±1.7	29.7±2.4	28.9±1.4	p1=0.56 p2=0.85
Prothrombin time (sec)	8.8±1.2	12.1±1.9	8.1±1.3	8.3±1.6	p1=0.32 p2=1.00
Prothrombin index%	1.2±0.01	0.9±0.01	1.1±0.03	1.0±0.02	p1=0.32 p2=1.00
Fibrinogen (g/l)	5.6±1.1	4.1±1.4	5.9±2.1	5.7±1.7	p1=0.73 p2=1.00
INR	1.8±0.2	1.1±0.4	1.7±0.9	1.7±0.7	p1=1.00 p2=1.00

Note:p1-reliability of results between the first group before and after treatment. p2-p1 reliability of the results between the second group before and after treatment.

After therapy in the first group, the values of indicators were increased such as aPTT by 10.9%, PTI: 37.5%, and there was a decrease in Fibrinogen indicators by - 26.7%, and INR by - 38.8%.

In the second group, repeated laboratory tests revealed no statistically significant differences.

The results of the analysis showed that the use of the drug Dipyridamole in traditional therapy in pregnant women with TPB helps to improve the functional state of the endothelium. These results are achieved due to the effect of therapy on blood clotting mechanisms and the coagulation cascade, which reduces the risk of thrombosis. Considering that some known risk factors for PBL are associated with

changes in endothelial function, the use of the drug Dipyridamole has a positive effect in terms of prevention of PBL.

However, traditional parameters of hemostasis turned out to be less informative in relation to assessing the state of the endothelium, given the effect of the drug Dipyridamole on endothelial dysfunction.

Results of preventive measures during PB complicated by pathological bleeding

The study results show that the birth outcomes in women of the study groups showed that in the first group, urgent births occurred in 61.8% of women and only in 1.8% were complicated by pathological blood loss; in the first group, 38.1% of pregnant women had birth defects and 3.63% of pregnant women had pathological blood loss was diagnosed (Fig. 5.3).

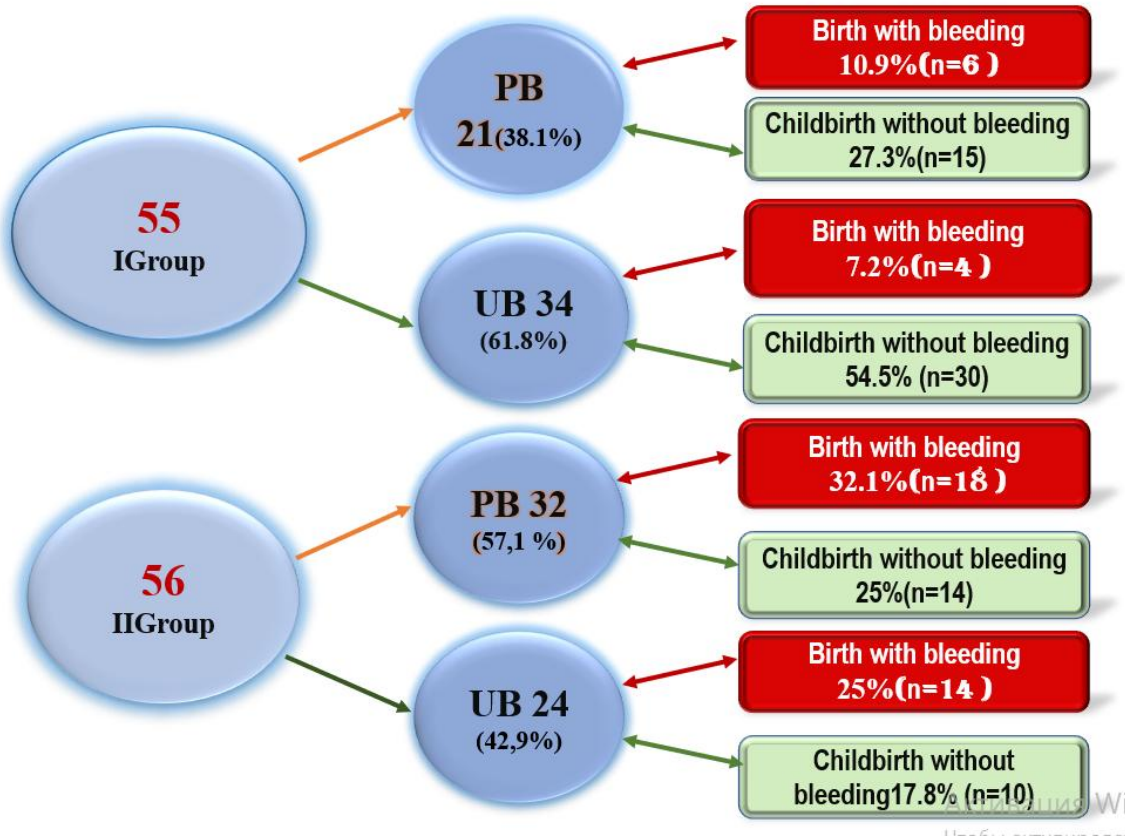

Figure 5.3. Birth outcomes in the examined groups.

In the II group, term births occurred in 42.9% of women and pathological blood loss was observed in 5.3%, birth defects were observed in 57.1% of women and pathological blood loss was diagnosed in 7.14% of pregnant women.

Considering that the causes of complicated childbirth are anhydrous interval and duration of labor, it was advisable to study these parameters.

Table 5.4.

Indicators of duration of anhydrous interval and childbirth

Options	M	Me	Min	Max	Q25	Q75	SD
Group I with premature birth (n=21)							
DurationBP, min	338.59	425	20	900	75	520	247.23
Durationbirths, min	395.68	383	150	810	235	530	174.34
Group I with term birth (n=34)							
DurationBP, min	135.32	10	10	679	10	256	219.47
Durationbirths, min	476.91	555	145	671	310	570	161.79
II Group with premature birth (n=32)							
DurationBP, min	628.70	320	10	7240	20	560	1475.42
Durationbirths, min	319.41	280	20	940	240	390	211.08
II Group with term delivery (n=24)							
DurationBP, min	189.74	18	15	790	19	300	201.39
Durationbirths, min	426.05	430	145	705	320	505	142.04

Note: BP – anhydrous interval.

From the presented data the following conclusions can be drawn:

- The duration of the water-free interval (AWR) differs depending on the groups: women from the second group with PB averaged 9 hours, and in the first group averaged 6 hours.
- The length of labor also varies between groups. The highest value of this parameter is observed in women from the first group, women with term birth,

on average, 7 hours, and the lowest - in women from the second group, with premature birth, on average, 3 hours.

The potential for obstetric hemorrhage in PTB is a serious concern. The data obtained show that pregnancy loss can be complicated by pathological blood loss as early as the 28th week of pregnancy (Fig. 5.4). In all study groups, a statistically significant correlation was found between gestational age and the amount of blood loss ($p<0.05$). Figure 5.4 shows a linear trend, indicating a decrease in the average volume of blood loss with increasing gestational age.

Figure 5.4. Linear trend of decreasing average blood loss with increasing gestational age.

The wide range of variations in height and weight of the women in the study groups made it challenging to assess and interpret the significance of blood loss in this study, in addition to the lack of a reliable method for its objective assessment (Figure 5.5).

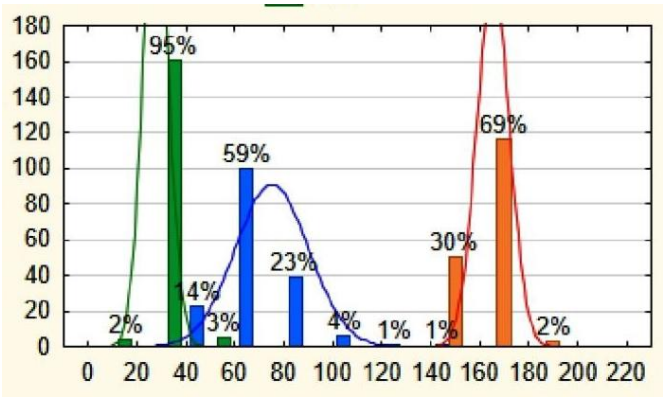

Figure 5.5– Height and weight parameters of women in the study groups

To comparatively assess the amount of blood loss, we analyzed the body mass index of the women in the study, as shown in Figure 5.5.

The women in the research groups varied greatly in their body weights, making it challenging to evaluate and understand the significance of blood loss volume. For instance, during a vaginal delivery, a pregnant woman weighing 51 kg may lose 500 ml of blood, or 9.8 ml/kg; however, in a woman weighing 141 kg, this amount decreases to 3.51 ml/kg. Blood loss during a caesarean section amounts to 19.61 milliliters per kilogram for a 51-kg woman and 7.09 milliliters per kg for a 141-kg woman. These figures carry various risks to a woman's life and health, and they have clinical significance.

Comparative characteristics of the structure of causes of bleeding

The study sample included only women with pathological blood loss during childbirth and the postpartum period (n=42).

Based on the results of birth outcomes, an analysis of the causes leading to PBL was carried out (Fig. 5.6).

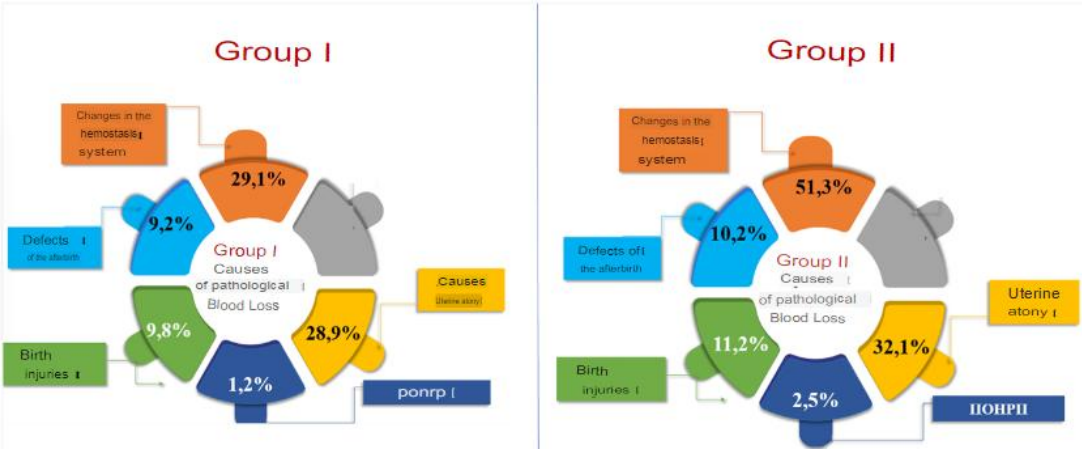

Figure 5.6. Analysis of the causes of pathological blood loss in PR.

The causes of bleeding during and in the postpartum period in group I were disorders of the hemostatic system (29.1%), uterine atony (28.9%), placenta defects (9.2%), birth injuries (9.8%) PPA (1.2%), in group II there were changes in the hemostatic system (51.3%), uterine atony (32.1%), placenta defects (10.2%), birth injuries (11.2%) PPA (1, 5%).

The volume of blood loss in the study groups is shown in Table 5.5.

Table 5.5.

Volume of blood loss in study groups

	Group I			II Group		
	PB_PBL		NB_PBL	PB_PBL		NB_PBL
	31-33 weeks	34-36 weeks	37 or more weeks	31-33 weeks	34-36 weeks	37 or more weeks
Volume blood loss (ml)	**1030.55±265.1**	**910.25±196.1**	**728.30 ± 140.91**	**1203.14 ± 349.02**	**1137.41 ± 296.12**	**788.12 ±127.27**

As shown in Table 5.5. the amount of blood loss in the first group with a gestation period of 31-33 weeks averaged 1030.55 ml., with a gestation period of 34-36 weeks it was 910.25 ml., with term birth 728.30 ml., in the second group with a gestation period 31-33 weeks averaged 1203.14 ml., with a gestation period of 34-36 weeks it was 1137.41 ml., with term birth 728.12 ml.

It should be noted that the volume of blood loss during premature birth was greater in the second group (by 200 ml), in women who did not receive complex preventive therapy during pregnancy.

At the stimulation stage, there is an increase in the production of vasodilating mediators such as nitric oxide and prostacyclin. At the activation stage, there is an increase in the synthesis of mediators that can constrict blood vessels, such as endothelin-1 and thromboxane A2 If placenta previa is suspected or diagnosed, a team of different specialists may be involved in the organisation and management of the birth. This team includes obstetricians, experts in maternal-fetal medicine, as well as anaesthetists and blood bank staff. Depending on the situation, possible treatment approaches may include a planned caesarean section. In this case, the uterus is removed along with the placenta to avoid the risk of significant blood loss [68, p. 28;]

In this regard, the severity of the condition of this population is certainly reflected in the frequency of these procedures over the years. According to the study,

the incidence of preterm delivery by caesarean section was sixty per cent. Analyse the etiological risk factors for massive obstetric haemorrhage. The scientists noted and praised these findings in their study [143, p.247;].

Changes in placental blood flow lead to tissue hypoxia and vascular damage, which increases vascular pathology during complicated pregnancy. Spontaneous abortion is accompanied by a decrease in NO concentration and an increase in the concentration of the vasoconstrictor endothelin-1 in the blood. Threatening spontaneous miscarriage causes an increase in the expression of VEGF and TNF-α. Thrombin deposition during hemorrhages provokes disruption of vasculo- and angiogenesis, vascular and endothelial remodeling, causing gestational complications [24; 63, p.77; 140, p.610;].

The postpartum period's complicated mechanism for halting bleeding frequently results from modifications to the hemostatic system.

The general hemostasis system, a collection of biological and biochemical mechanisms that guarantee the body avoids and halts bleeding and controls the aggregate state of the blood, is crucial in halting postpartum hemorrhage. It is well known that hypercoagulation phenomena, which are particularly prominent in the third trimester and near the start of childbirth, are a characteristic of physiologically occurring pregnancy.

In the general hemostasis system, four main links are conventionally distinguished:

acting in close cooperation with each other:

Vascular-platelet link.

Primary hemostasis is carried out through the implementation of the vascular-platelet mechanism, which ensures the stop of bleeding from microvessels. Then the coagulation mechanism - the plasma enzyme system - is turned on; their combined action ensures stopping bleeding from medium- and even large-caliber vessels.

Link of inhibitors of coagulation and fibrinolysis processes.

The key activation reaction of the fibrinolytic link is the conversion of plasminogen into plasmin, which ensures the lysis of fibrin in the bloodstream. Activation of the

fibrinolytic link can occur in two ways: internally due to the activation of high molecular weight caninogen (HMW) and externally due to tissue kinases synthesized by the endothelium of the vessels of the kidneys, uterus, and lungs.

In the foreign literature, there are a large number of works positioning endothelial dysfunction as well as a significant condition for notching the formation of midwifery and perinatal pathologies: early termination of pregnancy, preeclampsia (PE), fetoplacental insufficiency (FFI), fetal enlargement suspension syndrome (FGRS), etc. The establishment of the importance of the endothelium in the creation of the fetoplacental concept, as well as the study of the elements of venous pathologies in premature pregnancy, is considered one of the promising problems of current obstetrics. Perinatal medical science today often makes it possible to recognize a pregnancy complication only when medical signs occur; modeling methods are not always perfect, and the initial prevention is not available. This establishes the need to study the latest methods of modeling, prevention, and premature diagnosis of acute pathology. According to Rostov scientists (E.M. Glushchenko et al., 2020), in women with placental attachment anomalies, typical blood loss ranges from 3000 to 5000 ml. Placenta previa and placenta accreta increase the risk of major bleeding followed by hysterectomy by up to 51%. The number of abnormal placentation increases annually by 15.6%. The number of cesarean sections increases every year, and the risk of this complication increases accordingly. Additionally, the study found that women with a history of cesarean section had an increased risk of placental abnormalities and subsequent PPH [12, p.27;]. Not so long ago, the achievements in the field of cytological methods made it possible to better understand the dynamics of the endothelium, revealing a difficult balance that should be maintained in order to rationalize the capital of the blood vessel. The recognition of peculiar biomarkers in these desquamated cells can increase diagnostic abilities, allowing clinicians, together with great fidelity, to reveal various levels of endothelial non-functionality. Moreover, combining these cytological data together with modern imaging methods is able to provide a comprehensive understanding of the microvascular concept, which can help detect

painful changes in a premature period. But the use of cytological methods will require a painstaking study of the methods used to select checks, and in addition the ability to misinterpret due to cellular relics or variability among observers. [149, pp. 81-89;]. Disturbances of all or individual links of the general hemostatic system, an imbalance between them, as well as disturbances of other components of hemostasis can lead to the development of massive coagulopathic bleeding in the early postpartum period.

All women with pathological blood loss were prescribed uterotonics.

To stop bleeding, all women used traditional therapy (According to the National Clinical Protocol of the Ministry of Health of the Republic of Uzbekistan, order No. 273 dated November 30, 2021, “Anesthetic management and infusion-transfusion therapy for obstetric hemorrhage”).

The technique for managing women with pathological blood loss should consist of the following steps: Catheterization of 2 peripheral veins with catheters > 16 G, initiation of uterotonic therapy after fetal extraction. According to the standards, women with pathological bleeding during childbirth and the postpartum period were prescribed the following drugs:Oxytocin10–20 IU per 500 ml saline. IV solution or Ringer's solution; 60 drops per minute / 125 ml/h Maintenance dose: 10 IU per 500 ml saline. IV solution or Ringer's solution; 40 drops per minute /120 ml/hour.

Methyl-ergometrine0.2 mg IM or IV (slow) Maintenance dose: 0.2 mg IM or IV (slow) every 4 hours.Misoprostol (prost-glandin E1)200-800 mcg sublingually, without exceeding the dose of 800 mcg. In response to a prolonged purulent inflammatory process, the body tries to fight the inflammation, if it lacks strength, the disease worsens and is of diffuse peritonic origin. In most cases, if secondary peritonitis cannot be prevented, leafletting comes subsequently [133, pp. 1-8; 113, pp.81-85; 118, p.1-12;].

Ispite of to foreign scientists who have studied preterm labour in women, they encounter some symptoms of dehydration associated with blood loss within one day after natural childbirth or surgery. Initial therapy for this condition includes medical

treatment, therapeutic tampons, arterial ligation and compression sutures on the uterus. Also uterine artery embolisation is performed in women with severe uterine artery disease [134, p. 363;].

Preterm labour is undoubtedly one of the most urgent and serious problems worldwide. This phenomenon is of great concern to both medical professionals and expectant parents, as it is associated with many risks and complications for both the pregnant woman and the foetus. The incidence of PB in the world ranges from about 5% in some European countries to 18% [9, p.148; 47, p.11; 148, p.46].

According to the literature, obstetric haemorrhages is unfortunately very common in the world before delivery. It is worth noting, however, that the incidence of bleeding in preterm labour varies within a few per cent. These figures emphasise the importance of close monitoring and timely intervention in case of such situations to ensure the safety of both mother and newborn [139, p. 63].

In addition to traditional therapy, when pathological blood loss occurred, in order to prevent the progression of intravascular coagulation, 4-factor PCC (prothrombin complex concentrate) “Octaplex-500”. Selection and adjustment of the individual dose was carried out on the basis of regular determinations of the concentration of specific coagulation factors in the blood plasma, prothrombin time and MHO.

The condition was assessed during the first 20 minutes after the end of the infusion.

For PB with atonic bleeding, use 4-factor PCC (prothrombin complex concentrate) gave positive results in group I in women who took Dipyridamole compared to group II by 29.5%, respectively, $p<0.004932$.

The results obtained indicate that women with PB (with endothelial dysfunction) exhibit unique features of the myometrium associated with impaired contractility of the uterus during childbirth and the development of atonic bleeding. These results open new possibilities for future research.

The obtained data are significant for further studies of the role of endothelial dysfunction and hemostasis for predicting aspects of uterine involution that are

associated with various factors, including gestational age, delivery method, volume of blood loss and the course of the postpartum period.

The analysis of the results showed a favorable effect of Dipyridamole therapy in women with TPB, on the functional state of the endothelium during pregnancy and on the outcome of labor.

Application 4-factor PCC (prothrombin complex concentrate) “Octaplex-500”in cases of PB with pathological blood loss, they are a valuable contribution to stopping bleeding.

Thus, Dipyridamole therapy caused changes in the parameters of endothelial function in pregnant women. The study demonstrated statistical comparability of the compared groups of patients in the presence of possible risk factors for the development of endothelial dysfunction during pregnancy. The conducted analysis demonstrates the positive effect of Dipyridamole on the functional state of the endothelium during pregnancy, and also confirms the informativeness of the sICAM-1, sVCAM-1, vFW factor and p53U/ml protein in assessing endothelial dysfunction during pregnancy. The study of these parameters can be used to monitor the effectiveness of treatment, prognosis and prevention of preterm labor.

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Imprisonment.

Postpartum hemorrhage is a major direct cause of maternal morbidity and mortality in women in many countries worldwide.

The problem of preterm birth requires adequate attention and treatment to prevent complications such as hemorrhage, which can have serious consequences. Improved strategies for the prevention and management of preterm birth, as well as early detection of abnormal placental attachment, can help reduce the incidence of hemorrhage and related complications. In addition, measures such as timely administration of uterotonics, active management of the third stage of labor, and judicious use of blood transfusion can help prevent severe maternal morbidity and mortality due to postpartum hemorrhage. Modern features of obstetric hemorrhage risk factors are that the following trends are increasingly observed: the frequency of bleeding associated with preeclampsia, HELLP syndrome, premature placental abruption, placenta previa, fetal loss syndromes increases, this indicates a relationship between disorders of the trophoblast invasion process and placentation with hereditary and acquired forms of hemostasis disorders [139, p. 610].

Biochemical diagnostics of endothelial dysfunction is a method for studying human biological environments in order to detect endothelial mediators and other active substances associated with endothelial dysfunction.

Modern science studies endothelial function using biochemical methods, but most of them do not reflect the exact state of this apparatus. Evaluation of endothelial dysfunction through markers is difficult due to many reasons, such as instability of the NO molecule, concomitant pathology and changes in physiological conditions. Many synthesized markers are also present in other cells of the body, which reduces their diagnostic value. All of the above markers do not provide a direct assessment of the morphofunctional state of the endothelium; their interpretation depends on the accompanying pathology.

Despite advances in obstetric care, obstetric hemorrhage continues to be a significant cause of maternal morbidity and mortality worldwide. To address this

ongoing problem, further research is needed to expand our understanding of the etiopathogenesis of obstetric hemorrhage, as well as the possibilities for improving prognosis, prevention, and treatment.

Obstetric hemorrhage remains a serious problem in obstetric care, and further research is needed to expand our understanding of this complex problem. Through an interdisciplinary approach that includes research, education, and innovation, we can improve maternal and child health outcomes and reduce the time of obstetric bleeding worldwide.

The study was conducted in the period 2021-2023 at the branch of the RSNPMZMIR in Samarkand.

This study used a comprehensive approach that included various methods of clinical, laboratory, ultrasound and statistical research.

The retrospective study consisted of examining 171 birth histories of patients with premature birth complicated by obstetric hemorrhage for the period 2016-2021.

The initial clinical characteristics, as well as the features of the course of pregnancy and childbirth, were prospectively analyzed. Pregnant women were included in the study as they sought help.

In accordance with the stated goals and objectives, a cohort controlled study was conducted, based on the data of which the following clinical groups were formed:

A total of (n=111) pregnant women with threatened preterm labor were examined, who were divided into two clinical groups: The main group I consisted of (n=55) women with TPB, and group II - (n=56) women with TPB. The control group consisted of (n=40) women with a physiological course of pregnancy and childbirth.

In accordance with the planned clinical and laboratory examinations, diagnosis and developed methods, the inclusion criteria for the study were compiled.

The inclusion criteria for the study were:

pregnant women with a period of 28-34 weeks, the age of pregnant women from 17 to 37 years, informed consent to participate in the study, women with a

history of premature birth and rupture of membranes, obsetric hemorrhage in the anamnesis.

Exclusion criteria:

isthmic-cervical insufficiency, multiple pregnancy, preeclampsia/eclampsia, fetal developmental abnormalities, abnormalities and tumors of the uterus and ovaries, severe somatic pathology, pregnancy after IVF, women with hereditary and congenital blood diseases.

When studying the anamnesis, lifestyle, past illnesses, bad habits, personal and family history were taken into account. The state of menstrual function and gynecological history were studied, and a general examination was also conducted.

All pregnant women with TPB underwent all regulated laboratory tests.

Complete blood count, blood group and Rh factor, (APTT), (PTI), prothrombin time, fibrinogen, (INH), (ELISA) D-dimer, blood endothelial dysfunction markers (thrombomodulin, soluble adhesion molecules - ICAM-1 and VCAM-1), von Willebrand factor (vWf), p53 protein - transcription factor.

All studies were conducted at the laboratory of the branch of the RSNPMCZMIR in Samarkand and the private medical center "MedSI"

The retrospective stage was carried out to identify the causes of bleeding among women who gave birth prematurely. This is necessary to determine measures to prevent PBL in PB.

All 171 birth histories of women who gave birth prematurely, which were complicated by pathological blood loss in the gestation period of 28-34 weeks of pregnancy, were studied. The analysis of the study revealed that the average age of women was ±27 years, ranging from 17 to 37 years.

When studying the nature of the menstrual function, the onset of menstrual function was 12±3.1 years, the duration of menstruation was 5.07±2.1 days, the onset of sexual activity on average was 18±3.1 years.

The menstrual function of pregnant women was assessed by the age of menarche, the time of establishment of a regular cycle, the duration of menstruation, the amount of blood lost, complaints of pain.

It was revealed that pregnant women most often noted complaints about the following: frequent stress, bad habits, occupational hazards, a history of threatened miscarriage, a history of toxicosis, a history of preeclampsia, oligohydramnios, polyhydramnios, and extragenital pathology. An important role in the development of complications was played by the presence and frequency of EGP in the examined women. During the collection of the gynecological anamnesis, the main pathology was revealed - inflammatory diseases of the genital tract, among which the most common were colpitis (61.4%), inflammatory diseases of the uterus (39.3%), and menstrual dysfunction (16.2%). Of no small importance for the current pregnancy are the outcomes of previous pregnancies in the examined women. A distinctive feature of the obstetric history in pregnant women with TPB is a high frequency of abortions (42.6%), threatened premature birth (95.9%), detachment of a normally located placenta (2.9%), and hypertensive disorders (19.3%).

When studying the parity of women, it was revealed:

1st birth - 15 women (30%), 2-3 births - 13 women (25%), 4th and more births - 22 women (45%). Most women with complicated preterm births were multiparous (63.1%), primiparous made up (39.6%).

In the Samarkand region, as well as throughout the country as a whole, there is a general trend towards an increase in the frequency of premature births and hypotonic bleeding during preterm births. According to the data, for the period from 2016 to 2018, the frequency of hypnic bleeding during childbirth and in the postpartum period during premature births increases from year to year. This undoubtedly leads to an increase in the social problem, in particular, to an increase in the number of premature babies and obstetric complications. Analyzing the outcome of childbirth in a retrospective group of 171 women, it was found that

childbirth ended through the natural birth canal in 74% of cases and by cesarean section in 26%.

According to the literature, physiological blood loss is considered to be blood loss up to 10% of the BV (up to 500 ml) NB, up to 1000 ml - CS, pathological - 10-30% of the BV (> 500 ml) - NB, > 1000 ml CS, massive more - 30% of the BV.

Among the studied birth histories in the retrospective group, it was found that pathological blood loss occurred in 100% of cases, taking into account the special selection of histories.

When analyzing the causes of bleeding, it was found that the following were common causes of bleeding: preterm labor rupture of the uterus 19.1%, postpartum rupture of the uterus 3.3%, uterine atony 28.9%, chorioamnionitis 2.9%, uterine scar 4.2%, placental defects 9.5%, injuries 11.4%, and changes in the hemostasis system 54.7%. In some cases, there were combined causes of PBL.

PBL therapy was carried out according to the standard.

PBL was stopped by drug and surgical intervention.

PBL drug cessation was 92.4%, surgical in 7.6% of cases, which is apparently associated with untimely detection of the causes of bleeding and their elimination in premature birth.

We were faced with the question? What additional measures could prevent PBL in time and in the postpartum period? It is advisable to carry out additional research methods to solve this problem. Considering that one of the causes of PBL is a violation of hemostasis in 54.7% of cases, we were faced with the task of studying hemostatic parameters as a trigger mechanism of PBL.

When studying a retrospective group of women with PB complicated by pathological blood loss, the greatest attention was paid to the coagulogram data: changes in the hemostasis system in the form of shifts in the coagulogram were observed in almost 50% of cases, which in turn proves the above opinions.

In pregnant women with premature birth, there is an increase in the level of prothrombin, which indicates excessive activation of the external coagulation pathway. Shortening of APTT indicates increased activity of the internal coagulation

pathway. An increase in the level of fibrinogen in combination with the above activity of coagulation processes leads to the development of hypercoagulation syndrome in pregnant women, which contributes to PBL in premature birth.

Thus, the study of the pathology of the coagulation system during pregnancy and ways to correct it is a priority area of modern obstetrics.

Studying the data of the hemostasis system in pathological blood loss of women who gave birth prematurely, we can conclude that the study of biochemical markers of the hemostasis system is insufficient, as well as the possible role of endothelial dysfunction in the development of these complications. In addition, the development of effective methods of pathogenetic treatment of hypercoagulation syndrome in pregnant women in the early stages will allow for the prevention of premature birth.

Prospective stage of the study:

For the clinical study, 151 pregnant women were examined, who were divided into three groups. During the study, it will be possible to compare the data of the three groups and evaluate the differences in parameters that may be associated with the risk of developing PBL during PB.

The study included women aged 18 to 36 years, with the majority of them falling between 25 and 30 years old (45%), followed by 31-36 years (30%) and 18-25 years (25%).

Social status: 28% were housewives, and 27% were students, 45% were employed.

Distribution of women by place of residence: 52% of women live in the city and 48% in the regions. It is noteworthy that half of the women who had bleeding during premature birth were from rural areas.

The BMI analysis showed that in Group I the average BMI value was 32.87±4.68; in Group II 33.00±4.66.

When analyzing the reproductive history of the compared groups, it was revealed: the average age of menarche was 13.1±1.21 years; the duration of menstruation was 5.10±2.08 days;

A distinctive feature of the obstetric history of pregnant women with TPB is the high frequency of spontaneous abortions in Group I (70.7%); in Group II (67.6%), the threat of premature birth in Group I (57.8%); in Group II (78.6%), premature birth in the anamnesis in Group I (62.4%); in Group II (61.3%).

When studying the parity of women, it was revealed: 45% were primiparous, and 55% were multiparous. The first birth was in 12 women (22%), the second birth was in 13 women (23.6%), the third birth was in 21 women (38.1%), the fourth or more births were in 9 women (16.3%), in the second group the first birth was in 8 women (14.3%), the second birth was in 11 women (19.6%), the third birth was in 23 women (41.1%), the fourth or more births were in 14 women (25%) in the control group the first birth was in 26 women (65%), the second birth was in 9 women (22.5%), the third birth was in 4 women (10%), the fourth birth was in 1 woman (2.5%). Various gynecological diseases, such as vaginitis, cervical pathology, endocervicitis, chronic metroendometritis and endometriosis, were detected with varying frequency in women of all clinical groups during the year before pregnancy.

Thus, the presence of gynecological diseases can significantly increase the risk of pathological blood loss in premature birth.

Among extragenital diseases (EGD) in the anamnesis, chronic arterial hypertension (CAH), chronic pyelonephritis, obesity of varying degrees, myopia, varicose veins (VV) of the lower extremities, iron deficiency anemia (IDA) were more common.

The obtained ultrasound data showed that women in the first group had a higher proportion of uteroplacental blood flow disorder of the 1st degree than in the control group. Chronic placental insufficiency was detected only in women with premature birth. The frequency of placental insufficiency was higher in the second group (35%) than in the first group (45%) and the control group (2%).

When analyzing the outcome of labor, it was found that 70.9% of cases of delivery occurred through NB in the first group and 26.7% in the second group.

The frequency of cesarean section (CS) was significantly higher in the second group 73.1% of cases ($p < 0.001$), while in the first group 29.1% of cases.

Indications for cesarean section were an inconclusive condition of the fetus, PDLNP, PROM.

The fourth chapter of the monography describes biochemical research methods.

The course of pregnancy is accompanied by adaptive changes in the hemostasis system, which plays an important role in the gestation process. The average APTT was 29.4±3.24 sec. in the control group and 30.1±3.52 sec. in the main group ($p>0.05$). PTI: 93.4±14.23% in the control group and 88.0±10.21% in the main group ($p>0.05$). Fibrinogen: 3.9±0.93 g/l in the control group and 4.3±0.84 g/l in the main group ($p>0.05$). INR: 1.1±0.12 in the control group and 1.1±0.08 in the main group ($p>0.05$). The study of the coagulation system in pregnant women also includes the analysis of the cellular component of hemostasis. The scientific literature has demonstrated the role of platelets in ensuring trophism of the vascular intima: electron microscopy confirmed the angiotrophic function of platelets [2; 42]. This additionally justifies the inclusion of an analysis of the state of the cellular component of coagulation in our study, which provides a more complete study of the factors affecting the morphofunctional state of the endothelium.

The average value of the platelet count in patients in the main group was 335.5 ± 69.12 × 109 / l and 234.2 ± 69.11 × 109 / l in the control group ($p> 0.05$). Determination of the average platelet volume also did not demonstrate reliable differences 11.7 ± 0.93 fl in the main group and 9.1 ± 1.32 fl in the control group ($p> 0.05$). Thus, when analyzing the hemostasis parameters, no reliable differences were found in the groups of participants.

During the study, biochemical markers of endothelial dysfunction were determined in the participants of the first stage of the work. The indicators that are available for laboratory analysis and objectively reflect changes in the functional state of the endothelium were selected.

The most reliable and accessible laboratory indicators of the pathology under study were: highly sensitive von Willebrand factor (vWf), p53 apoptosis protein,

soluble vascular cell adhesion molecule-1 and soluble intercellular adhesion molecule-1

The study was conducted among 111 pregnant women, in whom various indicators of the endothelial state were assessed.

The average indicators of biochemical markers - von Willebrand factor (vWf) and the p53 protein apoptosis marker were compared between two groups of women - with TPB (main groups) and women with a physiological course of pregnancy (control group).

The concentration of the p53 apoptosis protein in the peripheral blood plasma of women with normal pregnancy was 0.003 U/ml, with a range of 0.001 to 0.01 U/ml and a standard deviation of 0.0013 U/ml.

The value of the concentration of the p53 apoptosis protein in the blood serum was also higher in the main group - 0.01 ± 0.011 U / ml compared with 0.003 ± 0.0013 U / ml in the control group. The difference was statistically significant ($p = 0.009$).

The average von Willebrand factor in the main group of women with TPB was - 120.0 ± 20.18%, compared with the control group with 101.6 ± 9.47%. The difference between them was also statistically significant ($p = 0.0005$). In 49.8% of women with TPB, an increase in the D-dimer content in the blood above 300 ng/ml was detected. This indicates the processes of cross-polymerization of fibrin in the process of intravascular blood coagulation. This confirms the participation of endothelial dysfunction and apoptosis in the possible development of obstetric hemorrhage during premature birth and in the postpartum period.

sICAM (intercellular adhesion molecule) and sVCAM (vascular cell adhesion molecule) are functional endothelial markers that play an important role in the pathophysiology of obstetric hemorrhage in preterm labor. These markers are expressed on the surface of endothelial cells and mediate adhesion, migration, and transendothelial migration of leukocytes.

sICAM-1 was upregulated by 1.3-fold and sVCAM-1 by 1.1-fold, which was confirmed by a significant increase in serum levels in pregnant women compared to healthy pregnant women.

Thus, functional endothelial markers are valuable tools for the assessment of endothelial dysfunction in pregnant women and may provide important insights into the pathogenesis of obstetric hemorrhage in preterm labor.

In addition to their role in leukocyte recruitment, sICAM-1 and sVCAM-1 are also involved in the regulation of vascular tone and permeability. Increased expression of these markers may lead to endothelial dysfunction and impaired vasodilation, which may further exacerbate the risk of obstetric hemorrhage.

These markers may serve as potential targets for the development of new therapeutic strategies aimed at reducing the risk of obstetric hemorrhage and improving maternal and fetal outcomes in preterm birth.

Preventive measures: The results of the study of the anamnesis of the retrospective and prospective group showed that a history of complicated labor, repeated births, miscarriage, a history of multiple non-viable pregnancies, medical abortion, chronic inflammatory diseases of the reproductive system are triggers in the development of preterm birth.

To identify risk factors for PBL in PB, we conducted a number of laboratory research methods such as determining endothelial dysfunction and the activity of the homeostasis system in the study groups.

The inclusion criteria for both groups were pregnant women with TPB, progressive pregnancy, the absence of arterial hypertension, diabetes mellitus and other chronic diseases in the acute stage. The study assessed the hemostasis system.

The study included 111 pregnant women with TPB (the main 2 groups) to evaluate antiplatelet therapy on the functional state of the endothelium during pregnancy. Group I consisted of 55 pregnant women with TPB who received the proposed therapy, the comparison group II consisted of 56 pregnant women with TPB who received standard therapy.

After laboratory tests and detection of changes in hemostasis, all women in Group I were prescribed 4,8-Di-1-piperidinylpyrimidole pyrimidine-2,6-diyl under the control of the coagulation system. In our study, we used Dipyridamole tablets. Dipyridamole was prescribed at a dosage of 75 mg / day, 1 tablet x 2 times a day for 14 or more days under the control of the coagulation system.

When the onset of labor, Dipyridamole was stopped immediately, with a normal course of pregnancy, therapy continued until the end of the prescribed period. Dipyridamole did not exceed 34 weeks.

Women in the second group received standard therapy.

Standard therapy included tocolytic, hormonal therapy and FRD prevention.

After the prescribed therapy, coagulogram parameters were studied: activated partial thromboplastin time, prothrombin index, fibrinogen, international normalized ratio, average platelet counts and average platelet volume.

To assess the risk of bleeding in preterm birth, the methods of delivery and birth outcome, causes of bleeding, correlation between gestational age and blood loss, analysis of blood parameters and characteristics of the course of labor were studied.

The frequency of cesarean section (CS) was significantly higher in the second group 73.1% of cases in pregnant women with TPB who received standard therapy ($p < 0.001$), while in the first group cesarean section occurred in 29.1% of cases.

In this study, the results of biochemical studies were used to assess the effect of Dipyridamole therapy on the functional state of the endothelium in pregnant women diagnosed with TPB.

In this study, no significant differences were found between the groups in age, lifestyle, anthropometric indicators and chronic pathology.

After the proposed and standard therapy, laboratory parameters were re-evaluated.

Analysis of the obtained laboratory studies showed that after the prescribed therapy (Dipyridamole), there was a significant improvement in the indicators of vascular endothelial markers. The content of sICAM-1 after therapy approached the

outcome and the indicators improved in 76.7%, sVCAM-1 - 68.3%, Von Willebrand factor in 82.9%, p53 protein in 40.0% and D-dimer in 63.5% of cases ($p<0.05$). Whereas in the second group, laboratory indicators remained unchanged and no statistically significant differences were observed.

A coagulogram study was conducted for all pregnant women before treatment, after treatment, during childbirth and in the postpartum period before discharge.

After the therapy in the first group, the values of indicators increased such as APTT by 10.9%, PTI: 37.5%, and there was a decrease in Fibrinogen indicators by - 26.7%, and INR by - 38.8%.

In the second group, no statistically significant differences were found during repeated laboratory testing.

The results of the analysis showed that the use of Dipyridamole in standard therapy in pregnant women with PB improves the functional state of the endothelium. These results are achieved due to the effect of therapy on blood coagulation mechanisms, on the coagulation cascade, which reduces the risk of thrombosis. Considering that some known risk factors for PC are associated with changes in endothelial function, the use of Dipyridamole had a positive effect.

However, traditional hemostasis parameters were less informative in relation to assessing the state of the endothelium, given the effect of Dipyridamole on endothelial dysfunction.

In the first group, urgent births occurred in 61.8% (34) of women and only 11.7% (4) were complicated by pathological blood loss, PB in the first group occurred in 38.1% (21) of pregnant women and 28.5% (6) of pregnant women were diagnosed with pathological blood loss. In the second group, 42.8% (24) of women delivered urgently and 58.3% (14) had pathological blood loss, 58.1% (32) of women had preterm labor and 56.2% (18) of pregnant women were diagnosed with pathological blood loss.

The possibility of obstetric hemorrhage during preterm labor is of serious concern. The data obtained show that preterm labor can be complicated by pathological blood loss as early as the 28th week of pregnancy.

A statistically significant correlation was found between the gestational age and the volume of blood loss ($p < 0.05$) in all study groups. A decrease in the average volume of blood loss was found with increasing gestational age, but the degree of approximation accuracy was not significant ($R2 = 0.59$). The causes of bleeding were soft tissue ruptures 2.38% (1), placental defects 4.76% (2), hypotonic bleeding during labor 2.38% (1), in the second group of pregnant women with timely births, hypotonic bleeding during labor was most common 11.9% (5) and hypotonic bleeding in the early and late postpartum period 9.52% (4).

The volume of blood loss in the study groups showed that pathological blood loss in the first group with premature birth was 1.3 less than in the second group.

The mechanism for stopping bleeding in the postpartum period is quite complex, often arising due to changes in the hemostasis system. All women with pathological blood loss were prescribed uterotonics and uterotonics to prevent bleeding during childbirth:

To stop bleeding, all women were given standard therapy (According to the Standards of the Ministry of Health of the Republic of Uzbekistan № 273 dated November 30, 2021, management of women with pathological blood loss included).

The technique for managing women with pathological blood loss consisted of the following steps: Catheterization of 2 peripheral veins with catheters> 16 G, initiation of uterotonic therapy after fetal extraction. According to the standards, women with pathological bleeding during childbirth and in the postpartum period were prescribed the following drugs: Oxytocin 10-20 IU per 500 ml of saline or Ringer's solution intravenously; 60 drops per min. / 125 ml / h Maintenance dose: 10 IU per 500 ml of saline. solution or Ringer's solution intravenously; 40 drops per minute / 120 ml / h.

Methylergometrine 0.2 mg intramuscularly or intravenously (slowly) Maintenance dose: 0.2 mg

Vascular-platelet stimulants (dicynone or etamsylate 4 ml, 0.5 g of active substance, intravenously.)

Tranexamic acid (transamcha, cyclo-F) - antiplasmin drug at a dose of 500-750 mg in saline.

In case of unstable hemodynamics and ongoing bleeding, glucocorticoid therapy was prescribed - prednisolone at least 10 mg / kg / h or hydrocortisone at least 100 mg / kg / day.

In addition to standard therapy, 4-factor PCC (prothrombin complex concentrate) "Octaplex-500" was used at a dose of at least 10 mg / kg / h, which contributed to the rapid normalization of hemostasis system parameters, hemoglobin, hematocrit and platelets. In case of PB with hypotonic bleeding, the use of protease inhibitors gave positive results in group I in women who took Dipyridamole compared to group II with 29.5% ($p<0.004932$).

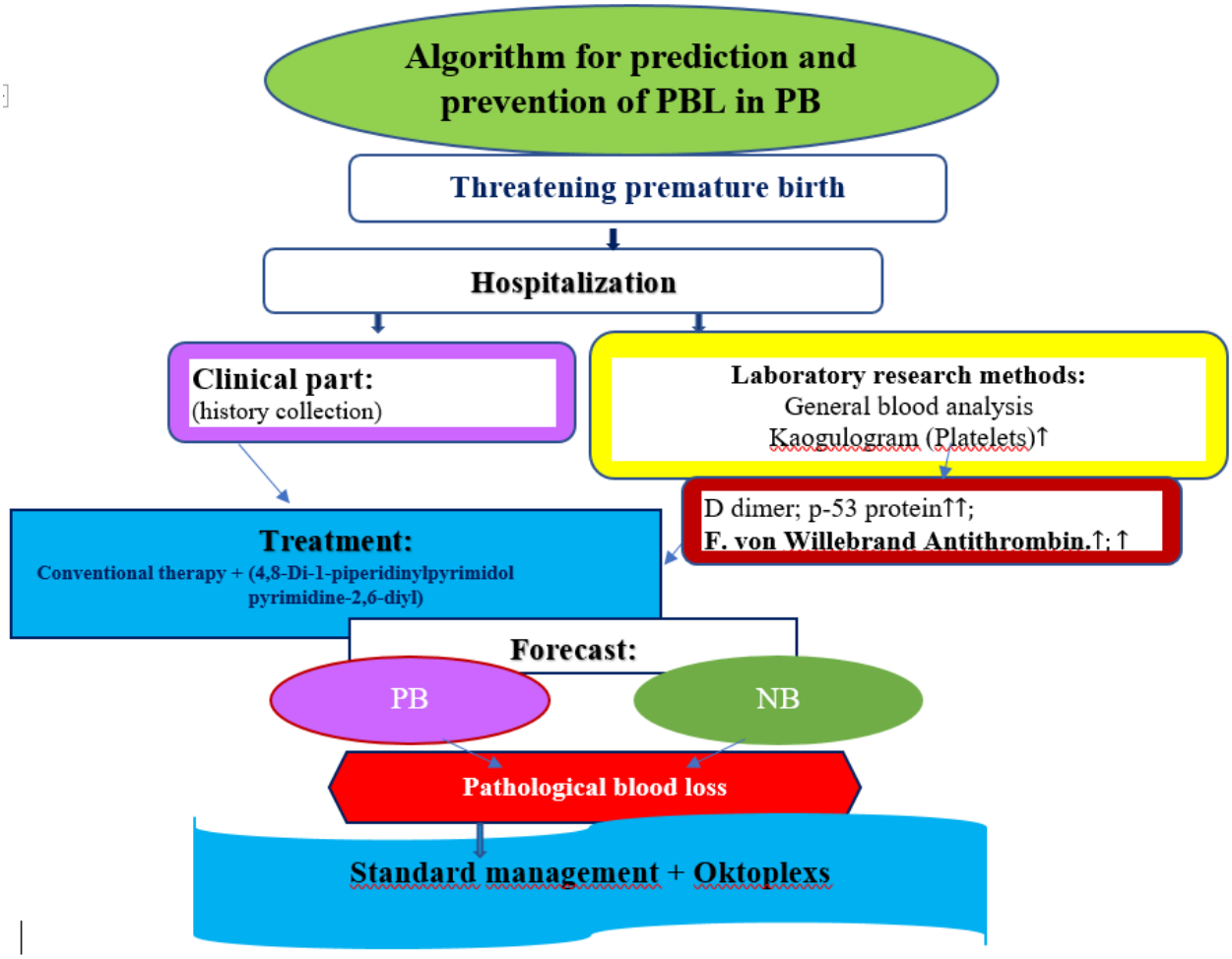
The obtained results indicate that women with PBL (with endothelial dysfunction) exhibit unique features of the myometrium associated with impaired uterine contractility during labor, the development of hypotonic bleeding and late postpartum hemorrhage. These results open up new opportunities for future research.

The obtained data are significant for further studies of the role of endothelial dysfunction and hemostasis for predicting aspects of uterine involution that are associated with various factors, including gestational age, delivery method, blood loss volume and the course of the postpartum period.

The analysis of the results showed a favorable effect of Dipyridamole therapy in women with PB of the main group on the functional state of the endothelium during pregnancy and on the outcome of labor. The use of protease inhibitors in PB with pathological blood loss is a valuable contribution to stopping bleeding.

Thus, Dipyridamole therapy caused changes in the parameters of biochemical indices of the endothelium in pregnant women. The analysis demonstrated a positive effect of Dipyridamole on the functional state of the endothelium during pregnancy, and also confirmed the informativeness of the sICAM-1, sVCAM-1, vFW factor and protein p53, U/ml in assessing the impairment of endothelial dysfunction during

pregnancy. The study of these parameters can be used to monitor the effectiveness of treatment, prognosis and prevention of PB.



Note: PB – premature birth; NB - normal birth.

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