Mielikova T. A. Pathogenetic Substantiation of the Usability of the Natural Anticoagulant Sulodexide in a Combine Treatment of Pregnant Women with Premature Delivery. Journal of Education, Health and Sport. 2017;7(5):715-722. eISSN 2391-8306. DOI http://dx.doi.org/10.5281/zenodo.819429
http://ojs.ukw.edu.pl/index.php/johs/article/view/4567

The journal has had 7 points in Ministry of Science and Higher Education parametric evaluation. Part B item 1223 (26.01.2017).
1223 Journal of Education, Health and Sport eISSN 2391-8306 7

The authors declare that there is no conflict of interests regarding the publication of this paper.
Received: 05.05.2017. Revised: 23.05.2017. Accepted: 31.05.2017.

PATHOGENETIC SUBSTANTIATION OF THE USABILITY OF THE NATURAL ANTICOAGULANT SULODEXIDE IN A COMBINE TREATMENT OF PREGNANT WOMEN WITH PREMATURE DELIVERY

T. A. Mielikova

Kharkiv Medical Academy of Postgraduate Education, Kharkiv, Ukraine

Abstract

Clinical effectiveness of the Natural Anticoagulant Sulodexide at violations in system of a hemostasis at pregnant women with threat of premature births is studied. 57 pregnant women with threat of premature births are examined. At 31 women in a combine of treatment applied Sulodexide, at 26 – a heparin, at 20 the physiological current of a gestation is noted. Conducted all-clinical examination of pregnant women, estimated a condition of system of a hemostasis before combine treatment. At patients at threat of premature births essential have significant changes in the hemostatic system, manifested in thrombocyte hyper-aggregation and hyper-coagulation in the plasma link of hemostasis, as well as appearance of markers of activating the intravascular blood coagulation. Use of the natural anticoagulant sulodexide for pregnant women provided the high antithrombotic potential and moderate anti-coagulative activity, contributed to normalization of rheological behavior of blood by influence on all links of a hemostasis, to improvement of the course of the gestational period and the functional state of the fetus.

Key words: **pregnancy, premature birth, hemostasis, anticoagulant.**

The health care reforms conducted in Ukraine are aimed at maintaining a healthy nation. One of the lines of improving the health system in this country is the optimization of perinatal medicine. According to the literature of the recent years, recorded is a significant increase in frequency of premature deliveries (15–18 %), which complicates the course of the gestational period creating a threat to the health of a woman and a fetus, leading to an increase in maternal and perinatal mortality. In 50–70 % of cases, the complications caused by premature deliveries are responsible for perinatal mortality [1, 2].

Due to advances in medicine in the recent years, as well as a broad introduction of the achievements of clinical hemostasiology and immunology into clinical obstetrics, it became possible to evaluate the etiology and pathogenesis of obstetric complications such as the premature delivery, fetal loss syndrome, abruption of a normally placed placenta [2].

The delivery, which occurred at the gestation age from 22 to 37 weeks from the first day of the last menstruation, with the birth of a premature baby weighing from 1000 to 2500 g and less than 45–47 cm in height (length), are considered as those premature. The frequency of premature deliveries ranges from 15 to 18 % and in some regions, it reaches 21 % [3].

The premature delivery as well as miscarriage as a whole, are caused by various factors: socio-economic, financial, obstetric, placental and fetal. The onset of premature delivery should be considered as a consequence of the many reasons.

In the recent years among the major systemic causes of the premature delivery, certain authors focus on the hemostatic system as an important link in the development of complications of pregnancy, deliveries and the postnatal period [4].

Premature deliveries are characterized by frequent obstetric complications. In the complex of measures for treating and preventing from threatened miscarriage, the use of products reducing the contractile activity of the myometrium is of key importance. The prevention of the respiratory distress syndrome should be an integral part of the therapy. The treatment of fetal hypoxia is an essential component in treatment of threatened premature delivery. The question of caesarean-section delivery at premature pregnancy is solved individually. Women with premature delivery should be referred to high-risk patients [8, 10].

A delivery should be carried out in a specialized maternity obstetric hospital, which has conditions for preventing possible complications for the mother and fetus and nursing the premature baby.

Pregnancy is considered as the hypercoagulable state in consequence of an increase in concentrations of circulating procoagulant factors, reduction of the concentration of protein anticoagulants and fibrinogenesis [4, 7].

However, despite this, till today the physiological condition of the hemostasis system in obstetric pathology remains insufficiently elucidated, especially at premature deliveries, conditioning a high risk of thrombohemorrhagic and coagulopathic bleedings. The lack of specific information on the etiopathogenesis, clinical and laboratory monitoring of pregnancy complications in women with threat of premature deliveries does not allow evaluating the changes that take place in the hemostatic system [5, 6].

Despite the large volumes of information about premature deliveries, the question of the pathogenetic role of hemostatic disorders has not been studied; there is no uniform scheme of correction of these violations, which served as a basis for this study.

The goal of the study was to investigate the clinical effectiveness of the natural anticoagulant sulodexide at hemostatic system disorders in pregnant women with threatened premature deliveries.

The study involved 57 pregnant women with threatened premature deliveries: I group – 31 pregnant women whose combination treatment included sulodexide, II group – 26 pregnant women, receiving heparin in the combination treatment. Group III (control) – 20 pregnant women with physiological course of gestation.

The group of examined pregnant women included those women with a burdened obstetric and gynecological history (spontaneous abortion, non-developing pregnancy, premature deliveries history). In addition, the examined pregnant women were comparable for age, parity of deliveries, and frequency of extragenital pathology, which allows comparing of the obtained results.

Evaluation of the hemostatic system condition was carried out by the following parameters: the number of thrombocyte count (Tc), spontaneous thrombocyte aggregation index (STAI) were determined, the total capacity of the blood coagulation time was determined by the recalcification time (RT), prothrombin time (PTT). Activated partial thromboplastin time (APTT) was examined using reagents of the research firm “Simko Ltd”. Using the reagents of this company, determination of D-dimers, the level of soluble fibrin-monomer complexes (SFMC) was conducted. The determination of the concentration of fibrinogen (FG) in plasma was performed by the Rutberg’s method (1961), antithrombin III (AT III) and activity of plasminogen (AP) in the plasma were examined with the aid of NOR Partigen kits (Germany).

Statistical processing of results of the research was carried out on a PC, using parametric and non-parametric methods of variation statistics, with the aid of the applied software “Statistica” (Statsof, 2006) for biological research. The probability of differences in

the compared groups was determined by Student's tables. In this paper the results were considered significant at $P < 0.05$.

Results and their discussion. The obtained results of the research (Table) showed that the number of thrombocytes in pregnant women with threatened premature deliveries tended to decrease, due to the increased consumption that characterizes the growing index STAI (Tc before treatment/ after treatment: I group – $(190.1 \pm 1.5)\ 10^9$ / $(213.1 \pm 2.7)\ 10^9$; II group – $(186 \pm 5.4)\ 10^9$ / $(201.41 \pm 1.10)\ 10^9$; in the control group – $(223.4 \pm 1.90)\ 10^9$; $P < 0.05$). RT, that determines the 'internal' pathway of blood coagulation, increased in the main group, presumably by reducing the number of the free thrombocytes.

Hemostasis system indicators in the examined pregnant women during treatment

Indicators	Groups of the examined people				
	Group I (*n* = 31)		Group II (*n* = 26)		Group III (*n* = 20)
	Before treatment	After treatment	Before treatment	After treatment	Healthy pregnant women
Tc, 10^9	190.1 ± 7.5**	213.1 ± 2.7*	186.0 ± 5.4	201.41 ± 1.10*	223.4 ± 1.9
ISPA, unit	12.08 ± 1.10**	7.05 ± 0.90	13.07 ± 1.10**	8.25 ± 1.16*	6.41 ± 0.82
RT, sec	90.05 ± 1.02	84.17 ± 1.12	91.23 ± 1.01**	85.05 ± 1.07	83.03 ± 2.04
PTT, sec	15.08 ± 1.05	17.12 ± 1.59	15.46 ± 0.65	17.01 ± 2.70	18.04 ± 1.17
AT-III, %	79.17 ± 0.90	81.24 ± 1.10	78.43 ± 1.14	80.15 ± 0.93	84.10 ± 3.05
FG, g/l	5.9 ± 0.7	3.90 ± 1.05	5.82 ± 0.10	4.10 ± 1.05	3.65 ± 0.83
AP, %	91.4 ± 1.02**	110.20 ± 1.04*	90.40 ± 2.01**	109.41 ± 1.80*	117.34 ± 2.73
IPTT, sec	15.43 ± 1.,19**	21.34 ± 1.05	16.51 ± 1.17	20.64 ± 1.08	22.78 ± 1.17
D-dimers, ng/ml	1200 ± 115	960 ± 124	1140 ± 109	980 ± 135	950 ± 110
SFMC, µg/ml	35.32 ± 1.72**	24.01 ± 1.59*	42.1 ± 1.3**	30.14 ± 1.04	28.44 ± 1.15

* Reliability difference compared with the control group ($P < 0.05$).

** Difference in reliability compared before and after treatment ($P < 0.05$).

PTT, reflecting the activity of factors of 'external' way of blood coagulation, decreased, thereby showed a hypercoagulable state in the pregnant women with threatened premature deliveries. In the course of pregnancy progress, in the mother's blood coagulation potential strengthens due to an increase in the amount of fibrinogen, the concentration of which in blood plasma increases from 3 months of pregnancy. The concentration of fibrinogen in the blood plasma of the main group was reliably increased relatively to the control group parameters (before treatment/after treatment: I group – (5.9 ± 0.7) g/l / (3.90 ± 1.05) g/l, II group – (5.82 ± 0.10) g/l / (4.10 ± 1.05) g/l, in the control group – (3.65 ± 0.83)

g/l; $P < 0.05$). The APPT is a parameter to measure the effectiveness of the "internal" and common way of blood coagulation; the examined patients had a decreasing tendency of this value, which is also indicative of an elevated thrombosis. Plasminogen activity decreased due to enhanced consumption of said proenzyme.

During long-term keeping of the balance between the activated factors of vascular-thrombocyte and coagulation links, on the one hand, and an increase in fibrinolysis, on the other hand, depletion of plasminogen and antithrombin III, which can lead to serious complications of the gestation age, occurs. Of all the anticoagulants, the greatest value has AT-III, which binds thrombin at a ratio of 1 : 1. The AT-III activity is potentiated in the presence of negatively charged glycosaminoglycans such as heparin sulphate, which is on the surface of endothelial cells. There were downward fluctuations of this indicator in comparison with the control group.

In pregnant women with a high risk of development of thromboembolic complications, in particular, the same as at threatened premature delivery, hemostatic system disorders develop from the I trimester of pregnancy, manifest themselves by activation of intravascular blood coagulation and by an increase of aggregation activity of thrombocytes, what was expressed in increasing the concentration of soluble fibrinogen-monomer complexes (SFMC) in the blood plasma and confirmed the importance of monitoring of the hemostasis system from early pregnancy. D-dimers are protein fragments formed as a result of the fibrin dissolution. In the group I and II an increase of this indicator was observed in comparison with the control group, what was confirmed by the state of a hypercoagulation (D-dimers before treatment/after treatment: I group – (1200 ± 115) ng/ml / (960 ± 124) ng/ml; II group – (1140 ± 109) ng/ml / (980 ± 135) ng/ml; the control group – (950 ± 110) ng/ml; $P < 0,05$).

Treatment of pregnant women with threatened premature deliveries and disorders in the hemostatic system is carried out by a scheme individually selected for each patient. In doing so, the basic principle of the therapeutic and preventive measures in this case was a sedative, spasmolytic therapy, beta-adrenergic agonists at the end of the II trimester of pregnancy, antiaggregant and anticoagulant therapy, conducting the preventive measures as to placental insufficiency.

Care of women at the stage of pregnancy is fundamentally differs and necessitates to search for products, which are safe for the mother and fetus at any stage of pregnancy, having an antiaggregant, hypocoagulation and immunocompetent action. In this regard, our attention was attracted by the natural anticoagulant sulodexide. In order to correct disorders in the hemostatic system, which adversely affect the course of pregnancy, causing threatened

premature deliveries in pregnant women, sulodexide was included by us into the combination treatment of the group I, pregnant women of the group II in the combination treatment received heparin.

Sulodexide is an extract, isolated from mucous membrane of the pig's small intestine, which is a mixture of natural glycosaminoglycans, consisting of middle and lower molecular heparin-like fractions of 80 % and 20 % of dermatan sulpAzhate having a dual action caused by its two-component composition. The fast-flowing middle and lower molecular heparin-like fraction is affine to antithrombin III, and the dermatan fraction has an affinity to the heparin II cofactor II. Thus, the dual content of this product ensures its high anti-thrombotic potential and moderate anticoagulant activity. The product has a high degree of tropism to the vascular endothelium. Under the effect of sulodexide physiological function and a antithrombotic potential of the vascular endothelium were restored, the blood rheology properties were normalized by affecting all the links of hemostasis.

A favorable effect of sulodexide used in the obstetric practice on the utero-placental blood flow with a combination of such pregnancy complications as gestational toxicosis, feto-placental insufficiency, threatened miscarriage, is its significant achievement. Said anticoagulant, as compared with the heparin, has an apparent advantage, which consists in its effectiveness not only at parenteral administration, but when taken orally too, it was prescribed in the II trimester of pregnancy. At the beginning and end of the treatment course, it is necessary to control the APTT (sulodexide increases this index by 25–30 %), the fibrinogen level, prothrombin time and blood coagulation time [7, 9].

Inclusion into the combine treatment of pregnant women with threatened premature deliveries of the natural anticoagulant contributed to the pregnancy prolongation, normalization of aggregation state of blood, more expressed reduction of hypercoagulation and a profibrinous effect, prevented from the development of thrombosis in 10 % of cases compared with the group, into the combination treatment of which heparin was added. When analyzing the development criteria of the syndrome of chronic disseminated intravascular coagulation (DIC) of the blood of pregnant women with premature deliveries, it was found that it occurs in all the examined pregnant women of the main group. In connection with the findings, it can be concluded that in all the examined pregnant women with threatened premature deliveries the subclinical chronic form of the DIC-syndrome was observed.

Conclusions. Thus, the study of the hemostatic system in patients with threatened premature deliveries demonstrated that they have significant changes in the hemostatic system, manifested in thrombocyte hyper-aggregation and hyper-coagulation in the plasma

link of hemostasis, as well as appearance of markers of activating the intravascular blood coagulation. All the pregnant women with threatened premature deliveries and detected anomalies in the blood coagulation system are to be subjected to the antithrombotic therapy with the use of the natural anticoagulant sulodexide, having the dual action, conditioned by its two-component composition, which contributes to improvement of the course of the gestational period and the functional state of the fetus.

References

1. *Дудіна О. О., Пархоменко Г. Я., Горобець Ю. Ю.* Деякі характеристики репродуктивного здоров'я жінок України // Здоровье женщины. – 2011. – Вып. 68, № 7. – С. 146–151.

2. *Жук С. І.* Ефективне попередження передчасних пологів: від науки до практики // Жіночий лікар. – 2013. – Вып. 45, № 1. – С. 5 – 9.

3. Запорожан В. М., Чайка В. К., Маркін Л. Б. та ін. Акушерство та гінекологія: національне керівництво: у 4 т. – К.: Медицина, 2013. – Т. 1. – 1031–1058 с.

4. *Медянникова И. В.* Гемостазиологический контроль при беременности // Клиницист. – 2014. – № 1. – С. 47–52.

5. *Наказ* МОЗ України від 15 грудня 2003 р. № 582 «Про затвердження клінічних протоколів з акушерської та гінекологічної допомоги». – К., 2008. – С. 36–64.

6. *Наказ* МОЗ України № 676 від 31.12.2004 р. «Про затвердження клінічних протоколів з акушерської та гінекологічної допомоги». – К., 2004. – С. 52–56.

7. *Ройтман Е. В., Андрианова М. Ю., Колесникова И. М.* Вопросы выбора антитромботических препаратов // Тромбоз гемостаз и реология. – 2014. – № 4. – С. 18–22.

8. *Соколова М. Ю.* Экстрагенитальная патология у беременных. – М.: МИА, 2011. – 336 с.

9. *Шефер К., Шпильман Х., Феттер К.* Лекарственная терапия в период беременности и лактации: Пер. с нем. / Под ред. Б. К. Романова. – М.: Логосфера, 2010. – 768 с.

10. *Blencowe H., Cousens S., Oestergaard M.* et al. National, regional and worldwide estimates of preterm birth // The Lancet. – 2012. – Vol. 27, N 1. – P. 151–157.

References

1. Dudina O.O., Parkhomenko G.Ya., Gorobets Yu.Yu. Deyaki kharakteristiki reproduktivnogo zdorov'ya zhinok Ukraïni [Some characteristics of reproductive health of women of Ukraine]. Zdorove zhenshchiny, 2011; 7(68):146–151. [in Ukrainian]

2. Zhuk S.I. Yefektivne poperedzhennya peredchasnikh pologiv: vid nauki do praktiki. [Efficient prevention of premature births: from science before practice]. Zhinochiy likar, 2013; 1(45): 56–63. [in Ukrainian]

3. V.M. Zaporozhan, V.K. Chayka, L.B. Markin Akusherstvo ta ginekologiya: natsionalne kerivnitstvo. [Obstetrics and gynecology: national leaders]. T.1:Akusherstvo: natsionalniy pidruchnik, 2013; 1031-1058. [in Ukrainian]

4. Medyannikova I.V. Gemostaziologicheskiy kontrol pri beremennosti [Gemostaziologichesky monitoring at pregnancy]. Klinitsist, 2014; 1:7–52. [in Russian]

5. Nakaz MOZ Ukrayini «Pro zatverdzhennya klinichnikh protokoliv z akusherskoyi ta ginekologichnoyi dopomogi», vid 15 grudnya 2003 r. №582 [The order MOZ of Ukraine "About the adoption of clinical protocols on the obstetric and gynecologic care" on December 15, 2003] Kiev, 2008; 36–64.

6. Nakaz MOZ Ukrayini «Pro zatverdzhennya klinichnikh protokoliv z akusherskoyi ta ginekologichnoyi dopomogi», vid 31.12.2004 №676 [The order MOZ of Ukraine "About the adoption of clinical protocols on the obstetric and gynecologic care" December 31, 2004] Kiev, 2004; 52–56.

7. Ye.V. Roytman, M.Yu. Andrianova, I.M. Kolesnikova Voprosy vybora antitromboticheskikh preparatov [Questions of the choice antitromboticheskikh of medicines]. Tromboz gemostaz i reologiya, 2014; 4:18–22.

8. Sokolova M.Yu. Ekstragenitalnaya patologiya u beremennykh. [Extragenital pathology at pregnant women] MIA, 2011; 336. [in Russian]

9. K. Shefer, Kh. Shpilman, K. Fetter Lekarstvennaya terapiya v period beremennosti i laktatsii (per. s nem., pod red. B.K. Romanova).[Medicinal therapy during pregnancy and a lactation]. Logosfera, 2010; 2:768.

10. Blencowe H. Cousens S., Oestergaard M., Chou D., Moller A.B., Narwal R., Adler A., Garcia C.V., Rohde S., Say L., Lawn J.E. National, regional and worldwide estimates of preterm birth. The Lancet, 2012; 27(1):151–157.