NATURALISTA CAMPANO
ISSN: 1827-7160
Volume 28 Issue 1, 2024

Pathological Blood Loss in Women with Premature Birth

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Annotation: The study demonstrated the statistical comparability of the compared groups of patients in terms of the presence of possible risk factors for the development of endothelial dysfunction during pregnancy. The analysis demonstrates the positive effect of Dipyridamole on the functional state of the endothelium during pregnancy, and also confirms the informative value of the parameter sICAM-1, sVCAM-1, factor vFW and Protein p53Ed/ml in assessing endothelial dysfunction during pregnancy. The study of these parameters can be used to monitor the effectiveness of treatment, prognosis and prevention of diseases.

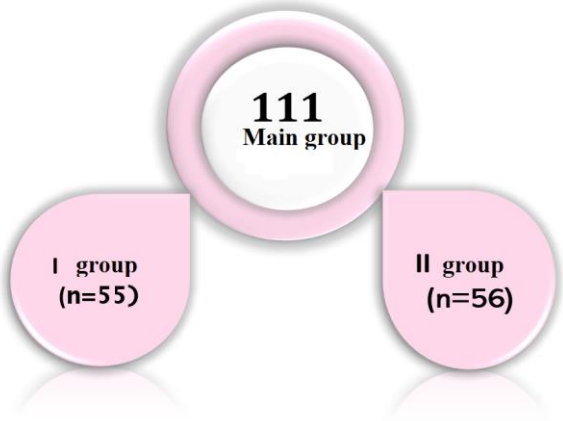
Keywords: Premature birth, pathological blood loss, endothelial dysfunction.

1. Introduction

Although global efforts are being made to prevent it, obstetric hemorrhage remains a significant risk to the health and lives of mothers and requires study of more effective prevention and treatment measures. Bleeding occurring during pregnancy, childbirth and pregnancy continues to be the leading cause of maternal morbidity and mortality throughout the world [7; 12;].
Quite often in the practice of an obstetrician-gynecologist, bleeding occurs after delivery and is considered atonic. In developing countries of the world, 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, methods of organ-preserving technologies have been developed [11;]

2. Materials and Methods:

To identify risk factors for PBL in PB, 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.
The inclusion criteria for both groups were pregnant women with TPB, progressive pregnancy, absence of arterial hypertension, diabetes mellitus and other chronic diseases in the acute stage. The study included an assessment of the hemostatic system.



Picture 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

received the proposed therapy in addition to pregnancy-preserving therapy, group II (comparison) (n=56) pregnant women with TPB received traditional therapy (Fig. 1).

3. Research results:

After laboratory tests were carried out and changes in the hemostatic system were identified, all women in 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 prophylaxis.
After prescribed therapy, coagulogram parameters were studied: activated partial thromboplastin time, prothrombin index, fibrinogen, international normalized ratio, mean platelet count and mean platelet volume (chapter 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 birth in group I was observed in 61.8% of cases, in group II in 42.9% of cases (Fig. 2).

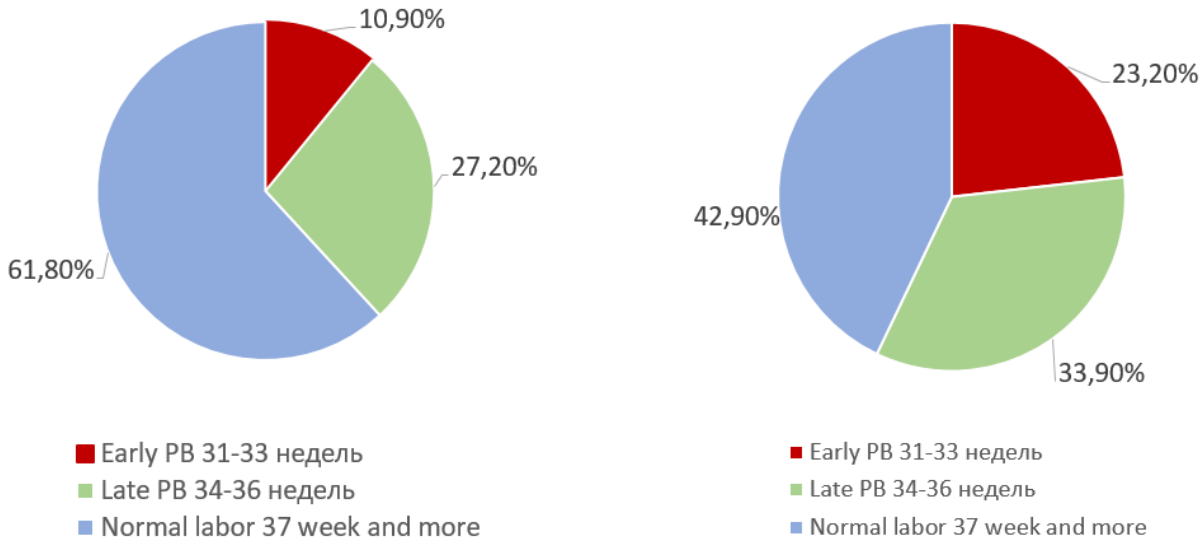


Figure 2. Timing of delivery in study groups

Table 1. Statistical data on modes of delivery for the study groups

Groups	(n=151)				
	Group I (n=55)		Group II (n=56)		R
Childbirth through ERP	**39**	**70.9%**	**15**	**26.7%**	R<**0.001**
Childbirth by intracranial surgery	**16**	**29.1%**	**41**	**73.1%**	R<**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 NL in the first group and 26.7% in the second group.
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.
After the proposed and traditional therapy, laboratory parameters were re-evaluated.

Table 2. Laboratory parameters among the study groups before and after therapy

Parameter	**Group I (n=55)**		**Group II (n=56)**		**R**
	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 withstatistically 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 3. Coagulogram results after therapy.

Parameter	**Group I**		**Group II**		**R**
	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.
The results of 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.
In the second 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.
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. Figure 3 shows a linear trend indicating a decrease in the average volume of blood loss with increasing gestational age.

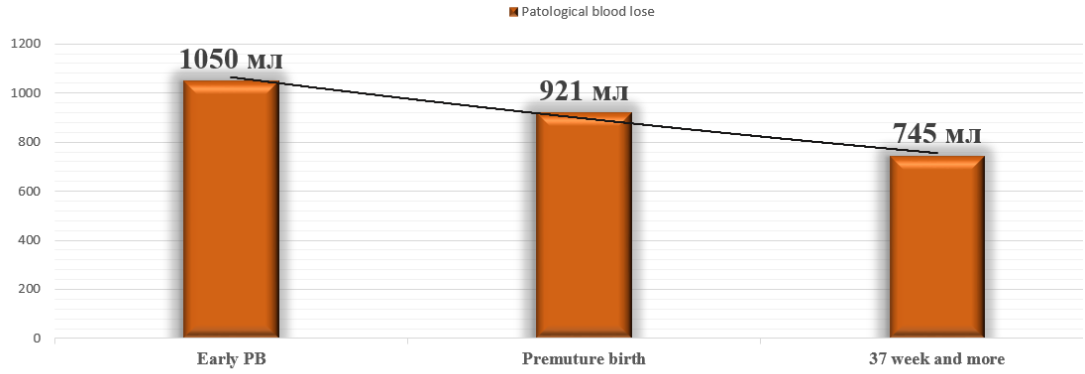


Figure 3. Linear trend of decreasing average blood loss with increasing gestational age.

Based on the results of birth outcomes, an analysis of the causes leading to PC was carried out (Fig. 5). The study sample included only women with pathological blood loss during childbirth and the postpartum period (n=42).

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%) PDNLP (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%) PDNLP (1, 5%).
The volume of blood loss in the study groups is shown in Table 4.

Table 4. Volume of blood loss in study groups

	Group I			**II Group**		
	PB_PBL		**NB_PBL** 37 or more weeks	**PB_PBL**		**NB_PBL** 37 or more weeks
	31-33 weeks	34-36 weeks		31-33 weeks	34-36 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 4, 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 of 31-33 weeks the average was 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.

The mechanism for stopping bleeding in the postpartum period is quite complex and often occurs due to changes in the hemostatic system.

The general system of hemostasis is of decisive importance in stopping postpartum hemorrhage - a set of biological and biochemical processes that ensure the body prevents and stops bleeding and regulates the aggregate state of the blood. It is known that physiologically occurring pregnancy is characterized by hypercoagulation phenomena, especially pronounced in the third trimester and towards the beginning childbirth

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. Carboprost (prostaglandin F2a) 0.25 mg IMM aintenance dose: every15 minutes. 0.25 mg IM

Stimulating vascular-platelet link (dicinone or etamsylate 4 ml, 0.5 g of active substance, intravenously.)

Tranexamic acid is an ant plasmin drug in a dose of 500–750 mg in saline solution.

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 traditional therapy in the event of pathological blood loss, in order to prevent the progression of intravascular coagulation,4-factor PCC (prothrombin complex concentrate) "Octaplex-500". The dose of the drug was in the therapeutic zone - 20-30 ml/kg, which corresponded to 1200-2000 ml. The entire calculated dose was diluted in 50 ml. saline solution for injection, the rate of drug administration was 3 ml/min. 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 INR.

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

For PB with atonic bleeding, use4-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 findings are significant for further research into the role of endothelial dysfunction and hemostasis in predicting aspects of uterine involution that are associated with various factors, including gestational age, method of delivery, volume of blood loss and the course of the postpartum period.

Analysis of the results showed a beneficial effect of therapy with Dipyridamole in women with TPB, on the functional state of the endothelium during pregnancy and on the outcome of childbirth.

Application4-factor PCC (prothrombin complex concentrate) "Octaplex-500"in cases of PB with pathological blood loss, they are a valuable contribution to stopping bleeding.

4. Conclusions

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

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