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Neonatal thrombosis: risk factors and principles of prophylaxis

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Abstract

Data analysis on the pathogenesis and risk factors of neonatal thrombosis was carried out. The main risk factor of any neonatal thrombosis is central catheter installment, but other maternal, fetal and neonatal factors should be taken into consideration. We discuss the epidemiology of neonatal thrombosis and the main features of the hemostasis system in newborns, the most significant risk factors, including genetic and acquired thrombophilia. We consider the von Willebrand factor activity and ADAMTS-13 (a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13) level in the development of neonatal thrombotic microangiopathy. Finally, we discuss the basic principles of prevented neonatal thrombosis by using low molecular weight heparins.

Keywords: neonatal thrombosis, risk factors, central venous catheter, von Willebrand factor, vWF, ADAMTS-13, thrombophilia, antiphospholipid antibody circulation, thrombotic microangiopathy, neonatal thrombosis prophylaxis

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Факторы риска и принципы профилактики неонатальных тромбозов

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Резюме

Проведен анализ данных о патогенезе и факторах риска неонатальных тромбозов. В обзор включены данные зарубежных и отечественных статей по данной теме. В значительной степени неонатальные тромбозы возникают из-за наличия центрального катетера, однако существуют и другие факторы риска как со стороны матери, так и со стороны самого новорожденного. Представлены данные по эпидемиологии неонатальных тромбозов, особенностям функционирования системы гемостаза у новорожденных, рассмотрены наиболее значимые факторы риска, в том числе генетическая и приобретенная тромбофилия. Рассмотрены вопросы значения активности фактора фон Виллебранда и уровня ADAMTS-13 (англ. a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13) в развитии тромботической микроангиопатии у новорожденных. Дана информация по основным принципам профилактики неонатальных тромбозов с применением низкомолекулярных гепаринов.

Ключевые слова: неонатальные тромбозы, факторы риска, центральный венозный катетер, фактор фон Виллебранда, vWF, ADAMTS-13, тромбофилия, циркуляция антифосфолипидных антител, тромботическая микроангиопатия, профилактика неонатальных тромбозов

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Introduction / Введение

A thrombotic event in the neonatal period is a significant cause of morbidity and mortality, especially in the neonatal intensive care unit [1]. The incidence of neonatal thrombosis is 4.0–5.5 per 100,000 cases [2, 3]. However, among newborns admitted to intensive care units, the incidence of thrombosis is 3–15 per 1000 [4, 5]. In addition, in premature newborns, numerous factors, including iatrogenic, can lead even greater to impairment of coagulation and fibrinolysis, which increases the risk of thrombotic complications [6, 7]. The exact number of neonatal thrombosis cases is still unknown and, probably, is vastly underestimated. In some cases, thrombosis is asymptomatic or characterized by nonspecific clinical picture. Moreover, not every case of suspected thrombosis may be examined by ultrasound scan, magnetic resonance imaging or venography [8]. Extensive studies on this topic have been carried out in the last years in Canada, Germany, and the Netherlands [3, 9, 10].

Summarizing notes on the international data / Обобщение международных данных [3–11]

- 2.5 per 100,000 hospitalreported cases, of which 80 % are due to the catheters used;
- the incidence of thrombosis due to the placement of an umbilical catheter ~ 13 %; renal vein thrombosis ~ 10 % of total venous thrombosis, including 1/4 bilateral catheters;
- the rate of cerebral venous thrombosis – 41 per 100,000;
- rate of cerebral arterial thrombosis – 28.6–90.3 per 100,000 live newborns;
- rate of thrombosis when using a catheter:
  – clinical trials – 13–30 %;
  – autopsy data – 20–65 %;
- the use of umbilical catheter leads to subclinical portal thrombosis in 43 % of patients, with complete or partial recanalization – in 56 %.

Usually, most frequent features are renal vein thrombosis, cerebral vein thrombosis, portal or mesenteric

Highlights

What is already known about this subject?

- The state in newborn vs. adult coagulation system differs significantly.
- Level and activity of clotting factors in preterm infants differ significantly from those in healthy infants born at term.
- Most thrombogenic factor is installed central venous catheter and catheter-associated infection.

What are the new findings?

- Serious risk factors for neonatal thrombosis are maternal thrombophilia and genetic forms of neonatal thrombophilia.
- The upward trend in the number of cases for venous thrombosis can be accounted for by the progress in management of complex neonatal conditions and increasing survival rate in severe premature newborns.
- Prevention of neonatal thrombosis should be started at the pregravid stage, i. e., at the planning stage for women with high risk: with history of obstetric complications, systemic inflammatory diseases, diabetes mellitus, genetic or acquired thrombophilia.

How might it impact on clinical practice in the foreseeable future?

- Further study of the informative predictors of neonatal thrombosis is necessary.
- Screening for thrombophilia in mothers and newborns at risk for thrombotic complications in the neonatal period is required.

Основные моменты

Что уже известно об этой теме?

- Состояние системы коагуляции у новорожденных и взрослых в значительной степени различается.
- Уровни и активность факторов свертывания у недоношенных и здоровых доношенных детей в значительной степени различаются.
- Наиболее тромбогенным является наличие центрального венозного катетера и катетер-ассоциированной инфекции.

Что нового дает статья?

- Серьезными факторами риска неонатальных тромбозов являются тромбофилия у матери и генетические формы тромбофилии у новорожденных.
- Тенденцию к росту числа случаев венозного тромбоза можно объяснить успехами в лечении сложных неонатальных состояний и увеличением выживаемости глубоко недоношенных детей.
- Профилактика неонатальных тромбозов должна начинаться на прегравидарном этапе у женщины, входящей в группу риска: с отягощенным акушерским анамнезом, системными воспалительными заболеваниями, сахарным диабетом, генетической или приобретенной тромбофилией.

Как это может повлиять на клиническую практику в обозримом будущем?

- Необходимо дальнейшее изучение информативных предикторов неонатальных тромбозов.
- Необходимо проведение скрининга на наличие тромбофилии у матерей и новорожденных, входящих в группу риска по развитию тромботических осложнений в неонатальном периоде.

vein thrombosis in the neonatal period. Symptoms arising from thrombosis in newborns are most often associated with renal vascular thrombosis, cerebral thrombosis, and nonspecific manifestations, predominantly presented as apnea, respiratory failure, and thrombocytopenia [10]. More than 60 % of newborns develop post-thrombotic syndrome even during anticoagulant therapy. Post-thrombotic syndrome, a complication resulting from neonatal thrombosis, can develop within a month after an episode of thrombosis or several years later. It is characterized by chronic swelling of the limbs and skin, skin pigmentation changes, and impaired wound healing.

The neonatal death often occurs from causes resulting from thrombosis, but is not directly related to it [12].

One of the highly unfavorable variants of thrombotic complications in newborns is the so-called fulminant purpura manifested as an acute, rapidly progressive skin lesion caused by thrombotic occlusion of the small and medium dermis blood vessels and progressive bleeding into the skin. It is associated with a high risk of thrombosis of the cerebral veins, retina, large vessels, and disseminated intravascular coagulation (DIC). This condition is associated with a deficiency of protein C or, less frequently of protein S or antithrombin (AT) [13]. In this case, the capillaries of the skin, kidneys, and brain are affected because protein C exerts its action right in the microvasculature. Skin lesions begin as slight ecchymosis, gradually expanding with bullae formation, leading to necrosis and gangrena. Lesions are mainly localized on the extremities, but given that DIC develops rather quickly, they tend to spread fast.

Also, fetal thrombotic vasculopathy (FTV), characterized by fetal vessel thrombosis and/or thrombosis of the fetal vascularization of the placenta, proceeds extremely unfavorably [14]. This complication, in turn, causes a high incidence of hypoxic-ischemic brain injury and perinatal mortality. FTV may be suspected due to an indication for microscopic examination of the placenta and ultrasound examination of the newborn to exclude thrombosis of large vessels. In all patients with fetal growth retardation and severe fetal hypoxia (including cases of diagnosed maternal thrombophilia), FTV should be excluded and newborn screening for thrombophilia is recommended [15].

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The main features of newborn hemostasis / Особенности функционирования системы гемостаза у новорожденных

The coagulation system in newborns markedly differs that one in adults [16–26]. In addition, the levels and activity of clotting factors in premature babies are extremely distinct to those found in healthy babies born at term. Coagulation factors levels, anticoagulants, and fibrinolytic factors change during the neonatal period. Initially, the lower level of procoagulants in the first 3–4 days after birth significantly increases by day 10–14 of the postpartum period [17].

Immediately after childbirth, production of coagulation factors synthesis is markedly reduced, and the concentration of vitamin K-dependent coagulation factors (II, VII, IX, X) and contact coagulation factors (XI, XII, prekallikrein and high molecular weight kininogen) comprises about 50 % of the corresponding concentrations in adults [18]. In the postnatal period, the liver synthetic function gradually increases, and the concentration of coagulation factors elevates – factors VII and XIII correspond to the adult level by 3–4 weeks of life, whereas other hemostasis components – factors II, IX, XI, prekallikrein, AT and protein C increase to the adult level within 3–6 months after childbirth [23]. Immediately after childbirth, fibrinolysis becomes activated, possibly being associated with the need to compensate for the stimulating coagulation effect of maternal and placental factors, soon leading to fibrinolytic system depletion and decreased levels of AT, plasminogen, proteins C and S [24].

The number of platelets after birth increases unevenly, with the peak at 2–3 weeks of the postpartum period due to increased thrombopoietin production immediately after childbirth [25]. At the same time, platelet activity is slightly reduced. The ability to activate platelets by collagen, thrombin, and thromboxane is efficient 5–10 days of the postpartum period, whereas the von Willebrand factor (vWF) activity also increases parallelly in newborns [26].

Thus, the balance of the procoagulants factor, platelet activators, and the fibrinolytic system change several times during the early postpartum period. Also, significant differences in the activity and concentration of hemostasis components in term and premature infants are noted (**Table 1**).

In general, all newborns are characterized by a prothrombotic status: low level of fibrinolysis factors (AT, proteins C and S), especially in premature infants, in combination with high level of vWF, V and VIII factors. In addition, neonatal hemostasis exerts less buffering, compensatory capacity [16–26].

Thus, the first months of life are the high-risk period for thromboembolic events. The above-described differences in the function of the hemostasis system in the neonatal period, along with congenital risk factors (genetic thrombophilia) and perinatally acquired risk factors, create together a high level of thrombotic risk in newborns.

Risk factors for thrombosis in the neonatal period / Факторы риска тромбозов у новорожденных

Any thrombotic complication is associated with the classic Virchow triad: hypercoagulation, wall damage of blood vessels, and blood stagnation. The same trend can be tracked down to neonatal thrombosis. All risks of neonatal thrombosis can be divided into:

- associated with installed venous catheter;
- directly related to the condition of the newborn and the mode of delivery;
- related to the maternal condition.

Catheter-associated risk factors for neonatal thrombosis / Катетер-ассоциированные факторы риска неонатальных тромбозов

The presence of a central venous catheter is the most thrombogenic factor, accounting for 80 % of all cases of venous thrombosis and 90 % of all arterial thrombosis are being associated, and in addition, 60 % of thrombosis occurring during the first year of life, whereas as few as 5 % of them display symptoms [27]. Ultrasound examination and venography can already detect up to a 30 % and 75 %, respectively, of all thrombosis cases [28].

A venous catheter placement, promotes thrombus formation, enhancing the absorption of proteins, adhesion of platelets, leukocytes, and increased thrombin production. In addition, one of the neonatal thrombosis mechanisms due to venous catheter is the catheter-associated infection [29]. Electron microscopy studies have shown that bacteria can migrate from the skin along the lumen of the catheter and infect it within a few hours after installment [30, 31]. This accounts for an increased incidence of thrombosis after 3–4 days from placement. Also, situations that contribute to the risk of developing catheter-associated thrombotic complications are presented as parenteral nutrition and the need for blood transfusion or its components.

Risk factors for neonatal thrombosis associated with the neonatal condition / Факторы риска неонатальных тромбозов, связанные с состоянием новорожденного

Factors associated with the neonatal condition include gestational age, the intensive care unit stay, infection complications, septic conditions, immobilization, concomitant neoplasms, surgical procedures, systemic viral infection, congenital heart defects, asphyxia episodes in childbirth and dehydration. It was found that the risk of thrombosis in newborns born after 37 weeks of gestational age is significantly lower than in premature babies [32].

Conditions associated with the immune system activation and increased proinflammatory cytokine

Table 1. Features of neonatal hemostasis [16–26].

Таблица 1. Особенности системы гемостаза у новорожденных [16–26].

Parameter Показатель	Comparison of the parameters in premature and full-term newborns Сравнение показателей у недоношенных и доношенных новорожденных	Comparison of the parameters in full-term newborns and adults Сравнение показателей у доношенных новорожденных и взрослых
Platelet count Число тромбоцитов	Reduced, especially prior to 32 weeks Снижено, особенно до 32 нед	Slightly reduced Незначительно снижено
Platelet activity Активность тромбоцитов	Reduced Снижена	Slightly reduced, increases by 5–10 days Незначительно снижена, нарастает к 5–10-у дню
Von Willebrand factor Фактор фон Виллебранда	Elevated Повышен	Elevated Повышен
ADAMTS-13 ADAMTS-13	Reduced Снижен	Slightly reduced Незначительно снижен
Factor V Фактор V	Reduced Снижен	Slightly reduced Незначительно снижен
Factor VIII Фактор VIII	Elevated Повышен	Slightly reduced Незначительно снижен
Factor IX Фактор IX	Reduced Снижен	Reduced Снижен
Factor XII Фактор XII	Reduced Снижен	Reduced Снижен
Fibrinogen level Уровень фибриногена	Similar Аналогичный	Similar Аналогичный
Fibrinogen activity Активность фибриногена	No data Нет данных	Reduced Снижен
Antithrombin Антитромбин	Reduced Снижен	Reduced Снижен
Protein C Протеин С	Reduced Снижен	Reduced Снижен
Protein S Протеин S	Reduced Снижен	Reduced Снижен
Plasminogen level Уровень плазминогена	Reduced Снижен	Reduced Снижен
Tissue factor pathway inhibitor (TFPI) Ингибитор пути тканевого фактора (TFPI)	No data Нет данных	Reduced Снижен
Tissue plasminogen activator (tPA) Тканевой активатор плазминогена (tPA)	Similar Аналогичный	Elevated Повышен
Plasminogen activator inhibitor-1 (PAI-1) Ингибитор активатора плазминогена-1 (PAI-1)	Similar Аналогичный	Slightly increased Незначительно повышен

expression, are also risk factors for thrombosis: sepsis in newborns, infectious complications, systemic viral infection, catheter-associated infection [33]. Similar to adults, inflammation causes hemostasis activation, but with the less compensatory potential of the neonatal coagulation system. This leads to a significant percentage of thrombotic complications. Proinflammatory agents induce damage to the endothelium and exposure of the procoagulant surface of the subendothelial matrix, which contains various components, including collagen, vWF, etc., which provide adhesion and platelets activation [34]. During inflammation, coagulation activation leads to excessive thrombin generation, which is a potent platelet activator. Endotoxins and cytokines promote platelet activation, with aggregation stimulants being released (adrenaline, ADP, serotonin, thromboxane). In addition, inflammatory mediators influence endothelial dysfunction due to the coagulation system activation, the complement system, and blood cells, primarily macrophages and neutrophils [35].

Many studies indicate an importance of delivery mode as a risk factor: the use of venthouse delivery or emergency cesarean section in 5–6 % of cases is associated with the developing neonatal thrombosis [36].

Maternal risk factors for neonatal thrombosis / Факторы риска неонатальных тромбозов, связанные с состоянием матери

Maternal risk factors for neonatal thrombosis include a negative obstetric history, complications of the actual pregnancy – such as preeclampsia (about 13 % of cases of thrombosis) [37], placental insufficiency, the presence of systemic inflammatory diseases, gestational diabetes mellitus, or complications pre-pregnancy (about 5 % of cases of neonatal thrombosis) [38, 39] and finally the presence of maternal thrombophilia [40].

Preeclampsia is always associated with a placental blood flow decline; the pathogenesis being accounted for by impaired placentation, and/or vascular defects in the placental bed, which is associated with a maternal hypercoagulation state. All these factors may promote activation of the neonatal coagulation cascade [41].

Diabetes mellitus is associated with vascular wall damage and endotheliopathy that increases the coagulation potential and a risk of placental infarction as well as directly acts on the risk of neonatal thrombosis [42].

Thrombophilia-related risks of neonatal thrombosis / Тромбофилия-обусловленные риски неонатальных тромбозов

A serious risk factor for neonatal thrombosis is the presence of maternal thrombophilia and/or genetic forms of thrombophilia in the newborn. However, little knowledge about the specific pathophysiological mechanisms responsible for most cases of neonatal thrombosis is available. Maternal thrombophilia can increase coagulation potential and pre-thrombotic state during pregnancy, as well thrombotic vasculopathy at the placental level [43].

The most dangerous risk factor is AT deficiency. The homozygous form is incompatible with life. AT is an essential physiological protease inhibitor, mainly acting on thrombin and factor Xa [44]. AT deficiency increases the risk of developing venous and arterial thrombosis. Two forms of hereditary AT deficiency are distinguished: type I – quantitative with AT low level and activity, and type II – qualitative with AT dysfunction. Type II is characterized by normal AT levels but decreased AT activity.

The management of neonates with thrombosis along with AT deficiency is a challenging task associated with insufficient effectiveness of any heparin-based anticoagulant therapy. In some cases, it is required to inject AT-concentrate together with anticoagulants to achieve an adequate response to therapy [45]. It usually takes several days to reach normal anti-Xa levels. In each case of an inadequate response to heparin therapy, it should be remembered about such opportunity and timely diagnose AT deficiency.

In a homozygous form of protein C deficiency, neonates develop the so-called fulminant purpura [46], a severe, but extremely rare condition – less than a hundred cases have been reported since its first description in 1984. In most of protein C deficiency cases, antenatal fetal death occurs. Treatment should be applied as soon as possible consisting in the substitutive therapy: it is necessary to transfuse blood plasma, which contains protein C, or directly protein C concentrates, especially in severe cases; finally, liver transplantation is required in order to provide the protein C production [47, 48].

Several studies have shown that the mutations of factor V Leiden (FV G1691A) and prothrombin G20210A (FII G20210A) are associated with a higher incidence of neonatal thrombosis, although the evidence remains controversial [49, 50]. A mutation in the methylenetetrahydrofolate reductase C677T gene (MTHFR C677T) is also considered as potentially thrombogenic factor.

Two meta-analyses have been published investigating the prevalence of FV G1691A and FII G20210A mutations in children with thrombosis. G. Kenet et al. found a positive association of FV G1691A and FII G20210A with cerebral sinus thrombosis but did not separate from the whole neonatal thrombosis group [51]. Meta-analysis by R. Laugesaar et al. showed that the neonatal cohorts were separated, and an association of FV G1691A with thrombotic episodes was found. Still, this meta-analysis showed no association of the FII G20210A mutation with neonatal thrombosis, although an association was found for childhood [52]. In addition, studies report an independent pathogenetic role of genetic thrombophilia in newborns in emerging thrombotic complications [53]. In contrast, other authors observe that genetic thrombophilia causes thrombotic events in newborns only together with additional risk factors, such as dehydration, polycythemia, infectious complications, and most commonly placement of catheters [54]. Thus, routine screening for thrombophilia is not so crucial. However, in the presence of conditions associated with impaired hemostasis function – aggravated obstetric history, complications of the actual pregnancy (preeclampsia, placental insufficiency, the presence of systemic inflammatory diseases), it is recommended to test mothers and newborns for congenital and acquired thrombophilia.

A similar trend has been observed for circulating maternal antiphospholipid antibodies (APA) because it appears not to be a significant independent risk factor for thrombosis in newborns [55]. However, in the presence of at least one additional risk factor, more often such as catheter, sepsis, asphyxia, especially combined with genetic thrombophilia, 60 % of newborns developed thrombotic complications [56]. The pathogenesis of perinatal thrombosis associated with APA circulation can be accounted for by both the transplacental passage of

maternal antibodies and the *de novo* APA production in newborn [57]. Another feature of thrombotic complications in newborns associated with APA circulation is that most newborns develop arterial thrombosis, including thrombosis of the cerebral arteries.

One of the severe thrombotic variants is neonatal microangiopathy, particularly thrombotic thrombocytopenic purpura (TTP) caused by the congenital defect in the ADAMTS-13 (a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13) gene [58]. ADAMTS-13 deficiency leads to increased vWF multimer level, which in turn causes the development of microvascular thrombosis and thrombocytopenia by consumption. TTP may result from congenital ADAMTS-13 deficiency or due to anti-ADAMTS-13 antibodies blocking its activity [59].

The majority of authors found that the level of vWF in newborns increases after childbirth. In addition, stress and inflammation are the factors that stimulate vWF expression. The stress-related increase in its expression during childbirth can also account for the higher level of vWF in the neonatal period [60]. However, similar to APA circulation, neither ADAMTS-13 decline nor vWF increase in newborns lead to developing thrombotic complications, but can lead to thrombosis when concomitant additional risk factors such as hypoxia, sepsis, and other acute diseases, and, of course, the placement of a long-term central catheter exists. Nevertheless, an imbalance in the vWF/ADAMTS-13 ratio is indeed a risk factor for developing thrombosis in newborns.

To summarize the data noted above, the risk factors for neonatal thrombosis are presented below (**Table 2**).

Hemostasis testing in newborns / Исследование гемостаза у новорожденных

For the newborns, especially at premature stage, whose hemostasis balance differs from that one in adults even under physiological conditions, the use of global tests can solve the problem of the low specificity of standard tests as predictors of thrombohemorrhagic complications and control of therapeutic efficacy. The search for informative predictors is a highly urgent task because in practice the pathological state can predispose newborns to both thrombosis and bleeding. The attending physician is forced to focus mainly on the clinical picture, which in most cases becomes evident after the thrombohemorrhagic event appears.

Principles of prevention of neonatal thrombosis in risk groups / Принципы профилактики неонатальных тромбозов в группах риска

Prevention of neonatal thrombosis is a challenging and non-obvious task since its main features are not related to anticoagulant therapy directly in newborns, but:

- the identification of genetic and acquired defects of hemostasis in mothers (genetic thrombophilia, especially homozygous forms, antiphospholipid syndrome, hyperhomocysteinemia);
- the possible identification of genetic thrombophilia in fathers;
- the correct and careful management of pregnancy, aimed at preventing the fetal-placental insufficiency and the prevention of preterm birth;
- the prevention and early diagnosis of perinatal infections;
- the critical analysis of early neonatal manifestations of the thrombotic process. It should remember that any cerebral circulation disorder form which happens not so rarely, can be aggravated or be a manifestation of a latent thrombotic process.

Choice of anticoagulant therapy in groups at risk of neonatal thrombosis / Выбор антикоагулянтной терапии в группах риска неонатальных тромбозов

Anticoagulant therapy in newborns is not an easy management. Despite the multiple differences described above in adults and newborns hemostatic system, current anticoagulants are used by extrapolating data mainly from studies performed in adults. In addition, most neonates requiring anticoagulant therapy may have morbidity or conditions that additionally affect the choice of drugs and their dosage associated with the risk of bleeding.

Among the numerous drugs used as anticoagulants in obstetric and pediatric practice, the most studied are warfarin, unfractionated heparin (UFH), and low molecular weight heparin (LMWH). Compared to warfarin and UFH, LMWH is less susceptible to the effects of nonspecific plasma factors and displays more stable pharmacokinetics [45]. As a result, patients require fewer daily injections and less dose adjustments. Studies to determine the appropriate dosage of LMWH in newborn have not been conducted yet; therefore most often the choice of dosage in newborns follows the "therapeutic range": the level of anti-Xa 0.5–1.0 IU/ml 4–6 hours after administration, which is, however, based on study conducted for adults [45]. Some dosage recommendations are based on small studies reporting the average dose needed to reach the therapeutic range, and some differences between these recommendations have been noted as well [45, 61–64].

Efficacy of low molecular weight heparin preparations in prevention of neonatal thrombosis / Эффективность препаратов низкомолекулярного гепарина при профилактике неонатальных тромбозов

Study by C.H. van Ommen et al. showed that the starting dose of nadroparin calcium was set at 85.5 IU/kg twice a day. In newborns, the maintenance dose was 448 ± 42 IU/kg/day (6 subjects), 253 ± 22 IU/kg/day in infants from 2 to 12 months (10 subjects), and 214 ± 8 IU/kg/day in children from 2 to 11 years old (13 subjects). Neonates

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Table 2. Risk factors for neonatal thrombosis [27–29, 32, 33, 37–42, 43–54].

Таблица 2. Факторы риска неонатальных тромбозов [27–29, 32, 33, 37–42, 43–54].

Mother-related Связанные с состоянием матери	Neonate-related Связанные с новорожденным	Catheter-associated Катетер-ассоциированные
Negative obstetric history Отягощенный акушерский анамнез	Method of delivery: emergency caesarean section, obstetric forceps Способ родоразрешения: экстренное кесарево сечение, применение акушерских щипцов	Central venous catheter Центральный венозный катетер
Preeclampsia and fetal-placental insufficiency Преэклампсия и фетоплацентарная недостаточность	Gestational age Гестационный возраст	Catheter-associated infection Катетер-ассоциированная инфекция
Systemic inflammatory diseases Системные воспалительные заболевания	Infectious complications and septic conditions Инфекционные осложнения и септические состояния	Parenteral nutrition Парентеральное питание
Diabetes mellitus, including gestational Сахарный диабет, в том числе гестационный	Duration of intensive care unit stay and immobilization Продолжительность пребывания в отделении интенсивной терапии и иммобилизация	The need for transfusion of blood and its components Необходимость переливания крови и ее компонентов
Genetic or acquired thrombophilia Генетическая или приобретенная тромбофилия	Concomitant neoplasm Наличие новообразования у новорожденного	
	Surgical procedures Необходимость хирургического вмешательства	
	Congenital heart defects Врожденные пороки сердца	
	Asphyxia episodes in childbirth Эпизоды асфиксии в родах	
	Dehydration Обезвоживание	
	Systemic hypotension Системная гипотензия	

require more often and longer dose adjustments to reach the “therapeutic range” taking about 6 days on average [62]. A significant advantage of using LMWH compared to UFH is the platelet factor 4 and the osteoblasts reduced binding, which decreases a risk of heparin-induced thrombocytopenia and osteopenia.

In a study with Enoxaparin use for newborns (Enoxaparin is contraindicated in children and adolescents under the age of 18 in the Russian Federation), an initial dose of 1.5 mg/kg [63] or 1.7 mg/kg [64] every 12 hours was recommended. The duration of anticoagulation therapy in neonates usually ranges from 6 weeks to 3 months [45].

It should be noted that due to some differences in the pharmacokinetics of various forms of low molecular weight heparin, the expected anticoagulant effect of various drugs especially in the neonatal period, is not identical, so that the results of therapy with one drug cannot be directly extrapolated for others.

Safety of low molecular weight heparin in prevention of neonatal thrombosis / Безопасность препаратов низкомолекулярного гепарина при профилактике неонатальных тромбозов

Concerning the therapeutic safety of LMWH drugs used in newborns, the C.H. van Ommen et al. study demonstrated the high safety of nadroparin calcium while used in children: none of the 39 patients had any severe hemorrhagic complication [62]. Other researchers reported the occurrence of severe hemorrhagic complications in 0–5.6 % cases after using drugs other than LMWH (enoxaparin) in pediatrics [64–68].

Conclusion / Заключение

Thrombotic complications in newborns are rare and usually occur as complications of an underlying medical condition, such as sepsis or congenital heart defects,

or they may be caused by exogenous triggers such as placement of an intravascular catheter.

Rate of neonatal venous thrombosis increases because of the progress in the treatment of complex neonatal conditions and due to elevated survival rate of early premature infants.

The main risk factor of any neonatal thrombosis is the placement of central catheter, but there are other maternal, fetal and neonatal risk factors to be considered both related to mother and newborn.

One of the essential factors in the pathogenesis of neonatal thrombosis is the function of the blood coagulation system in newborns.

The thrombosis significantly complicates the neonatal condition and is the cause for more extended hospitalization, the need to remove or rearrange the central catheter, and an increased risk of bleeding associated with anticoagulant therapy.

The pathogenetic role of maternal and neonatal thrombophilia is appreciated, but due to the limited number of observations, a degree of pathogenetic significance for various forms of thrombophilia is not fully clarified, and a question regarding a need to screen for thrombophilia in mothers and newborns remains open.

The administration of anticoagulant therapy should be based on knowledge of the characteristics of neonatal hemostasis and its changes in pathological syndromes. Understanding about a mechanism for activity of low molecular weight heparins (as the drug of choice in preventing/treating neonatal thrombosis) is critical for the personalized management of such newborns. The scarce knowledge regarding pharmacodynamics of anticoagulants and the pathophysiology of neonatal thrombosis in the context of anticoagulant therapy may be even more dangerous than the causative pathological condition.

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References:

1. Volodin N.N., Roitman E.V., Rumyantsev A.G., Shneyder M.M. Thromboses in the neonate: pathogenesis, diagnosis, treatment. [Trombozy u novorozhdennyh: patogenez, diagnostika, lechenie]. *Voprosy prakticheskoj pediatrii*. 2012;7(4):34–43. (In Russ.).
2. Saracco P., Bagna R., Gentilomo C. et al.; Neonatal Working Group of the Registro Italiano Trombosi Infantili (RITI). Clinical data of neonatal systemic thrombosis. *J Pediatr*. 2016;171:60–6.e1. https://doi.org/10.1016/j.jpeds.2015.12.035.
3. Bhatt M.D., Chan A.K. Venous thrombosis in neonates. *Fac Rev*. 2021;10:20. https://doi.org/10.12703/r/10-20.
4. Raffini L., Huang Y.S., Witmer C., Feudtner C. Dramatic increase in venous thromboembolism in children's hospitals in the United States from 2001 to 2007. *Pediatrics*. 2009;124(4):1001–8. https://doi.org/10.1542/peds.2009-0768.
5. Saxonhouse M.A. Thrombosis in the neonatal intensive care unit. *Clin Perinatol*. 2015;42(3):651–73. https://doi.org/10.1016/j.clp.2015.04.010.
6. Saracco P., Parodi E., Fabris C. et al. Management and investigation of neonatal thromboembolic events: genetic and acquired risk factors. *Thromb Res*. 2009;123(6):805–9. https://doi.org/10.1016/j.thromres.2008.12.002.
7. Strauss T., Levy-Shraga Y., Ravid B. et al. Clot formation of neonates tested by thromboelastography correlates with gestational age. *Thromb Haemost*. 2010;103(2):344–50. https://doi.org/10.1160/TH09-05-0282.
8. Kenet G., Nowak-Gottl U. Venous thromboembolism in neonates and children. *Best Pract Res Clin Haematol*. 2012;25(3):333–44. https://doi.org/10.1016/j.beha.2012.07.001.
9. El-Naggar W., Yoon E.W., McMillan D. et al.; Canadian Neonatal Network Investigators. Epidemiology of thrombosis in Canadian neonatal intensive care units. *J Perinatol*. 2020;40(7):1083–90. https://doi.org/10.1038/s41372-020-0678-1.
10. Kenet G., Cohen O., Bajorat T., Nowak-Göttl U. Insights into neonatal thrombosis. *Thromb Res*. 2019;181(Suppl 1):S33–S36.

https://doi.org/10.1016/S0049-3848(19)30364-0.
11. Haley K.M. Neonatal venous thromboembolism. *Front Pediatr*. 2017;5:136. https://doi.org/10.3389/fped.2017.00136.
12. Veldman A., Nord M.F., Michel-Behnke I. Thrombosis in the critically ill neonate: incidence, diagnosis, and management. *Vask Health Risk Manag*. 2008;4(6):1337–48. https://doi.org/10.2147/vhrm.s4274.
13. Martin G., Thomas M.A., Wei X.C., Le D. Diffuse intracerebral hemorrhage in an infant with a novel homozygous variant leading to severe protein C deficiency. *J Pediatr Hematol Oncol*. 2020 Nov 6. https://doi.org/10.1097/MPH.0000000000001993.
14. Kraus F.T. Fetal thrombotic vasculopathy: perinatal stroke, growth restriction, and other sequelae. *Surg Pathol Clin*. 2013;6(1):87–100. https://doi.org/10.1016/j.path.2012.10.001.
15. Young G., Albisetti M., Bonduel M. et al. Impact of inherited thrombophilia on venous thromboembolism in children: a systematic review and meta-analysis of observational studies, *Circulation*. 2008;118(13):1373–82. https://doi.org/10.1161/CIRCULATIONAHA.108.789008.
16. Monagle P., Ignjatovic V., Savoia H. Hemostasis in neonates and children: pitfalls and dilemmas. *Blood Rev*. 2010;24(2):63–8. https://doi.org/10.1016/j.blre.2009.12.001.
17. Shabalov N.P., Ivanov D.O., Shabalova N.N. Dynamic of hemostasis in first week of life as reflection of adaptive mechanisms to extrauterine life. [Gemostaz v dinamike pervoj nedeli zhizni kak otrazhenie mekhanizmov adaptacii k vneutrobnoj zhizni novorozhdennogo]. *Pediatriya. Zhurnal imeni G.N. Speranskogo*. 2000;79(3):22. 2000;79(3):22. (In Russ.).
18. Koltsova E.M., Balashova E.N., Panteleev M.A., Balandina A.N. Laboratory aspects of hemostasis in neonates. [Laboratornye aspekty gemostaza novorozhdennyh]. *Voprosy gematologii/onkologii i immunopatologii v pediatrii*. 2018;17(4):100–13. https://doi.org/10.24287/1726-1708-2018-17-4-100-113. (In Russ.).
19. Ignjatovic V., Pelkmans L., Kelchtermans H. et al. Differences in the mechanism of blood clot formation and nanostructure in infants and children compared with adults. *Thromb Res*. 2015;136(6):1303–9. https://doi.org/10.1016/j.thromres.2015.10.034.
20. Cherkasova S.V. Hemostasis of newborns. [Gemostaz novorozhdennyh]. *Praktika pediatra*. 2020;(1):49–52. (In Russ.).
21. Nowak-Gottl U., Limperger V., Kenet G. et al. Developmental hemostasis: a lifespan from neonates and pregnancy to the young and elderly adult in a European white population. *Blood Cell Mol Dis*. 2017;67:2–13. https://doi.org/10.1016/j.bcmd.2016.11.012.
22. Ignjatovic V. 30 years of developmental haemostasis: what have we learnt and how are we applying this knowledge. *Thromb Res*. 2018;172:188–9. https://doi.org/10.1016/j.thromres.2018.11.021.
23. Leonova E.Yu., Sinyakin O.Yu. Peculiarities of hemostasis system in newborns. [Osobennosti sistemy gemostaza u novorozhdennyh detej]. *Ohrana materinstva i detstva*. 2016;(2):76–81. (In Russ.).
24. Strauss T., Sidlik-Muskatel R., Kenet G. Developmental hemostasis: primary hemostasis and evaluation of platelet function in neonates. *Semin Fetal Neonatal Med*. 2011;16(6):301–4. https://doi.org/10.1016/j.siny.2011.07.001.
25. Wiedmeier S.E., Henry E., Sola-Visner M.C., Christensen R.D. Platelet reference ranges for neonates, defined using data from over 47,000 patients in a multihospital healthcare system. *J Perinatol*. 2009;29(2):130–6. https://doi.org/10.1038/jp.2008.14.
26. Strauss T., Elisha N., Ravid B. et al. Activity of Von Willebrand factor and levels of VWF-cleaving protease (ADAMTS13) in preterm and full-term neonates. *Blood Cell Mol Dis*. 2017;67:14–7. https://doi.org/10.1016/j.bcmd.2016.12.013.
27. van Ommen C.H., Sol J.J. Developmental hemostasis and management of central venous catheter thrombosis in neonates. *Semin Thromb Hemost*. 2016;42(7):752–9. https://doi.org/10.1055/s-0036-1592299.
28. Sirachainan N., Limrungsikul A., Chuansumrit A. et al. Incidences, risk factors and outcomes of neonatal thromboembolism. *J Matern Fetal Neonatal Med*. 2018;31(3):347–51. https://doi.org/10.1080/14767058.2017.1285892.
29. Marquez A., Shabanova V., Faustino E.V.S.; Northeast Pediatric Critical Care Research Consortium. Prediction of catheter-associated thrombosis in critically ill children. *Pediatr Crit Care Med*. 2016;17(11):e521–e528. https://doi.org/10.1097/PCC.0000000000000958.
30. Rupp M.E., Karnatak R. Intravascular catheter-related bloodstream infections. *Infect Dis Clin North Am*. 2018;32(4):765–87. https://doi.org/10.1016/j.idc.2018.06.002.
31. Thornburg C.D., Smith P.B., Smithwick M.L. et al. Association between thrombosis and bloodstream infection in neonates with peripherally inserted catheters. *Thromb Res*. 2008;122(6):782–5. https://doi.org/10.1016/j.thromres.2007.10.001.
32. Amankwah E.K., Atchison C.M., Arlikar S. et al. Risk factors for hospital-associated venous thromboembolism in the neonatal intensive care unit. *Thromb Res*. 2014;134(2):305–9. https://doi.org/10.1016/j.thromres.2014.05.036.
33. Andres O., Schulze H., Speer C.P. Platelets in neonates: central mediators in haemostasis, antimicrobial defence and inflammation. *Thromb Haemost*. 2015;113(1):3–12. https://doi.org/10.1160/TH14-05-0476.
34. Vorobev A., Makatsariya A., Bitsadze V. et al. Unusual thrombosis or pregnancy complications associated to ovarian cancers: two clinical cases. *J Matern Fetal Neonatal Med*. 2021;34(9):1430–4. https://doi.org/10.1080/14767058.2019.1638359.
35. Bhat R., Kumar R., Kwon S. et al. Risk factors for neonatal venous and arterial thromboembolism in the neonatal intensive care unit – a case control study. *J Pediatr*. 2018;195:28–32. https://doi.org/10.1016/j.jpeds.2017.12.015.
36. Kulkarni A.A., Osmond M., Bapir M. et al. The effect of labour on the coagulation system in the term neonate. *Haemophilia*. 2013;19(4):533–8. https://doi.org/10.1111/hae.12115.
37. Tuckuviene R., Christensen A.L., Helgested J. et al. Infant, obstetrical and maternal characteristics associated with thromboembolism in infancy: a nationwide population-based case-control study. *Arch Dis Child Fetal Neonatal Ed*. 2012;97(6):F417–22. https://doi.org/10.1136/archdischild-2011-300665.
38. Branchford B.R., Mourani P., Bajaj L et al. Risk factors for in-hospital venous thromboembolism in children: a case-control study employing diagnostic validation. *Haematologica*. 2012;97(4):509–15. https://doi.org/10.3324/haematol.2011.054775.
39. Motta M., Rodriguez-Perez C., Tincani A. et al. Neonates born from mothers with autoimmune disorders. *Early Hum Dev*. 2009;85(10 Suppl):S67–70. https://doi.org/10.1016/j.earlhumdev.2009.08.020.
40. van Ommen C.H., Nowak-Göttl U. Inherited thrombophilia in pediatric venous thromboembolic disease: why and who to test. *Front Pediatr*. 2017;5:50. https://doi.org/10.3389/fped.2017.00050.
41. Sharathkumar A.A., Mahajerin A., Heidt L. et al. Risk-prediction tool for identifying hospitalized children with a predisposition for development of venous thromboembolism: Peds-Clot clinical Decision Rule. *J Thromb Haemost*. 2012;10(7):1326–34. https://doi.org/10.1111/j.1538-7836.2012.04779.x.
42. Ovesen P.G., Jensen D.M., Damm P. et al. Maternal and neonatal outcomes in pregnancies complicated by gestational diabetes: a nation-wide study. *J Matern Fetal Neonatal Med*. 2015;28(14):1720–4. https://doi.org/10.3109/14767058.2014.966677.
43. Makatsariya A., Bitsadze V., Khizroeva J. et al. Neonatal thrombosis. *J Matern Fetal Neonatal Med*. 2020 Mar 23:1–9. https://doi.org/10.1080/14767058.2020.1743668. [Online ahead of print].
44. Kristensen S.R., Kaehne M., Petersen N.E. Hemizygous antithrombin-deficiency (Budapest III) in a newborn presenting with a thrombosis at birth. *Br J Haematol*. 2007;138(3):397–8. https://doi.org/10.1111/j.1365-2141.2007.06662.x.
45. Monagle P., Chan A.K., Goldenberg N.A. et al. Antithrombotic therapy in neonates and children: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest*. 2012;141(Suppl 2):e737S–801S. https://doi.org/10.1378/chest.11-2308.
46. Limperger V., Klostermeier U.C., Kenet G. et al. Clinical and laboratory characteristics of children with venous thromboembolism and protein C-deficiency: an observational Israeli-German cohort study. *Br J Haematol*. 2014;167(3):385–93. https://doi.org/10.1111/bjh.13039.
47. Lee M.J., Kim K.M., Kim J.S. et al. Long-term survival of a child with homozygous protein C deficiency successfully treated with living donor liver transplantation. *Pediatr Transplant*. 2009;13(2):251–4. https://doi.org/10.1111/j.1399-3046.2008.00972.x.
48. Klostermeier U.C., Limperger V., Kenet G. et al. Role of protein S deficiency in children with venous thromboembolism. An observational international cohort study. *Thromb Haemost*. 2015;113(2):426–33. https://doi.org/10.1160/TH14-06-0533.
49. Zharkov P.A. Influence of polymorphisms carriage of genes of the blood coagulation and folate metabolism on the risk for development of

thromboses in adults and children. [Vliyanie nositel'stva polimorfizmov genov svertyvayushchej sistemy krovi i folatnogo obmena na risk razvitiya trombozov u vzroslyh i detej]. *Voprosy prakticheskoj pediatrii*. 2012;7(5):26–32. (In Russ.).
50. Arnaez J., Arca G., Martin-Ancel A., Garcia-Alix A. Coagulation factor V G1691A, factor II G20210A and methylenetetrahydrofolate reductase C677T gene mutations do not play a major role in symptomatic neonatal arterial ischaemic stroke. *Br J Haematol*. 2018;180(2):290–2. https://doi.org/10.1111/bjh.14308.
51. Kenet G., Lutkhoff L.K., Albisetti M. et al. Impact of thrombophilia on risk of arterial ischemic stroke or cerebral sinovenous thrombosis in neonates and children: a systematic review and meta-analysis of observational studies. *Circulation*. 2010;121(16):1838–47. https://doi.org/10.1161/CIRCULATIONAHA.109.913673.
52. Laugesaar R., Kahre T., Kolk A. et al. Factor V Leiden and prothrombin 20210G>A [corrected] mutation and paediatric ischaemic stroke: a case-control study and two meta-analyses. *Acta Paediatr*. 2010;99(8):1168–74. https://doi.org/10.1111/j.1651-2227.2010.01784.x.
53. Turebylu R., Salis R., Erbe R. et al. Genetic prothrombotic mutations are common in neonates but are not associated with umbilical catheter-associated thrombosis. *J Perinatol*. 2007;27(8):490–5. https://doi.org/10.1038/sj.jp.7211786.
54. Neshat-Vahid S., Pierce R., Hersey D. et al. Association of thrombophilia and catheter-associated thrombosis in children: a systematic review and meta-analysis. *J Thromb Haemost*. 2016;14(9):1749–58. https://doi.org/10.1111/jth.13388.
55. Mekinian A., Lachassinne E., Nicaise-Roland P. et al. European registry of babies born to mothers with antiphospholipid syndrome. *Ann Rheum Dis*. 2013;72(2):217–22. https://doi.org10.1136/annrheumdis-2011-201167
56. Berkun Y., Simchen M.J., Strauss T. et al. Antiphospholipid antibodies in neonates with stroke – a unique entity or variant of antiphospholipid syndrome? *Lupus*. 2014;23(10):986–93. https://doi.org/10.1177/0961203314531842.
57. Gordon O., Almagor Y., Fridler D. et al. De novo neonatal antiphospholipid syndrome: a case report and review of the literature. *Semin Arthritis Rheum*. 2014;44(2):241–5. https://doi.org/10.1016/j.semarthrit.2014.04.003.
58. Fujimura Y., Matsumoto M., Kokame K. et al. Pregnancy-induced thrombocytopenia and TTP, and the risk of fetal death, in Upshaw-Schulman syndrome: a series of 15 pregnancies in 9 genotyped patients. *Br J Haematol*. 2009;144(5):742–54. https://doi.org/10.1111/j.1365-2141.2008.07515.x.
59. Strauss T., Elisha N., Ravid B. et al. Activity of Von Willebrand factor and levels of VWF-cleaving protease (ADAMTS13) in preterm and full term neonates. *Blood Cells Mol Dis*. 2017;67:14–7. https://doi.org/10.1016/j.bcmd.2016.12.013.
60. Katneni U.K., Ibla J.C., Hunt R. et al. von Willebrand factor/ADAMTS-13 interactions at birth: implications for thrombosis in the neonatal period. *J Thromb Haemost*. 2019;17(3):429–40. https://doi.org/10.1111/jth.14374.
61. O'Brien S.H., Kulkarni R., Wallace A. et al. Multicenter dose-finding and efficacy and safety outcomes in neonates and children treated with dalteparin for acute venous thromboembolism. *J Thromb Haemost*. 2014;12(11):1822–5. https://doi.org/10.1111/jth.12716.
62. van Ommen C.H., van den Dool E.J., Peters M. Nadroparin therapy in pediatric patients with venous thromboembolic disease. *J Pediatr Hematol Oncol*. 2008;30(3):230–4. https://doi.org/10.1097/MPH.0b013e31816356f8.
63. Malowany J.I., Knoppert D.C., Chan A.K. et al. Enoxaparin use in the neonatal intensive care unit: experience over 8 years. *Pharmacotherapy*. 2007;27(9):1263–71. https://doi.org/10.1592/phco.27.9.1263.
64. Bauman M.E., Belletrutti M.J., Bajzar L.et al. Evaluation of enoxaparin dosing requirements in infants and children. Better dosing to achieve therapeuticlevels. *Thromb Haemost*. 2009;101(1):86–92.
65. Klaassen I.L.M., Sol J.J., Suijker M.H. et al. Are low-molecular-weight heparins safe and effective in children? A systematic review. *Blood Rev*. 2019;33:33–42. https://doi.org/10.1016/j.blre.2018.06.003.
66. Witmer C., Raffini L. Treatment of venous thromboembolism in pediatric patients. *Blood*. 2020;135(5):335–43. https://doi.org/10.1182/blood.2019001847.
67. Romantsik O., Bruschettini M., Zappettini S. et al. Heparin for the treatment of thrombosis in neonates. *Cochrane Database Syst Rev*. 2016;11(11):CD012185. https://doi.org/10.1002/14651858.CD012185.pub2.
68. Monagle P., Newall F. Management of thrombosis in children and neonates: practical use of anticoagulants in children. *Hematology Am Soc Hematol Educ Program*. 2018;2018(1):399–404. https://doi.org/10.1182/asheducation-2018.1.399.

Литература:

1. Володин Н.Н., Ройтман Е.В., Румянцев А.Г., Шнейдер М.М. Тромбозы у новорожденных: патогенез, диагностика, лечение. *Вопросы практической педиатрии*. 2012;7(4):34–43.
2. Saracco P., Bagna R., Gentilomo C. et al.; Neonatal Working Group of the Registro Italiano Trombosi Infantili (RITI). Clinical data of neonatal systemic thrombosis. *J Pediatr*. 2016;171:60–6.e1. https://doi.org/10.1016/j.jpeds.2015.12.035.
3. Bhatt M.D., Chan A.K. Venous thrombosis in neonates. *Fac Rev*. 2021;10:20. https://doi.org/10.12703/r/10-20.
4. Raffini L., Huang Y.S., Witmer C., Feudtner C. Dramatic increase in venous thromboembolism in children's hospitals in the United States from 2001 to 2007. *Pediatrics*. 2009;124(4):1001–8. https://doi.org/10.1542/peds.2009-0768.
5. Saxonhouse M.A. Thrombosis in the neonatal intensive care unit. *Clin Perinatol*. 2015;42(3):651–73. https://doi.org/10.1016/j.clp.2015.04.010.
6. Saracco P., Parodi E., Fabris C. et al. Management and investigation of neonatal thromboembolic events: genetic and acquired risk factors. *Thromb Res*. 2009;123(6):805–9. https://doi.org/10.1016/j.thromres.2008.12.002.
7. Strauss T., Levy-Shraga Y., Ravid B. et al. Clot formation of neonates tested by thromboelastography correlates with gestational age. *Thromb Haemost*. 2010;103(2):344–50. https://doi.org/10.1160/TH09-05-0282.
8. Kenet G., Nowak-Gottl U. Venous thromboembolism in neonates and children. *Best Pract Res Clin Haematol*. 2012;25(3):333–44. https://doi.org/10.1016/j.beha.2012.07.001.
9. El-Naggar W., Yoon E.W., McMillan D. et al.; Canadian Neonatal Network Investigators. Epidemiology of thrombosis in Canadian neonatal intensive care units. *J Perinatol*. 2020;40(7):1083–90. https://doi.org/10.1038/s41372-020-0678-1.
10. Kenet G., Cohen O., Bajorat T., Nowak-Göttl U. Insights into neonatal thrombosis. *Thromb Res*. 2019;181(Suppl 1):S33–S36. https://doi.org/10.1016/S0049-3848(19)30364-0.
11. Haley K.M. Neonatal venous thromboembolism. *Front Pediatr*. 2017;5:136. https://doi.org/10.3389/fped.2017.00136.
12. Veldman A., Nord M.F., Michel-Behnke I. Thrombosis in the critically ill neonate: incidence, diagnosis, and management. *Vask Health Risk Manag*. 2008;4(6):1337–48. https://doi.org/10.2147/vhrm.s4274.
13. Martin G., Thomas M.A., Wei X.C., Le D. Diffuse intracerebral hemorrhage in an infant with a novel homozygous variant leading to severe protein C deficiency. *J Pediatr Hematol Oncol*. 2020 Nov 6. https://doi.org/10.1097/MPH.0000000000001993.
14. Kraus F.T. Fetal thrombotic vasculopathy: perinatal stroke, growth restriction, and other sequelae. *Surg Pathol Clin*. 2013;6(1):87–100. https://doi.org/10.1016/j.path.2012.10.001.
15. Young G., Albisetti M., Bonduel M. et al. Impact of inherited thrombophilia on venous thromboembolism in children: a systematic review and meta-analysis of observational studies, *Circulation*. 2008;118(13):1373–82. https://doi.org/10.1161/CIRCULATIONAHA.108.789008.
16. Monagle P., Ignjatovic V., Savoia H. Hemostasis in neonates and children: pitfalls and dilemmas. *Blood Rev*. 2010;24(2):63–8. https://doi.org/10.1016/j.blre.2009.12.001.
17. Шабалов Н.П., Иванов Д.О., Шабалова Н.Н. Гемостаз в динамике первой недели жизни как отражение механизмов адаптации к внеутробной жизни новорожденного. *Педиатрия. Журнал имени Г.Н. Сперанского*. 2000;79(3):22.
18. Кольцова Е.М., Балашова Е.Н., Пантелеев М.А., Баландина А.Н. Лабораторные аспекты гемостаза новорожденных. *Вопросы гематологии/онкологии и иммунопатологии в педиатрии*. 2018;17(4):100–13.

https://doi.org/10.24287/1726-1708-2018-17-4-100-113.
19. Ignjatovic V., Pelkmans L., Kelchtermans H. et al. Differences in the mechanism of blood clot formation and nanostructure in infants and children compared with adults. *Thromb Res*. 2015;136(6):1303–9. https://doi.org/10.1016/j.thromres.2015.10.034.
20. Черкасова С.В. Гемостаз новорожденных. *Практика педиатра*. 2020;(1):49 –52.
21. Nowak-Gottl U., Limperger V., Kenet G. et al. Developmental hemostasis: a lifespan from neonates and pregnancy to the young and elderly adult in a European white population. *Blood Cell Mol Dis*. 2017;67:2–13. https://doi.org/10.1016/j.bcmd.2016.11.012.
22. Ignjatovic V. 30 years of developmental haemostasis: what have we learnt and how are we applying this knowledge. *Thromb Res*. 2018;172:188–9. https://doi.org/10.1016/j.thromres.2018.11.021.
23. Леонова Е.Ю., Синякин О.Ю. Особенности системы гемостаза у новорожденных детей. *Охрана материнства и детства*. 2016;(2):76–81.
24. Strauss T., Sidlik-Muskatel R., Kenet G. Developmental hemostasis: primary hemostasis and evaluation of platelet function in neonates. *Semin Fetal Neonatal Med*. 2011;16(6):301–4. https://doi.org/10.1016/j.siny.2011.07.001.
25. Wiedmeier S.E., Henry E., Sola-Visner M.C., Christensen R.D. Platelet reference ranges for neonates, defined using data from over 47,000 patients in a multihospital healthcare system. *J Perinatol*. 2009;29(2):130–6. https://doi.org/10.1038/jp.2008.14.
26. Strauss T., Elisha N., Ravid B. et al. Activity of Von Willebrand factor and levels of VWF-cleaving protease (ADAMTS13) in preterm and full-term neonates. *Blood Cell Mol Dis*. 2017;67:14–7. https://doi.org/10.1016/j.bcmd.2016.12.013.
27. van Ommen C.H., Sol J.J. Developmental hemostasis and management of central venous catheter thrombosis in neonates. *Semin Thromb Hemost*. 2016;42(7):752–9. https://doi.org/10.1055/s-0036-1592299.
28. Sirachainan N., Limrungsikul A., Chuansumrit A. et al. Incidences, risk factors and outcomes of neonatal thromboembolism. *J Matern Fetal Neonatal Med*. 2018;31(3):347–51. https://doi.org/10.1080/14767058.2017.1285892.
29. Marquez A., Shabanova V., Faustino E.V.S.; Northeast Pediatric Critical Care Research Consortium. Prediction of catheter-associated thrombosis in critically ill children. *Pediatr Crit Care Med*. 2016;17(11):e521–e528. https://doi.org/10.1097/PCC.0000000000000958.
30. Rupp M.E., Karnatak R. Intravascular catheter-related bloodstream infections. *Infect Dis Clin North Am*. 2018;32(4):765–87. https://doi.org/10.1016/j.idc.2018.06.002.
31. Thornburg C.D., Smith P.B., Smithwick M.L. et al. Association between thrombosis and bloodstream infection in neonates with peripherally inserted catheters. *Thromb Res*. 2008;122(6):782–5. https://doi.org/10.1016/j.thromres.2007.10.001.
32. Amankwah E.K., Atchison C.M., Arlikar S. et al. Risk factors for hospital-associated venous thromboembolism in the neonatal intensive care unit. *Thromb Res*. 2014;134(2):305–9. https://doi.org/10.1016/j.thromres.2014.05.036.
33. Andres O., Schulze H., Speer C.P. Platelets in neonates: central mediators in haemostasis, antimicrobial defence and inflammation. *Thromb Haemost*. 2015;113(1):3–12. https://doi.org/10.1160/TH14-05-0476.
34. Vorobev A., Makatsariya A., Bitsadze V. et al. Unusual thrombosis or pregnancy complications associated to ovarian cancers: two clinical cases. *J Matern Fetal Neonatal Med*. 2021;34(9):1430–4. https://doi.org/10.1080/14767058.2019.1638359.
35. Bhat R., Kumar R., Kwon S. et al. Risk factors for neonatal venous and arterial thromboembolism in the neonatal intensive care unit – a case control study. *J Pediatr*. 2018;195:28–32. https://doi.org/10.1016/j.jpeds.2017.12.015.
36. Kulkarni A.A., Osmond M., Bapir M. et al. The effect of labour on the coagulation system in the term neonate. *Haemophilia*. 2013;19(4):533–8. https://doi.org/10.1111/hae.12115.
37. Tuckuviene R., Christensen A.L., Helgested J. et al. Infant, obstetrical and maternal characteristics associated with thromboembolism in infancy: a nationwide population-based case-control study. *Arch Dis Child Fetal Neonatal Ed*. 2012;97(6):F417–22. https://doi.org/10.1136/archdischild-2011-300665.
38. Branchford B.R., Mourani P., Bajaj L et al. Risk factors for in-hospital venous thromboembolism in children: a case-control study employing diagnostic validation. *Haematologica*. 2012;97(4):509–15. https://doi.org/10.3324/haematol.2011.054775.
39. Motta M., Rodriguez-Perez C., Tincani A. et al. Neonates born from mothers with autoimmune disorders. *Early Hum Dev*. 2009;85(10 Suppl):S67–70. https://doi.org/10.1016/j.earlhumdev.2009.08.020.
40. van Ommen C.H., Nowak-Göttl U. Inherited thrombophilia in pediatric venous thromboembolic disease: why and who to test. *Front Pediatr*. 2017;5:50. https://doi.org/10.3389/fped.2017.00050.
41. Sharathkumar A.A., Mahajerin A., Heidt L. et al. Risk-prediction tool for identifying hospitalized children with a predisposition for development of venous thromboembolism: Peds-Clot clinical Decision Rule. *J Thromb Haemost*. 2012;10(7):1326–34. https://doi.org/10.1111/j.1538-7836.2012.04779.x.
42. Ovesen P.G., Jensen D.M., Damm P. et al. Maternal and neonatal outcomes in pregnancies complicated by gestational diabetes: a nation-wide study. *J Matern Fetal Neonatal Med*. 2015;28(14):1720–4. https://doi.org/10.3109/14767058.2014.966677.
43. Makatsariya A., Bitsadze V., Khizroeva J. et al. Neonatal thrombosis. *J Matern Fetal Neonatal Med*. 2020 Mar 23:1–9. https://doi.org/10.1080/14767058.2020.1743668. [Online ahead of print].
44. Kristensen S.R., Kaehne M., Petersen N.E. Hemizygous antithrombin-deficiency (Budapest III) in a newborn presenting with a thrombosis at birth. *Br J Haematol*. 2007;138(3):397–8. https://doi.org/10.1111/j.1365-2141.2007.06662.x.
45. Monagle P., Chan A.K., Goldenberg N.A. et al. Antithrombotic therapy in neonates and children: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest*. 2012;141(Suppl 2):e737S–801S. https://doi.org/10.1378/chest.11-2308.
46. Limperger V., Klostermeier U.C., Kenet G. et al. Clinical and laboratory characteristics of children with venous thromboembolism and protein C-deficiency: an observational Israeli-German cohort study. *Br J Haematol*. 2014;167(3):385–93. https://doi.org/10.1111/bjh.13039.
47. Lee M.J., Kim K.M., Kim J.S. et al. Long-term survival of a child with homozygous protein C deficiency successfully treated with living donor liver transplantation. *Pediatr Transplant*. 2009;13(2):251–4. https://doi.org/10.1111/j.1399-3046.2008.00972.x.
48. Klostermeier U.C., Limperger V., Kenet G. et al. Role of protein S deficiency in children with venous thromboembolism. An observational international cohort study. *Thromb Haemost*. 2015;113(2):426–33. https://doi.org/10.1160/TH14-06-0533.
49. Жарков П.А. Влияние носительства полиморфизмов генов свертывающей системы крови и фолатного обмена на риск развития тромбозов у взрослых и детей. *Вопросы практической педиатрии*. 2012;7(5):26–32.
50. Arnaez J., Arca G., Martin-Ancel A., Garcia-Alix A. Coagulation factor V G1691A, factor II G20210A and methylenetetrahydrofolate reductase C677T gene mutations do not play a major role in symptomatic neonatal arterial ischaemic stroke. *Br J Haematol*. 2018;180(2):290–2. https://doi.org/10.1111/bjh.14308.
51. Kenet G., Lutkhoff L.K., Albisetti M. et al. Impact of thrombophilia on risk of arterial ischemic stroke or cerebral sinovenous thrombosis in neonates and children: a systematic review and meta-analysis of observational studies. *Circulation*. 2010;121(16):1838–47. https://doi.org/10.1161/CIRCULATIONAHA.109.913673.
52. Laugesaar R., Kahre T., Kolk A. et al. Factor V Leiden and prothrombin 20210G>A [corrected] mutation and paediatric ischaemic stroke: a case-control study and two meta-analyses. *Acta Paediatr*. 2010;99(8):1168–74. https://doi.org/10.1111/j.1651-2227.2010.01784.x.
53. Turebylu R., Salis R., Erbe R. et al. Genetic prothrombotic mutations are common in neonates but are not associated with umbilical catheter-associated thrombosis. *J Perinatol*. 2007;27(8):490–5. https://doi.org/10.1038/sj.jp.7211786.
54. Neshat-Vahid S., Pierce R., Hersey D. et al. Association of thrombophilia and catheter-associated thrombosis in children: a systematic review and meta-analysis. *J Thromb Haemost*. 2016;14(9):1749–58. https://doi.org/10.1111/jth.13388.
55. Mekinian A., Lachassinne E., Nicaise-Roland P. et al. European registry of babies born to mothers with antiphospholipid syndrome. *Ann Rheum Dis*. 2013;72(2):217–22. https://doi.org10.1136/annrheumdis-2011-201167.
56. Berkun Y., Simchen M.J., Strauss T. et al. Antiphospholipid antibodies in neonates with stroke – a unique entity or variant of antiphospholipid syndrome? *Lupus*. 2014;23(10):986–93. https://doi.org/10.1177/0961203314531842.
57. Gordon O., Almagor Y., Fridler D. et al. De novo neonatal antiphospholipid

syndrome: a case report and review of the literature. *Semin Arthritis Rheum*. 2014;44(2):241–5. https://doi.org/10.1016/j.semarthrit.2014.04.003.
58. Fujimura Y., Matsumoto M., Kokame K. et al. Pregnancy-induced thrombocytopenia and TTP, and the risk of fetal death, in Upshaw-Schulman syndrome: a series of 15 pregnancies in 9 genotyped patients. *Br J Haematol*. 2009;144(5):742–54. https://doi.org/10.1111/j.1365-2141.2008.07515.x.
59. Strauss T., Elisha N., Ravid B. et al. Activity of Von Willebrand factor and levels of VWF-cleaving protease (ADAMTS13) in preterm and full term neonates. *Blood Cells Mol Dis*. 2017;67:14–7. https://doi.org/10.1016/j.bcmd.2016.12.013.
60. Katneni U.K., Ibla J.C., Hunt R. et al. von Willebrand factor/ADAMTS-13 interactions at birth: implications for thrombosis in the neonatal period. *J Thromb Haemost*. 2019;17(3):429–40. https://doi.org/10.1111/jth.14374.
61. O'Brien S.H., Kulkarni R., Wallace A. et al. Multicenter dose-finding and efficacy and safety outcomes in neonates and children treated with dalteparin for acute venous thromboembolism. *J Thromb Haemost*. 2014;12(11):1822–5. https://doi.org/10.1111/jth.12716.
62. van Ommen C.H., van den Dool E.J., Peters M. Nadroparin therapy in pediatric patients with venous thromboembolic disease. *J Pediatr Hematol Oncol*. 2008;30(3):230–4. https://doi.org/10.1097/MPH.0b013e31816356f8.
63. Malowany J.I., Knoppert D.C., Chan A.K. et al. Enoxaparin use in the neonatal intensive care unit: experience over 8 years. *Pharmacotherapy*. 2007;27(9):1263–71. https://doi.org/10.1592/phco.27.9.1263.
64. Bauman M.E., Belletrutti M.J., Bajzar L.et al. Evaluation of enoxaparin dosing requirements in infants and children. Better dosing to achieve therapeuticlevels. *Thromb Haemost*. 2009;101(1):86–92.
65. Klaassen I.L.M., Sol J.J., Suijker M.H. et al. Are low-molecular-weight heparins safe and effective in children? A systematic review. *Blood Rev*. 2019;33:33–42. https://doi.org/10.1016/j.blre.2018.06.003.
66. Witmer C., Raffini L. Treatment of venous thromboembolism in pediatric patients. *Blood*. 2020;135(5):335–43. https://doi.org/10.1182/blood.2019001847.
67. Romantsik O., Bruschettini M., Zappettini S. et al. Heparin for the treatment of thrombosis in neonates. *Cochrane Database Syst Rev*. 2016;11(11):CD012185. https://doi.org/10.1002/14651858.CD012185.pub2.
68. Monagle P., Newall F. Management of thrombosis in children and neonates: practical use of anticoagulants in children. *Hematology Am Soc Hematol Educ Program*. 2018;2018(1):399–404. https://doi.org/10.1182/asheducation-2018.1.399.

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