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REVIEW ARTICLE

Thromboembolic complications in newborns – diagnostic value of D-dimers concentration and proposed outline of enoxaparin use

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Abstract

Introduction and Objective. Among paediatric patients, thromboembolic complications (TECs) are most often observed in newborns, especially premature infants requiring intensive care and the use of central vascular accesses. Prognosis depends on the presence of comorbidities, maturity of the newborn, and the location and size of the thrombus. The basic laboratory test that allows for the exclusion of TECs is assessment of the plasma D-dimers concentration, the correct value of which sufficiently excludes the presence of TECs.

Review methods. The review attempts to systematize existing knowledge on the plasma D-dimers concentration in newborns, and creates a scheme for using enoxaparin (EX), helpful in everyday clinical practice.

Brief description of the state of knowledge. There are single studies devoted to assessing the plasma D-dimers concentration in newborns, but they agree that the concentration in normal healthy adults does not apply to newborns, regardless of the postmenstrual age (PMA), because the plasma D-dimers concentration found in newborns are significantly higher, despite the lack of clinical and ultrasound features of thrombosis and normal results of other parameters of the coagulation system. Increased plasma D-dimers concentration in newborns may be due to delayed renal clearance of D-dimers and to physiological mechanisms related to the closing of the venous duct (DV) and arterial duct (DA) in the newborn.

Summary. Plasma D-dimers concentration is one of the basic laboratory markers of TECs, and is a starting point for further diagnostics and a valuable guide when making decisions about prophylactic and therapeutic procedures. The use of EX, as well as other LMWHs, is slowly becoming the treatment of choice in paediatric patients and is increasingly more often recommended in newborns.

Key words

D-dimer, thromboembolic complications, newborn, enoxaparin

Abbreviations

ALP – alkaline phosphatase; **ALT** – alanin aminotransferase; **APTT** – activated partial-thromboplastin time; **AST** – asparaginian aminotransferase; **AT-3** – antithrombin-3; **BT** – bleeding time; **CB** – conjugated bilirubin; **DA** – ductus arteriosus; **DV** – ductus venosus; **ELISA** – enzyme-linked immunosorbent assay; **EX** – enoxaparin; **FB** – fibrinogen; **FPX** – fondaparinux; **GC** – glucocorticoids; **GGTP** – gamma-glutamyl transpeptidase; **Hb** – haemoglobin; **HCT** – haematocrit; **HIT** – heparin-induced thrombocytopenia; **HP** – heparin; **IMH** – intramedullary haemorrhage; **INR** – international normalized ratio; **IUGR** – intrauterine growth retardation; **LMWH** – low-molecular weight heparin; **LP** – lumbar puncture; **NFH** – non-fractionated heparin; **OMP** – omeprazole; **PMA** – postmenstrual age; **PT** – prothrombin time; **TB** – total bilirubin; **TCT** – thrombin clotting time; **TEC** – thromboembolic complication; **TEI** – thromboembolic incident; **TT** – thrombolytic treatment

INTRODUCTION

The review was prepared based on the analysis of available data in 3,430 publications on the plasma concentration of D-dimers and the principles of enoxaparin use in newborns. The essential elements of the selection of publications were their clinical usefulness in everyday neonatological practice, and the date of their preparation. Articles older than eight years were not included, except for articles necessary to present the overarching purpose of the review.

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The probability of thromboembolic complications (TECs) in the neonatal period is approximately 40 times higher than in any other period of life [1, 2]. The incidence of TECs in newborns is 2.4 per 1,000 live births [2, 3]. About 90% of the TECs concern newborns undergoing central vessel cannulation [1, 2]. In neonates with central vascular access, asymptomatic TECs are found in about 20% – 30% of cases, while clinical symptoms of thrombosis are observed in about 1% of cases [4–6].

The basic laboratory test that allows for the exclusion of TECs is assessment of the concentration of plasma D-dimers, the correct value of which sufficiently excludes the presence of TECs [7]. D-dimers are a unique indicator of fibrin degradation and are formed as a result of the action of three enzymem – thrombin, plasmin and factor XIIIa [8]. In the first stage of

fibrin degradation by thrombin, the fibrin monomers that produce fibrinogen (FB) are cleaved, which polymerize and serve as a matrix for the synthesis of plasmin and factor XIIIa. Thrombin activates factor XIII bound in plasma with fibrin polymers and lead to the production of factor XIIIa, which is an active transglutaminase [9, 10]. Factor XIIIa catalyses the formation of covalent bonds between D-domains in polymerized fibrin, and then, as a result of plasmin, cross-linked fibrin is degraded resulting in the release of fibrin degradation products and D-dimers (Fig. 1) [11–18]. There are four basic methods of determining the concentration of plasma D-dimers: the enzyme immunoassay method (ELISA), the latex method, whole blood agglutination, and the method using technetium Tc99m-labeled antibodies [19–22]. Four methods listed, not three.

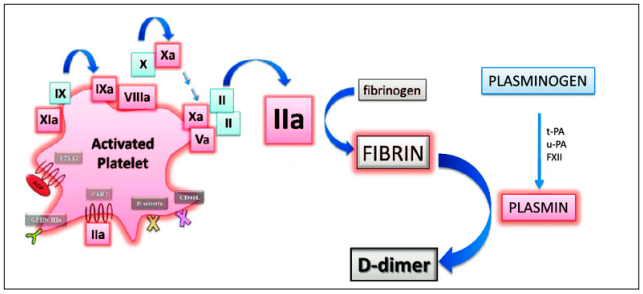

Figure 1. Dynamics of D-dimers formation. The prothrombinase complex, created by Xa factor and Va factor, generates large amounts of thrombin (IIa factor) on the activated platelet surface during the propagation phase of coagulation. Thrombin (IIa factor) then cleaves fibrinogen to fibrin and fibrin network is formed. In the next stage, proteolytic degradation of fibrin by plasmin takes place and the release of D-dimers, which are products of fibrin degradation [17, modified]

Enoxaparin EX is a glycosaminoglycan, which is low molecular weight heparin (LMWH) with a mass of 4500 Da, obtained by depolymerization of heparin (HP) [23]. It has a strong inhibitory effect on the activity of factor Xa and a weaker inhibitory effect on factor IIa and thrombin [24]. In addition, EX has the ability to inhibit factor VIIa and reduce the release of the von Willebrand factor from the vascular endothelium into the blood, which is mediated by antithrombin III (AT-3) [25]. EX shows a strong and long-lasting anticoagulant effect, and does not significantly affect the bleeding time (BT), general blood coagulation parameters, platelet aggregation or FB binding to platelets [26]. The bioavailability of EX is approximately 100% and the maximum anti-Xa activity occurs 3–5 hours after administration. The serum EX half-life ($t_{1/2}$) is about 5 hours after a single administration and about 7 hours after repeated administration [27]. EX metabolism occurs mainly in the liver by breaking disulphide bonds and depolymerization [28]. Due to the ease of use and favourable pharmacokinetic parameters, among LMWH it is EX that is recommended in TECs therapy in newborns [29, 30].

Risk factors of thromboembolic complications in newborns. The tendency to develop TECs in the neonatal period is most often a consequence of physiological hypercoagulability, low volume reserve in the venous system, and slow venous flow [31, 32]. There are a number of risk factors for TECs in the neonatal period, the most common of which are prematurity, severe general condition, infection, and central vessel cannulation [33–35]. Numerous other disorders also contribute to the disease, the greater the number, the greater the risk of TECs (Tab. 1) [35–38].

Reference value of d-dimers concentration in newborns. There are single studies devoted to the assessment of plasma D-dimers concentration in newborns, the most important of which seems to be the study by Hudson et al., which included 15 preterm infants, 45 term newborns and 17 pregnant women in which the plasma D-dimers concentration was determined using the latex method. All newborns in the study received an intramuscular injection of vitamin K in a dose adequate to body weight and postmenstrual age (PMA). Material for tests in preterm newborns was collected on the 1st day of life, and in term newborns between the 1st – 5th day of life. Non-haemolytic jaundice was observed in 27 newborns, intrauterine growth retardation (IUGR) was observed in 6, vomiting in 4, neonatal toxic erythema in 3, foetal-maternal leakage in 3 newborns. Two newborns were assisted by ventilation for less than 24 hours, and 2 newborns were born by mothers with diabetes. All newborns were fed enteral nutrition with breast milk or with modified milk. Bacteraemia was not detected in any of the newborns. Eighteen newborns required phototherapy due to severe jaundice [39].

In the current study whole blood for morphology was collected in EDTA tubes and assessed on a Coulter s880 cell counter. In order to determine the coagulation system indices, including the plasma D-dimers concentration, plasma was collected in a sodium citrate tube [39,40]. The following values of the coagulation parameters were obtained in the study: post-activation partial thromboplastin time (APTT) measured with Actin FS (Dade, American Hospital Supply) in the tested neonates ranged from 24–40 seconds, which was also normal for adults, with an average value of 32.8 seconds. The prothrombin time (PT) measured by rabbit brain thromboplastin (Manchester Thrombosis Research Foundation) in the tested neonates was in the range of 14–18 seconds, which was also normal for adults, with an average value of 16 seconds. The thrombin-calcium time (TCT) measured with bovine thrombin (Dade, American Hospital Supply) in the tested newborns ranged from 9–13 seconds, which was also normal for adults, with an average value of 11.1 seconds. The concentration of FB measured by the Clauss-thrombin method in the tested newborns was in the range of 1.6–4.2 g/l, which was also normal for adults, with an average value of 2.8 g/l. All neonates included in the study had normal platelet counts, ranging from 150–400 K/µl [39].

The results of measuring the plasma D-dimers concentration in newborns showed that the range of plasma D-dimers concentration in healthy adults should not be used in newborns, regardless of the PMA, because the plasma D-dimers concentration found in newborns was higher (Tab. 2) [39, 41]. There were no clinical signs of thrombosis in any of the newborns, and all newborns had normal results for other coagulation parameters (Tab. 3). There was no significant relationship between the plasma D-dimers concentration and the duration of pregnancy, method of feeding newborns, or the use of phototherapy and time of blood sampling [39].

The passage of D-dimers through the placenta is unlikely because the plasma D-dimers concentration found in the perinatal period in 17 pregnant women was normal [39,42]. Increased plasma D-dimer concentration in newborns compared to adults may be due to delayed renal clearance

Table 1. Risk factors of thromboembolic complications in newborns [35,36,37,38]

Risk factors of thromboembolic complications		
Occurring in the mother		
antiphospholipid syndrome	decompensated diabetes	preeclampsia
chorioamnionitis	eclampsia	premature rupture of the membranes > 18 hours
COVID-19 disease	neoplastic disease	venous thromboembolism
Related to the type of delivery		
delivery with obstetric forceps	delivery with vacuum extractor	traumatic delivery
Occurring in the newborn		
acute liver failure	COVID-19 disease	MTHFR C677T gene congenital polymorphism
acute renal failure	ECMO therapy	necrotizing enterocolitis
antithrombin congenital deficiency	extensive head trauma	persistent pulmonary hypertension
apolipoprotein A congenital elevation	factor II G20210A congenital mutation	polycythemia
central catheter	factor V Leiden G16091A congenital mutation	prematurity =< 32 weeks of pregnancy
circulatory failure	factor VIII, IX, I concentration congenital increased	protein C congenital deficiency
congenital arteriovenous fistula	factor XII concentration congenital decreased	protein C inhibitor congenital deficiency
congenital cyanotic heart defect	haemorrhagic stroke	protein S congenital deficiency
congenital defects of the head and neck	heparin cofactor II congenital deficiency	respiratory failure
congenital diaphragmatic hernia	HIV infection	sepsis
congenital dysfibrinogenaemia	hypernatraemia	septic shock
congenital homocystinuria	hypotension	severe dehydration
congenital hyperhomocysteinaemia	hypothyroidism	surgery
congenital nephrotic syndrome	intracranial abscess	therapeutic hypothermia
congenital tumours	intrauterine hypoxia	thrombocytosis
congenital venous malformation	meningoencephalitis	trisomy 21

ECMO – extracorporeal membrane oxygenation; HIV – human immunodeficiency virus; MTHFR - methylenetetrahydrofolate reductase

Table 2. Distribution of tested newborns based on plasma D-dimers concentration [39]

Evaluated variables		
D-dimer concentration [ng/ml]	Number of newborns	Percentage of newborns [%]
<500	47	79
500 – 1,000	8	13
1,001 – 2,000	3	5
2,001 – 4,000	2	3

Table 3. Coagulation parameters of tested newborns [39]

Evaluated variables		
Parameter and unit of measurement	Range	Mean
PT [s]	14 .0 – 18.0	16.0
APTT [s]	24.0 – 40.0	32.8
TCT [s]	9.0 – 13.0	11.1
FB [g/l]	1.5 – 4.0	2.8
PLT [K/µl]	150.0 – 400.0	no data

APTT – activated partial-thromboplastin time; FB – fibrinogen; PLT – trombocytes; PT – prothrombin time; TCT - thrombin clotting time

of D-dimers, and to physiological mechanisms related to the closing of the venous duct (DV) and arterial duct (DA) in the newborn [43, 44].

In adults, the plasma D-dimers concentration at which thrombosis is unlikely, is considered to be <500 ng/ml [45–47]. In newborns, based on the results of the above-mentioned study and the authors own extensive clinical and laboratory experience, it is proposed to adopt the following reference ranges of plasma D-dimers concentration: <500 ng/ml – normal concentration, sufficient to exclude TECs, 500 ng/ml–4,000 ng/ml – concentration requiring the extension of diagnostics with additional laboratory and imaging tests, and detailed analysis of TECs risk factors; a concentration of >4,000 ng/ml indicates the presence of TECs and is an indication for pharmacological treatment [39, 48, 49].

Proposed clinical procedure depending on D-dimers concentration in newborns. It is recommended that coagulation parameters, including plasma D-dimers concentration, should be determined in all neonates with TECs risk factors (Tab. 1), regardless of the presence of clinical, radiological or ultrasound symptoms that may indicate the presence of TECs, and in neonates with clinical, radiological and ultrasound symptoms, which may indicate the presence of TECs, regardless of the coexistence of risk factors for these complications [50].

Routine determination of coagulation parameters, including plasma D-dimers concentration, should also be performed prior to surgery or invasive diagnostic procedures associated with an increased risk of neonatal bleeding without TECs risk factors, and without clinical, radiological or ultrasound symptoms of thrombosis [51–53].

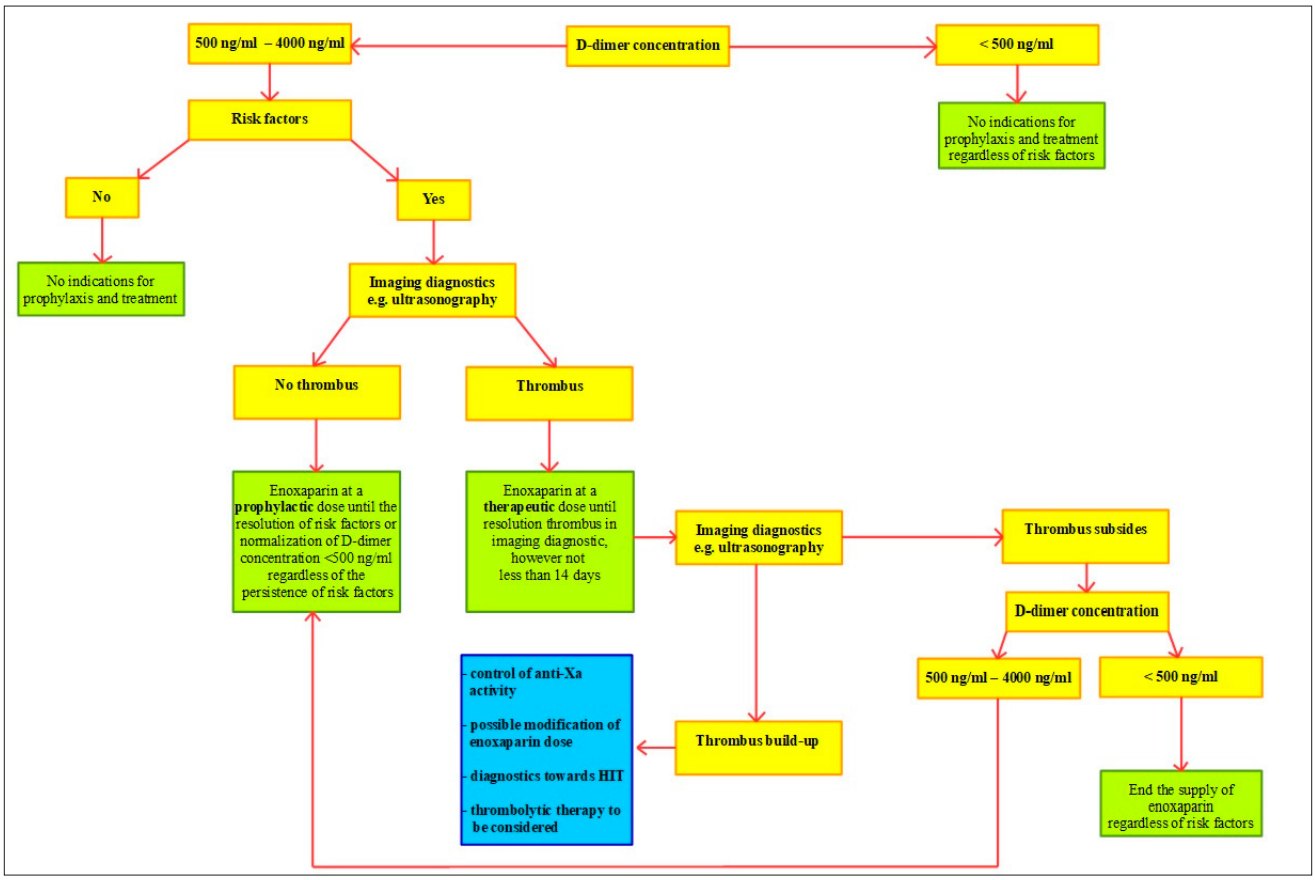

Figure 2a. Procedure for suspected or confirmed neonatal thrombosis. HIT – heparin-induced thrombocytopenia

Management of plasma D-dimers concentration <500 ng/ml. A plasma D-dimers concentration of <500 ng/ml sufficiently excludes TECs and does not indicato the need for pharmacotherapy or pharmacoprophylaxis, regardless of the presence of risk factors, and in the case of coexistence of any clinical symptom suggesting thrombosis, it requires looking for another cause of symptoms [45–47]. The proposed procedure at a plasma D-dimers concentration <500 ng/ml is shown in Figure 2a.

Management of plasma D-dimers concentration 500 ng/ml – 4000 ng/ml. Plasma D-dimers concentration of 500 ng/ml – 4000 ng/ml requires a detailed analysis of TECs risk factors and clinical symptoms, the presence of which necessitates the extension of diagnostics with additional laboratory and imaging diagnostics [39, 45–47]. The proposed procedure at a plasma D-dimers concentration of 500 ng/ml – 4,000 ng/ml is shown in Figure 2a.

Without risk factors for thromboembolic complications. Plasma D-dimers concentration of 500 ng/ml – 4,000 ng/ml in the absence of any TECs risk factors and the absence of any clinical symptoms suggesting thrombosis, indicates no need for pharmacotherapy and pharmacoprophylaxis, and does not constitute an indication for extending the diagnosis with additional laboratory tests and imaging diagnostics [39, 54]. Plasma D-dimers concentration of 500 ng/ml – 4,000 ng/ml in the absence of any TECs risk factor, but with any clinical symptom suggesting thrombosis, is an indication to extend the diagnosis by additional laboratory and imaging diagnostics [39, 43, 45, 54]. Plasma D-dimers concentration of 500 ng/ml – 4,000 ng/ml in the absence of any TECs risk factor, but in the presence of any clinical symptom suggesting thrombosis and in the absence of evidence of thrombosis in imaging diagnostics, indicates no need for pharmacotherapy and pharmacoprophylaxis and requires seeking another cause of symptoms [39, 43, 45, 55]. Plasma D-dimers concentration of 500 ng/ml – 4,000 ng/ml in the absence of any risk factor for TECs, but with any clinical symptom suggesting thrombosis and the presence of signs of thrombosis in imaging diagnostics, indicates the need for the EX treatment dose [55]. The therapeutic dose should be continued until the signs of thrombosis have fully resolved in imaging diagnostics, howee, not less than 14 days. After complete resolution of the signs of thrombosis in imaging diagnostics and after a minimum of 14 days of therapeutic doses of EX, in the event that the plasma D-dimers concentration is <4000 ng/ml in control studies, treatment with EX should be discontinued without prior prophylactic doses, and in the case of maintaining. When clinical symptoms develop, another cause of symptoms should be sought for [39, 56–58].

With risk factors for thromboembolic complications. Plasma D-dimers concentration of 500 ng/ml – 4,000 ng/ml in the presence of any TECs risk factor requires extended imaging diagnostics in the newborn for TECs, regardless of the presence or absence of clinical symptoms suggesting thrombosis [39, 43, 45, 55].

Plasma D-dimers concentration of 500 ng/ml – 4,000 ng/ml in the presence of any TECs risk factor and no evidence of thrombosis in imaging diagnostics, indicates the need for a

prophylactic dose of EX, regardless of the presence or absence of clinical symptoms [55]. The prophylactic dose should be used until the TECs risk factors disappear and/or the plasma D-dimers concentration drops to <500 ng/ml, regardless of the persistence of TECs risk factors, and in the case of persistent clinical symptoms, another cause of symptoms should be sough for [39, 56–58].

Plasma D-dimers concentration of 500 ng/ml – 4,000 ng/ml in the presence of any TECs risk factor and in the presence of signs of thrombosis in imaging diagnostics indicates the need for a therapeutic dose of EX, regardless of the presence or absence of clinical symptoms [55, 58]. The therapeutic dose should be continued until the signs of thrombosis have fully resolved in imaging diagnostics, however, not less than 14 days. After complete resolution of the signs of thrombosis in imaging diagnostics and after a minimum of 14 days of therapeutic doses of EX, if the plasma D-dimers concentration is <500 ng/ml in control studies, treatment with EX should be discontinued without prior administration of prophylactic doses, regardless of maintenance risk factors for TECs, and if the clinical symptoms persist, another cause of the symptoms should be sought for. After complete resolution of the signs of thrombosis in imaging diagnostics and after at least 14 days of therapeutic doses of EX, in the case of monitoring plasma D-dimers concentration of 500 ng/ml – 4,000 ng/ml, the administration of EX should be continued, but in a prophylactic dose regardless of the presence or absence of clinical symptoms until the TECs risk factors have resolved and/or the plasma D-dimers concentration has fallen to <500 ng/ml, regardless of the persistence of TECs risk factors, and in the case of persistence of clinical symptoms, another cause of symptoms should be sought for [39, 55–58].

Management of plasma D-dimers concentration >4,000 ng/ml. Plasma D-dimers concentration of >4,000 ng/ml is an indication for the inclusion of EX in therapeutic doses, regardless of the presence or absence of clinical symptoms suggesting thrombosis, and requires a detailed analysis of TECs risk factors and the extension of diagnostics to additional laboratory and imaging diagnostics [39, 43, 45, 54, 55, 58]. The proposed treatment with plasma D-dimers concentration >,000 ng/ml is shown in Figure 2b.

Without risk factors for thromboembolic complications. Plasma D-dimers concentration >4,000 ng/ml in the absence of any TECs risk factor requires extended imaging diagnostics in the newborn for TECs, regardless of the presence or absence of clinical symptoms of thrombosis [39, 43, 45, 54, 55, 59].

Plasma D-dimers concentration of >4,000 ng/ml in the absence of any TECs risk factor and no evidence of thrombosis in imaging diagnostics requires a therapeutic dose of EX, regardless of the presence or absence of clinical symptoms of thrombosis, until the plasma D-dimers concentration decreases to <4,000 ng/ml, at which point EX treatment should be terminated without prior prophylactic doses, and if clinical symptoms persist, another cause of symptoms should be sought for [39, 55–58].

Plasma D-dimers concentration of >4,000 ng/ml in the absence of any TECs risk factor, but in the presence of signs

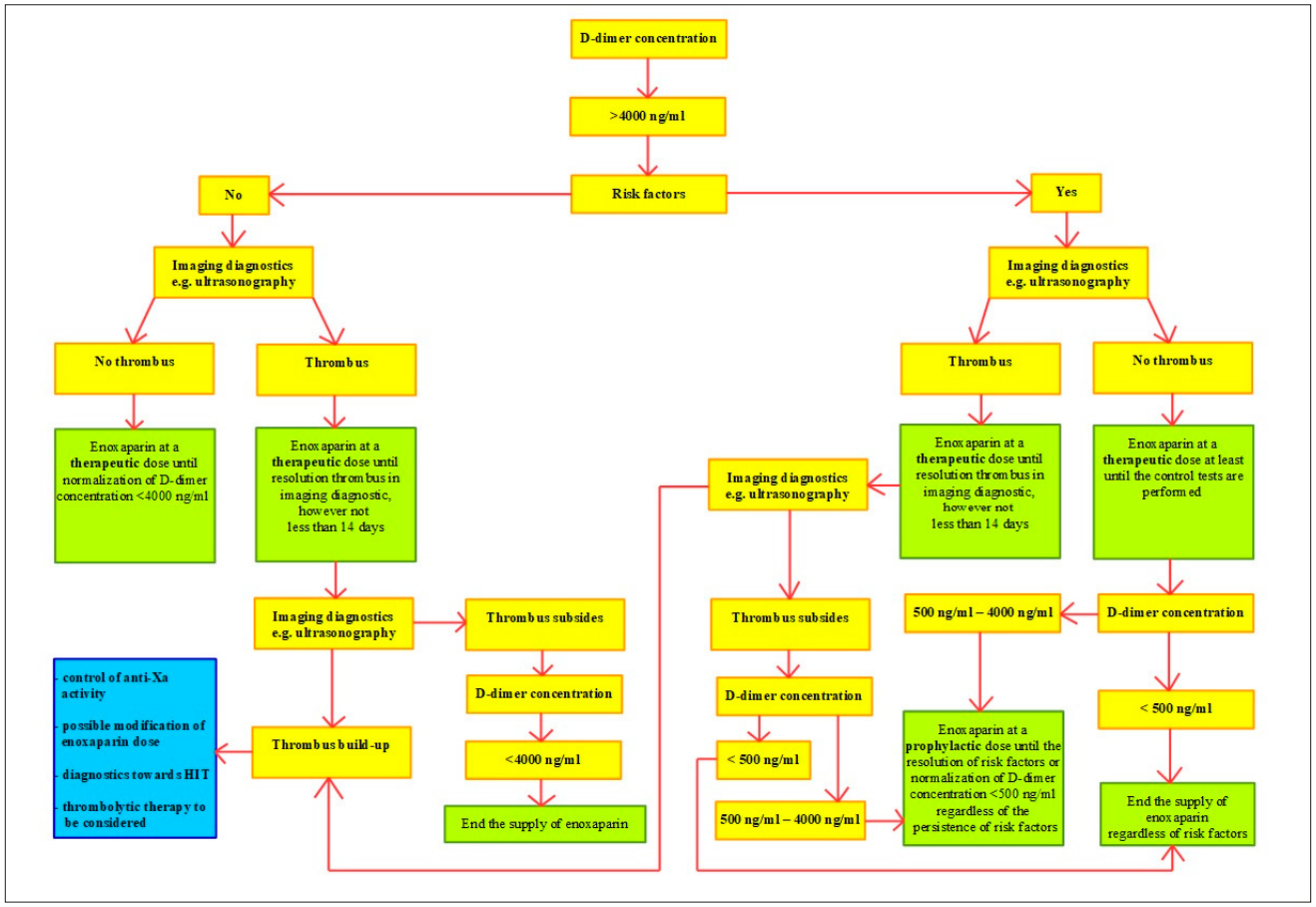

Figure 2b. Procedure for suspected or confirmed neonatal thrombosis. HIT – heparin-induced thrombocytopenia

of thrombosis in imaging diagnostics, makes it necessary to use a therapeutic dose of EX, regardless of the presence or absence of clinical symptoms of thrombosis until full resolution of the signs of thrombosis in imaging diagnostics, however, not less than 14 days. After complete resolution of the signs of thrombosis in imaging diagnostics and after a minimum of 14 days of therapeutic doses of EX, in the event that the plasma D-dimers concentration is <4,000 ng/ml in control tests, treatment with EX should be discontinued without the prior administration of prophylactic doses and in the clinical symptoms, another cause of symptoms should be soughtfor [39, 55–58].

With risk factors for thromboembolic complications. Plasma D-dimers concentration of >4000 ng/ml in the presence of any TECs risk factor requires extended imaging diagnostics in the newborn for TECs, regardless of the presence or absence of clinical symptoms of thrombosis [39, 54–58].

Plasma D-dimers concentration of >4,000 ng/ml in the presence of any TECs risk factor and no evidence of thrombosis in imaging diagnostics requires a therapeutic dose of EX, regardless of the presence or absence of clinical symptoms of thrombosis at least until follow-up examinations. If the plasma D-dimers concentration is found in control tests <500 ng/ml, treatment with EX should be discontinued without prior prophylactic doses, regardless of the persistence of TECs risk factors, and in the case of persistent clinical symptoms, another cause of symptoms should be sought for. If the control tests show a plasma D-dimers concentration of 500 ng/ml – 4,000 ng/ml, the administration of EX should be continued, but in a prophylactic dose, regardless of the presence or absence of clinical symptoms of thrombosis, until the risk factors for TECs disappear and/or the plasma D-dimers concentration is decreased to <500 ng/ml, regardless of the persistence of TECs risk factors. In the case of persistent clinical symptoms, another cause of symptoms should be sought for [39,55–58].

Plasma D-dimers concentration of >4000 ng/ml in the presence of any TECs risk factor and in the presence of signs of thrombosis in imaging diagnostics indicates the need for a therapeutic dose of EX, regardless of the presence or absence of clinical symptoms of thrombosis until full resolution of the signs of thrombosis in imaging diagnostics, however, not less than 14 days. After complete resolution of the signs of thrombosis in imaging diagnostics and after a minimum of 14 days of therapeutic doses of EX, if the plasma D-dimers concentration is <500 ng/ml in control studies, treatment with EX should be discontinued without prior administration of prophylactic doses, regardless of maintenance risk factors for TECs. If the clinical symptoms persist, another cause of the symptoms should be sought for. After complete resolution of the signs of thrombosis in imaging diagnostics and after at least 14 days of therapeutic doses of EX, in the case of control plasma D-dimer concentration of 500 ng/ml – 4000 ng/ml, the administration of EX should be continued, but in a prophylactic dose regardless of the presence or absence of clinical symptoms of thrombosis until the TECs risk factors have resolved and/or the plasma D-dimer concentration has fallen to <500 ng/ml, regardless of the persistence of TECs risk factors, and in the case of persistent clinical symptoms, another cause of symptoms should be sought for [39, 55–58].

Frequency of coagulation parameters monitoring. Measurement of coagulation parameters, including plasma D-dimers concentration, should be routinely performed prior to surgery or invasive diagnostic procedures associated with an increased risk of bleeding in all neonates, including those with no risk factors for TECs and no clinical, radiographic or ultrasound symptoms of thrombosis. [51, 54, 60].

In newborns with risk factors for TECs who do not have clinical, radiological or ultrasound symptoms suggesting TECs, determination of coagulation parameters, including plasma D-dimers concentration, should be performed at least once during the hospital stay [60].

In newborns with clinical, radiological or ultrasound symptoms that may indicate the presence of TECs, regardless of the coexistence of risk factors for these complications, the determination of coagulation parameters, including plasma D-dimers concentration, should be performed immediately after finding these symptoms and then monitored with the frequency depending on the clinical situation [54, 60, 61].

In clinically stable patients receiving EX, monitoring of the coagulation parameters should be performed every 48–96 hours, while in the case of evidence of thrombus build-up in imaging diagnostics, clinical symptoms that may indicate progression of TECs or symptoms of bleeding, control of the parameters of the coagulation system should be performed immediately [62].

Imaging diagnostics. Due to the easy and wide availability, TECs imaging diagnostics in neonatology is most often performed with the use of ultrasound with the colour Doppler option [62–64]. Other studies include magnetic resonance (MR) and computer tomography (CT) with a vascular option [65–67]. In the case of venous thrombosis within the central nervous system, ultrasound with the colour Doppler option detects about 50% of cases of dural sinus thrombosis, but does not allow the visualization of deep vein thrombosis of the brain [68]. Intraventricular and periventricular haemorrhage (IVH), occurring for no apparent reason in a neonate aged >7 days, and thalamic haemorrhages, especially unilateral haemorrhages, are considered to be an ultrasound marker of thrombosis in the central nervous system [68–70]. In the case of coexistence of anatomical anomalies within the dural venous sinuses, the use of ultrasound may give false positive results, and besides, due to its low sensitivity, it is not recommended for diagnosis, but possibly for treatment monitoring [71, 72]. The study of choice for the diagnosis of TECs in neonates is MR with venography, with a sensitivity of approximately 90%. This examination is used not only to visualize the dural venous sinuses, but also allows identification of changes secondary to thrombosis, such as cerebral oedema, ischemic stroke or haemorrhagic stroke, and also allows monitoring the evolution of changes, detecting disorders of myelination, gliosis and post-haemorrhagic cavities [73].

The authors of this review propose that imaging diagnostics with the vascular option should be performed in all newborns with clinical symptoms that may indicate the presence of TECs and/or with plasma D-dimers concentration that are an indication for such diagnostics.

Based on clinical experience, the authors further recommend that when ultrasound is used in clinically stable patients, follow-up examinations should be performed every 48–96 hours as standard, while in the event of bleeding

symptoms, clinical deterioration and/or increase of D-dimers concentration despite treatment, a follow-up ultrasound scan should be performed immediately.

If it is necessary to perform an MR or CT diagnostics, the schedule of this diagnostics should be planned individually based on a detailed assessment of the clinical situation, and in the event that this diagnostics is not available in a given ward, the newborn should be transferred to a centre with a higher reference.

Principles of using enoxaparin in newborns. The use of EX, like other LMWHs, is slowly becoming the treatment of choice in paediatric patients and is increasingly recommended in newborns. LMWHs have an advantage over non-fractionated heparin (NFH) due to easier monitoring, fewer complications and less frequent interactions with other drugs and nutrients [29, 30].

Preparats containing enoxaparin. In Poland, EX is available as a solution for injection with the active substance concentration of 100 mg/ml, 120 mg/ml and 150 mg/ml. Trade names of preparations containing EX and registered in Poland are Clexane®, Clexane® Forte, Losmina®, Neoparin®, Neoparin® Forte and Neoparin Multi® [74].

Methods of enoxaparin administration. In neonates, EX can be administered deeply subcutaneously in undiluted form, intravenously diluted with 0.9% NaCl in the schedule of 1 mg EX in 1 ml of 0.9% NaCl and into the arterial line of extracorporeal circulation. Intramuscular administration is contraindicated [29, 55, 56, 75].

Enoxaparin dosing in children. Based on the few studies available, it has been concluded that the EX doses in neonates should be slightly higher than in elderly patients, as shown below [76–78].

In children <2 months of age, the initial prophylactic EX dose is 0.75 mg/kg b.w. every 12 hours s.c or i.v. and the initial EX treatment dose is 1.5 mg/kg b.w. every 12 hours s.c. or i.v.

In children >2 months of age, the initial prophylactic EX dose is 0.5 mg/kg b.w. every 12 hours s.c or i.v. and the initial EX treatment dose is 1.0 mg/kg b.w. every 12 hours s.c. or i.v.

The maximum therapeutic dose of EX in newborns and infants should be 2 mg/kg b.w. every 12 hours s.c. or i.v.

Contraindications to the enoxaparin use. Contraindications for the use of EX include hypersensitivity to EX, HP or its derivatives, including other LMWHs or any of its components, a history of immune heparin thrombocytopenia (HIT) within the last 100 days or the presence of circulating antibodies, active clinically significant bleeding, ulceration stomach or intestines, perforation of the gastrointestinal tract, presence of a malignant tumour with a high risk of bleeding, recent surgery of the brain, spinal cord or eye, diagnosis or suspicion of oesophageal varices, anatomical abnormalities in the cvardio-vascular system, vascular aneurysms or serious abnormalities of blood vessels in the spinal cord or brain, IVH III and IV grade in the Papille's classification, simultaneous use of Ibuprofen, time less than 6 hours from lumbar puncture (LP), severe, untreated and life-threatening metabolic disorders, such as hyperkalaemia, metabolic acidosis, hyperglycaemia, end-stage renal failure without dialysis, and concomitant use of thrombolytic therapy (TT) [79–83].

Precautions during enoxaparin treatment. In the case of using EX in newborns and infants, both in prophylactic and therapeutic doses, gastroprotective treatment is indicated, consisting in intravenous administration of Omeprazole (OMP) at a dose of 1 mg/kg b.w./day in a single daily dose every 24 hours [84–86].

The simultaneous use of glucocorticosteroids (GCs) and prophylactic and therapeutic doses of EX in newborns and infants is not contraindicate; however, in these situations, special caution should be exercised and gastroprotective treatment consisting in intravenous administration of OMP at a dose of 1 mg/kg b.w./day in a single daily dose every 24 hours. The use of enoxaparin during GCs therapy has been shown to inhibit GCs-induced necrosis of newly formed osteocytes [84–87].

Due to the risk of intramedullary haematoma (IMH), it is contraindicated to perform LP in a period shorter than 12 hours from the administration of the prophylactic dose of EX, and in the period shorter than 24 hours from the administration of the therapeutic EX dose [88, 89]. Based on the benefit-risk assessment, consideration should be given to not using EX for at least 6 hours after LP [90].

Monitoring of laboratory tests during enoxaparin treatment. Despite the fact that EX is a relatively safe and low-toxic drug, it is recommended that the patient's laboratory test results be monitored closely during its use in certain clinical situations.

When EX administration is administered to patients with hyperglycaemia, metabolic acidosis, renal failure and who are receiving potassium-sparing diuretics or potassium supplementation, serum potassium levels should be monitored every 48–96 hours before and during treatment in clinically stable patients, or immediately in the case of clinical deterioration or disturbing symptoms [91, 92].

When administering EX, patients should be monitored for the early diagnosis of bleeding. For this purpose, the concentration of haemoglobin (Hb), haematocrit (HCT) and faecal occult blood should be determined every 48–96 hours in clinically stable patients, or immediately in the case of clinical deterioration or symptoms of bleeding [93, 94].

With the administration of EX, it is not necessary to routinely monitor the anticoagulant effect by measuring anti-Xa activity. Monitoring is indicated if there has been a recent thromboembolic incident (TEI) or major bleeding during EX use, especially in patients with renal insufficiency. When EX is administered every 12 hours, anti-Xa activity should be maintained within 0.5–1.0 IU/ml in control tests performed 4–6 hours after administration [95]. The EX dosage should be modified depending on the anti-Xa activity (Tab. 4) [96,97].

When administering EX, monitoring of coagulation parameters such as plasma D-dimers concentration, APTT, FB concentration, prothrombin time (PT) and the international normalized ratio (INR) is recommended. In clinically stable patients, determination of the coagulation system parameters should be performed every 48–96 hours, and in the event of evidence of thrombus build-up in the imaging tests, clinical symptoms that may indicate TECs progression or bleeding symptoms, the coagulation parameters should be determined immediately [98, 99].

Table 4. Principles of monitoring the anticoagulant effect [96,97]

Enoxaparin dosing based on anti-Xa activity			
Activity of anti-Xa [U/ml]	Time to stop of enoxaparin supply [h]	Dose change [%]	Control of anti-Xa activity
<0.35	0	+25	4 hours after changing the dose
0.35 – 0.49	0	+10	4 hours after changing the dose
0.5 – 1.0	0	0	after 24 hours
1.1 – 1.5	0	-25	before the next dose
1.6 – 2.0	3	-30	before the next dose
>2.0	until the anti-Xa activity is reduced to <0.5	-40	before the next dose

When administering EX, monitoring of liver function parameters such as total bilirubin (TB), conjugate bilirubin (CB) and alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP) and gamma-glutamyltranspeptidase (GGTP) is recommended. Due to the risk of direct hepatic cytotoxicity EX, characterized by an increase in the concentration of miR-122 and the HMGB-1 protein specific for bile cells, and the risk of induction of cholestasis [100, 101]. The authors recommend that in patients without clinical symptoms of cholestasis and hepatic cytotoxicity EX, determination of liver function parameters should be performed every 48–96 hours, and in the case of clinical symptoms of liver injury or cholestasis, determination of liver function parameters should be performed immediately.

Although no complications in the form of HIT have been observed during the use of EX in the paediatric population, the platelet count should be monitored before starting treatment and every 48–96 hours during treatment in patients in stable clinical conditio, or immediately in the case of deterioration of the patient's condition, clinical symptoms of thrombocytopenia or, paradoxically, new TEI [102–104]. Classically, HIT occurs between 2 – 21 days after initiation of treatment, and the risk of its occurrence is greater after surgery, especially cardiac surgery, as well as in cancer patients [105–107]. If HIT is strongly suspected, EX administration should be stopped immediately, ultrasound diagnostics should be performed to exclude the presence of a thrombus, and anti-heparin antibodies and, possibly, functional tests should be determined [107–109]. If anticoagulation is required in neonates and infants with HIT, consideration should be given to using fondaparinux (FPX) at a dose of 0.1 mg/kg b.w. – 0.2 mg/kg b.w. every 24 hours [110].

CONCLUSIONS

Both clinical practice and the results of the conducted studies indicate that the plasma D-dimers concentration found in the neonatal population is substantially higher than in adults, and the norms of plasma D-dimers concentration in the adult population do not apply to newborns [39, 41]. The reasons for the increased plasma D-dimers concentration in newborns are not fully known, however, the passage of D-dimers through the placenta is unlikely and the probable cause is delayed renal clearance of D-dimers and the physiological processes related to DV and DA closing [43, 44].

Although the plasma D-dimers concentration in newborns may be physiologically higher than in adults, it is still one of the basic laboratory markers of TECs and is a starting point for further diagnostics and a valuable guide when making decisions about prophylactic and therapeutic procedures, especially in newborns burdened with risk factors [39, 48, 49].

The use of EX both in prophylactic and therapeutic management is slowly becoming the procedure of choice in paediatric patients, and is increasingly recommended in newborns due to its easy dosing, low number of complications and rare interactions with other drugs and nutrients [29, 30].

Although the tools for the diagnosis and monitoring of TECs in newborns and the methods of their treatment still require more extensive research, the range of reference values and guidance on how to proceed depending on the plasma D-dimers concentration in newborns, proposed by the authors of this review and based on extensive clinical and laboratory experience, can become a helpful tool in everyday neonatological practice.

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