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Review

Neonatal bleeding disorders. A practical diagnostic approach

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Abstract

Since developmental hemostasis was introduced by Andrew et al. in the early 90s, age-related variations in coagulation components have been a well-established knowledge. In parallel with age-dependent hemostatic status maturation, coagulation disorders assessment stands as an important prerequisite for bleeding management. However, discrepancies observed between neonatal coagulation reference ranges and standard coagulation assays extrapolated from adults make neonatal disease evaluation and therapeutic management challenging. This study aims to provide a diagnostic approach to neonatal bleeding based on a current literature search on bleeding disorders in the neonatal period.

Keywords

Developmental hemostasis, bleeding disorders, neonates, practical diagnostic approach, reference ranges, diagnostic algorithm.

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Introduction

The hemostatic system is a complex protective pathway against bleeding that begins as soon as an endothelial injury occurs and tissue factor (TF) is released.

The formation of a strong clot induced by activated platelets and fibrinogen aims to stop bleeding. Furthermore, the hemostatic system is protective against excessive fibrin formation and deposition, mainly by the inhibitory function of antithrombin and protein C. Fibrinolysis is an additional protective mechanism regarding the appropriate dissolution of the clot. Otherwise, the hemostatic system prevents both bleeding and thromboembolic events in a complex but well-balanced way, which is extended equally from the early neonatal period to later childhood and adult life [1].

Bleeding disorders are scarcely reported in the overall neonatal population, but, as commonly observed among hospitalized neonates, they pose a great challenge to the treating physician. Published studies have shown an incidence of 0.3% for bleeding disturbances in neonatal life [2]. Even though thrombocytopenia is the most common cause of disorders pertained to primary hemostasis, bleeding intension is equally observed at hemostasis dysregulation other than low platelet count (PLT). Major or minor bleeding occurs in hospitalized neonates, mostly secondary due to acquired rather than congenital disorders in hemostasis [3]. Since congenital coagulation factor deficiency is rarely recorded, causative agents of acquired coagulation deficiency, such as liver failure or disseminated intravascular coagulation (DIC) due to sepsis or asphyxia, have become prominent in Neonatal Intensive Care Units (NICUs). Consequently, a proper diagnosis of the underlying cause is challenging as misdiagnosis can lead to inadequate treatment with severe clinical implications [4]. The fact that hemostasis in newborns is still immature and differs significantly from that of older children and adults complicates the differential diagnosis. Particularly, the levels of plasma pro-coagulant proteins are low in neonates, except for those of factors V, VIII, XIII (FV, FVIII, FXIII) and von Willebrand factor (vWF), which almost reach adult values [5-7]. Natural anticoagulants are reduced except for α-macroglobulin, which is markedly increased. The activity of the plasmin/plasminogen system, additionally to the fibrinolysis capacity, decreases, although vitamin K-dependent coagulation proteins and thrombin generation capacity ensure the neonatal hemostasis balance [3, 8].

Diagnostic approach to the bleeding neonate

Optimal diagnosis and management of coagulation disorders depend on early assessment of clinical signs and proper laboratory tests evaluation. Bleeding in a healthy newborn is suggestive of an underlying congenital coagulation dysfunction or a quantitative coagulation defect, whereas a sick premature neonate is more likely to suffer from an acquired coagulation disorder, presented detrimental as DIC. A positive family history could be indicative of congenital coagulation factor deficiency, while obstetric complications and events during labor may also affect the fetal hemostatic system, resulting in coagulation activation and DIC. Finally, medication administered to the mother by interfering with vitamin K metabolism is strongly associated with bleeding events in the neonatal period (**Tab. 1**) [9, 10].

Regarding the laboratory tests, activated partial thromboplastin time (aPTT), prothrombin time (PT) or international normalized ratio (INR), complete blood count (CBC) along with PLT, fibrinogen and D-dimers should be included [11]. Reference ranges instead of normal values concerning coagulation components in full-term and preterm neonates have been published by few investigators according to gestational age. However, institutional reference ranges have been established based on particular reagent and analyzer settings which may widely vary among research centers. The latter make reference values not easily manageable for other institutes (**Tab. 2**)

Table 1. Possible causes of bleeding according to family, obstetric, perinatal and postnatal history.

Family history	Family bleeding disorder
Maternal illness	Chorioamnionitis
	HELLP syndrome
Maternal medication	Acetylsalicylic acid
	Warfarin
Obstetric/perinatal events	Placenta previa
	Abruption
	Vasa previa
	Cord accident
	Fetal-to-maternal transfusion
	TTTS
Newborn	Congenital infections
	Intracranial hemorrhage
	Cephalhematoma
	Subgaleal hemorrhage
	Hemolytic disease of the newborn
	Heparin-induced thrombocytopenia
	Polycythemia/hyperviscosity
	IUGR

HELLP: hypertension, elevated liver enzymes, low platelets; IUGR: intrauterine growth restriction; TTTS: twin-to-twin transfusion syndrome.

Table 2. Reference ranges of parameters of coagulation, inhibitors and fibrinolysis in healthy full-term, preterm, small for gestational age (SGA) and appropriate for gestational age (AGA) newborns.

	SGA full-term newborns (n = 90), mean ± SD [a]	AGA full-term newborns (n = 98), mean ± SD [a]	SGA preterm newborns (n = 68), mean ± SD [b]	AGA preterm newborns (n = 71), mean ± SD [b]	Laboratory reference range for healthy full-term newborns
INR	1.30 ± 0.21	1.23 ± 0.15	1.35 ± 0.22	1.32 ± 0.20	1.26 (1.15-1.35) [c]
PT (sec)	16.20 ± 2.40	15.50 ± 1.40	16.60 ± 2.10	16.40 ± 1.98	15.6 (14.4-16.4) [c]
aPTT (sec)	44.0 ± 8.0	42.0 ± 6.6	51.0 ± 11.0	51.0 ± 12.0	38.7 (34.3-44.8) [c]
Fibrinogen (mg/dL)	184 ± 55	185 ± 86	158 ± 46	183 ± 80	2.80 (1.92-3.74) (g/L) [c]
FII c (%)	42.0 ± 8.0	43.0 ± 7.0	37.6 ± 6.5	37.2 ± 9.0	54 (41-69) [c]
FV c (%)	67.0 ± 25.0	73.0 ± 24.0	61.0 ± 22.0	62.0 ± 20.4	81 (64-103) [c]
FVII c (%)	64.0 ± 19.0	67.0 ± 18.0	61.2 ± 20.5	68.8 ± 23.7	70 (52-88) [c]
FVIII c (%)	238 ± 167	212 ± 158	142 ± 80	116 ± 57	182 (105-329) [c]
FIX c (%)	37.0 ± 15.0	39.0 ± 13.6	32.0 ± 22.0	28.0 ± 11.0	48 (35-56) [c]
FX c (%)	42.0 ± 10.0	43.8 ± 10.0	41.2 ± 9.7	41.5 ± 10.0	55 (46-67) [c]
FXI c (%)	45.2 ± 17.0	45.0 ± 17.0	33.5 ± 14.2	30.5 ± 11.0	30 (7-41) [c]
FXII c (%)	55 ± 24	65 ± 30	50 ± 22	47 ± 24	58 (43-80) [c]
AT Act (%)	53.0 ± 17.0	51.0 ± 12.0	37.2 ± 11.0	39.0 ± 13.7	76 (58-90) [c]
Protein C Act (%)	31 ± 9	31 ± 8	24 ± 8	24 ± 9	28.2 (14-42) [d]
Free protein S Act (%)	34.7 ± 8.0	37.8 ± 6.8	31.5 ± 9.0	31.1 ± 5.9	36 (28-47) [c]
APCr	2.24 ± 0.47	2.21 ± 0.27	2.30 ± 0.30	2.20 ± 0.34	1.13 ± 0.22 [e]
tPA (ng/mL)	12.2 ± 7.7	8.5 ± 3.9	13.8 ± 8.2	11.4 ± 7.0	9.6 (5-18.9) [f]
PAI-1 (ng/mL)	63.0 ± 35.0	67.0 ± 33.0	55.3 ± 24.4	46.0 ± 24.0	6.4 (2-15.1) (U/mL) [f]
vWF Ag (%)	210 ± 85	219 ± 71	202 ± 64	193 ± 59	153 ± 67 (U/mL) [g]

Act: activity; Ag: antigenic value; AGA: appropriate for gestational age; APCr: activated protein C resistance; aPTT: activated partial thromboplastin time; AT: antithrombin; c: coagulant activity; CBC: complete blood count; DIC: disseminated intravascular coagulation; FII: factor II; FV: factor V; FVII: factor VII; FVIII: factor VIII; FIX: factor IX; FX: factor X; FXI: factor XI; FXII: factor XII; INR: international normalized ratio; PAI-1: plasminogen activator inhibitor-1: PT: prothrombin time; SGA: small for gestational age; tPA: tissue plasminogen activator; vWF: von Willebrand factor.
[a] Mitsiakos et al., 2009 [16]; [b] Mitsiakos et al., 2010 [17]; [c] Monagle et al., 2006 [12], values: median (IQR); [d] Reverdiau-Moalic et al., 1996 [14], values: median (IQR); [e] Sifontes et al., 1997 [13], values: mean ± SD; [f] Andrew et al., 1987 [15], values: mean (IQR); [g] Andrew et al., 1987 [15], values: mean ± SD.

[12-17]. When interpreting abnormal coagulation test results, further evaluation is required to distinguish between factor deficiencies and factor inhibitors. The mixing test with normal plasma is a method that aids the clinician in resolving such discrepancies. If a mixing test corrects PT or aPTT, then a factor deficiency is present, but if there is no correction, a factor inhibitor is the cause of the bleeding [18]. In terms of platelet contribution to clot strength, little is known about platelet functionality which is better demonstrated by platelet activation than PLT itself. Platelet function in accordance with developmental hemostasis could provide valid information for bleeding etiology and treatment management.

Given the aforementioned concerns, a diagnostic algorithm was conducted for optimal management prevailing over misleading interpretations. At the end of this study, the neonate's clinical status (sick or healthy), along with the alterations of the coagulation system parameters, is included (**Fig. 1**). Health status terminology is critical for the clinical assessment of sick neonates. As coagulation disorders may appear with no specific clinical signs, sharing clinical traits of various neonatal morbidities and awareness of critical illness are essential. Heart rate alterations defined as tachycardia (> 180 beats/min) or bradycardia (< 90 beats/min) may early indicate neonatal disease. Abnormal respiratory rate and pattern may be slow (< 40 breaths/min) or rapid (> 60 breaths/min) and shallow, while the neonate may present with grunting, recession, gasping or apnoea. Furthermore, a sick neonate may be pale or severely jaundiced, hypothermic or pyrexial, lethargic or poorly feeding [19]. Consequently, abnormal traits may be indicative of an entire pathology. Particularly in sick neonates, acquired bleeding disorders lie on the underlying pathology. On the contrary, healthy neonates should be evaluated mainly in terms of inherited bleeding disturbances diagnosis.

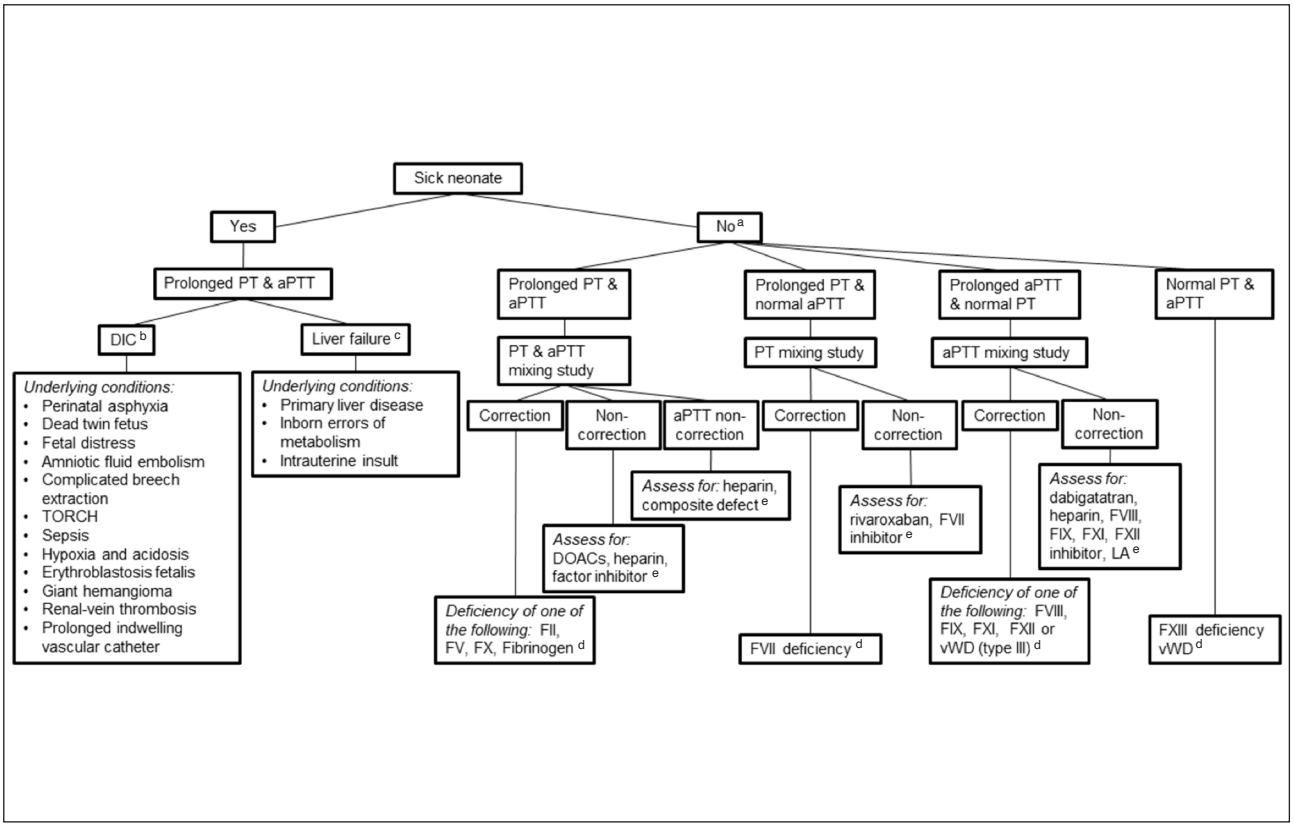

Figure 1. Algorithm for the diagnostic approach of the bleeding neonate (vitamin K given).
aPTT: activated partial thromboplastin time; CBC: complete blood count; DIC: disseminated intravascular coagulation; DOACs: direct oral anticoagulants; FII: factor II; FV: factor V; FVII: factor VII; FVIII: factor VIII; FIX: factor IX; FX: factor X; FXI: factor XI; FXII: factor XII; FXIII: factor XIII; LA: lupus anticoagulant; PLT: platelet count; PT: prothrombin time; RDS: respiratory distress syndrome; TORCH: Toxoplasma, Other, Rubella, Cytomegalovirus, Herpes, Hepatitis; vWD: von Willebrand disease.
[a] Normal PLT; [b] plus, laboratory test for DIC diagnosis (see **Tab. 3**), Go et al., 2020 [25]; [c] Henter et al., 2007 [30]; [d] Palla et al., 2015 [53]; [e] Favaloro, 2020 [18].

Bleeding disorders of the sick neonate

Disseminated intravascular coagulation

DIC is globally defined as a disorder pertaining to thrombotic and hemorrhagic irregularity, which affects the coagulation system's integrity. Regarding the microvasculopathy/microangiopathy damage, DIC is an over-activation condition of pro-coagulant proteins and fibrinolysis while being consumptive for coagulopathy inhibitors presenting clinical and biochemical evidence of end-organ failure [20]. Although data clearly reporting DIC incidence among term and preterm infants are lacking, its prevalence is worrisome among NICU hospitalized patients. Despite developmental hemostatic system evolution in newborns, the majority of authors refer that "healthy" neonates demonstrate a balanced hemostatic system, delimited, neither providing thrombosis nor hemorrhage. Therefore, DIC manifests itself as a secondary event associated with many perinatal and neonatal complications. Sepsis or infection and hypoxic-ischemic encephalopathy are dominant risk factors for DIC in the neonatal population, others being shock, acidosis, hypothermia and scarcely met causes including vascular malformations and metabolic diseases. Prompt DIC diagnosis is challenging. Clinical presentation and laboratory findings are constantly changing according to the severity of the underlying disease, liver function, bone marrow status and the function of the reticuloendothelial system [21, 22]. As a result, the laboratory findings of DIC are widely variable and time-dependent. Furthermore, the interpretation of neonatal coagulation assays needs the age-related reference ranges established for each laboratory institution. In addition, there is no reliable normal range for D-dimers, and the limited data from existing studies suggest that their concentration and reference values may be higher during the neonatal period [4, 23, 24]. Nevertheless, the DIC diagnostic criteria of the Japanese Society of Obstetrical, Gynecological & Neonatal Hematology (JSOGNH) (**Tab. 3**) can aid the Neonatologists significantly [25].

Table 3. Disseminated intravascular coagulation (DIC) diagnostic criteria of the Japan Society of Obstetrical, Gynecological & Neonatal Hematology (JSOGNH) (modified from: Go et al., 2020 [25]).

		BW ≥ 1,500 g	BW < 1,500 g
PLT	≥ 70 × 10^3/μL and 50% reduction within 24 hours	1 point	1 point
	≥ 50 × 10^3/μL and < 70 × 10^3/μL	1 point	1 point
	< 50 × 10^3/μL	2 points	2 points
Fibrinogen	≥ 50 mg/dL and < 100 mg/dL	1 point	-
	< 50 mg/dL	2 points	1 point
PT and INR	≥ 1.6 and < 1.8	1 point	-
	≥ 1.8	2 points	1 point
FDP or D-dimer	< 2.5-fold upper limit of normal range	-1 point	-1 point
	≥ 2.5-fold upper limit of normal range and < 10-fold upper limit of normal range	1 point	1 point
	≥ 10-fold upper limit of normal range	2 points	2 points

BW: birth weight; FDP: fibrin degradation products; PLT: platelet count; PT: prothrombin time; INR: international normalized ratio.

Notes:
- For a PLT of ≥ 70 × 10^3/μL, a point is added if the PLT is reduced by 50% within 24 hours. A point is not added if the patient had thrombocytopenia due to myelosuppression disease.
- For fibrinogen, a point is added if the underlying disease of the patient was an infection.
- Since the upper limit of D-dimer is different among D-dimer kits, a point is added if FDP and D-dimer increased by 2.5- or 10-fold of the upper limit of normal.

Interpretation:
- ≥ 4 points:
  - symptoms: overt DIC,
  - no symptoms: non-overt DIC;
- 3 points: suspected DIC;
- ≤ 2 points: low possibility for DIC.

Liver failure

Pro- and anticoagulant proteins, as well as thrombopoietin, are synthesized in the liver, with the exception of FVIII and vWF. Disruption of liver function results in dysregulation of the coagulation system, which in turn leads to bleeding or thrombotic diathesis [3, 4]. Probable causes of liver failure are primary liver disease, inborn errors of metabolism, bacterial or viral sepsis, hematologic disorders, hypoxic-ischemic injury (e.g., due to perinatal asphyxia) and fetal-maternal hemorrhage that can lead to intrauterine insult and multiorgan failure [26, 27]. Laboratory findings in liver failure are increased PT, aPTT and D-dimers and decreased fibrinogen activity and PLT [4]. Liver disease cannot easily be distinguished from DIC, as overlapping conditions may occur. Liver failure counter to DIC presents itself with PLT that is usually stable in low levels, D-dimers that are mildly increased and stable FXIII levels. Particularly, the alpha subunit of FXIII is produced in megakaryocytes and white blood cells, but not in the liver, where the production of the beta subunit of FXIII occurs [28]. Another severe disorder that can lead to liver failure is hemophagocytic lymphohistiocytosis. It is a condition characterized by an overabundance of tissue macrophages or histiocytes and is provoked by excessive immune system activation [29]. It is believed to be triggered by infections or other immune activators and may be congenital or idiopathic. It manifests clinically with fever and hepatosplenomegaly, while laboratory findings are increased serum ferritin, abnormal liver function tests, increased triglyceride levels, decreased fibrinogen and cytopenia [30].

Bleeding disorders of the healthy neonate

Vitamin K deficiency bleeding

Vitamin K deficiency bleeding (VKDB) appears as a consequence of inadequate levels of vitamin K during the first 6 months of life [31]. Concentrations of vitamin K-dependent FII, FVII, FIX and FX are reduced in the neonatal period due to vitamin K absence. VKDB has traditionally been classified in its early, classic, and late forms depending on the time of manifestation. The early form of VKDB is typically associated with maternal medication that blocks vitamin K metabolism, while the classic and late forms are related to breastfeeding and vitamin K malabsorption. Particularly, in the VKDB late form, there is a relatively high incidence of intraventricular hemorrhage (IVH), which is associated with morbidity and mortality. VKDB should be suspected when the results of conventional coagulation tests show prolongation of PT, followed by a prolongation of aPTT in combination with normal fibrinogen concentration and normal PLT. Proteins induced by vitamin K absence II (PIVKA-II), which are the inactive under-γ-carboxylated forms of vitamin K-dependent clotting factors, are greater diagnostic markers for VKDB. Confirmation of the diagnosis requires measurement of vitamin K-dependent factors [32, 33]. Regarding prophylaxis against VKDB, oral or intramuscular administration of

vitamin K prevents the classic form but not from the late one. This is why prolonged oral administration, especially in breastfed infants, is recommended [34]. In the last years, parents have started to refuse the administration of intramuscular vitamin K. The relief of harm from the injection, a desire to be natural, and the reliance on alternative methods of prophylaxis are the reported reasons for the observed refusal. The possible neurologic sequelae of VKDB, along with the observed aforementioned refusal, render it necessary for a renewed focus on the education of the parents [35].

Hemophilia

Hemophilia A and B (HA and HB) are the most common congenital bleeding disorders that occur in the neonatal period. These disorders are due to FVIII and FIX deficiencies, respectively, and of varying severity. Both show an X-linked recessive inheritance pattern, and clinical manifestations in early life are limited to males. A great number of hemophilia cases (1/3) occur in the absence of positive family history, and therefore, in these cases, there is no clinical suspicion at birth, while 15-33% of these cases may present with bleeding during the first month of life [10, 36]. While in older children with HA mucocutaneous and joint bleeding, and in those with HB muscle bleeding and deep tissue hematoma, as well as bleeding within the internal organs, are observed, in the neonatal population the sites of bleeding differ [37]. Prolonged bleeding or hematoma formation after a venous puncture or intramuscular administration of vitamin K are relatively common events in the affected newborn. Both large IVH and extracranial hemorrhage such as cephalhematoma are also observed in neonates with severe or even mild forms of the disease, especially in cases of dystocia [10]. In both HA and HB, conventional hemostasis tests usually reveal only prolonged aPTT. The diagnosis is confirmed by estimating FVIII and FIX levels. FVIII concentrations are within the normal range of adult values or slightly increased at birth. On the other hand, FIX concentrations are reduced at birth, which precludes the diagnosis of mild forms of HB by the age of 3-6 months due to overlap with the normal range of values at this age [38, 39].

von Willebrand disease

von Willebrand disease (vWD) is a relatively common inherited bleeding disorder, with 1.3% frequency in mixed population, due to quantitative or qualitative abnormalities of the vWF [40]. The disease can be subdivided into three types (**Tab. 4**); type I vWD is the most frequent and usually leads to a mild clinical phenotype [41, 42]. Due to the increased concentrations of vWF at birth, type I vWD usually does not manifest in the neonatal period, so that, even when there is a positive family history, a definite diagnosis during the neonatal period is quite difficult. Some subtypes of type II vWD are associated with thrombocytopenia, which may be evident during the neonatal period and can result in bleeding. Type III vWD is a rare autosomal recessive condition that is commonly found in populations where interracial marriages take place. Usually, both parents are asymptomatic and, because vWF concentrations are almost non-existent, the result is serious bleeding diathesis that occurs during the neonatal period. Clinical manifestations are variable, and mucosal bleeding is more frequently seen in type III vWD compared

Table 4. Classification of von Willebrand disease (vWD) and laboratory findings (from: Sadler et. al., 2006 [42], and Yawn et. al., 2009 [44]).

Classification	Pathophysiology	vWF RCo (IU/dL)	vWF Ag (IU/dL)	FVIII
Type I	Partial quantitative deficiency of vWF	< 30	< 30	↓ or normal
Type II	Qualitative vWF defects	-	-	-
Type II A	Decreased vWF-dependent platelet adhesion and a selective deficiency of high-molecular-weight vWF multimers	< 30	< 30 to 200	↓ or normal
Type II B	Increased affinity for platelet glycoprotein Ib	< 30	< 30 to 200	↓ or normal
Type II M	Decreased vWF-dependent platelet adhesion without a selective deficiency of high-molecular-weight vWF multimers	< 30	< 30 to 200	↓ or normal
Type II N	Markedly decreased binding affinity for FVIII	30 to 200	30 to 200	↓ ↓
Type III	Virtually complete deficiency of vWF	< 3	< 3	↓ ↓ ↓ (< 10 IU/dL)
Normal	-	50 to 200	50 to 200	Normal

Ag: antigen; FVIII: factor VIII; RCo: ristocetin cofactor activity; vWF: von Willebrand factor.

to hemophilia. Coagulation testing usually reveals prolongation of aPTT only, as in hemophilia, and the diagnosis is confirmed by measuring antigen levels and the activity of FVIII and vWF (**Tab. 4**) [43, 44]. The vWF activity (ristocetin cofactor activity) has been shown to be more sensitive (71-80%) than antigen levels of FVIII or vWF for the diagnosis of vWD [45-47]. It should be noted that retesting is needed for the diagnosis, because only 42% of the carriers of vWD may have abnormal vWF activity on their initial testing [48, 49]. This can be explained by the fact that in some cases of type I vWD there is a gene defect concerning the release of vWF from the endothelium and not a gene defect in the vWF gene [50].

Rare bleeding disorders

Rare coagulation disorders are defined as a group of autosomal recessive deficits of FII, FV, FVII, FX, FXI, FXII and FXIII, which in either homozygous or combined heterozygous heredity, may predispose to bleeding. These rare bleeding disorders represent 3-5% of all congenital coagulation factor deficiencies [51].

Due to the inheritance pattern, these abnormalities are usually found in populations or countries where marriage between relatives is common [32, 52]. Severe fibrinogen, FVII, FX and FXIII deficiencies are the most probable coagulation disorders that can occur during the neonatal period. Bleeding in the soft tissues and mucosal membranes, as well as the umbilical cord, is frequent. Umbilical cord bleeding after stump falling is noted in 80% of the cases with severe FXIII deficiency. It is also clear that IVH is a main feature of these disorders. FVII deficiency is expressed in some people with mild hemorrhagic diathesis, while in others with severe type, it can present from the first days of life. The severe form manifests with IVH. FXI and FXII deficiencies are mainly detected accidentally, as a result of routine preoperative testing. Neonates with severe FXI deficiency have excess hemorrhage only after injury or surgery. In contrast, FXII deficiency does not involve substantial bleeding, even after surgery. It is necessary to determine the specific factor deficiency so as to confirm the diagnosis [52, 53].

Finally, we must not neglect a possible Fletcher factor (prekallicrein) or Fitzgerald factor (high molecular weight kininogen – HMWK) deficiency when dealing with prolongation of aPTT, despite the fact that these deficits do not cause clinical bleeding [54, 55].

Viscoelastic tests

Despite conventional coagulation tests' omnipresence, aPTT, PT, fibrinogen levels and PLT fail to qualitatively illustrate intrinsic and extrinsic coagulation pathways, respectively [56]. As these tests are performed in plasma, in the absence of red blood cells and platelets, they are lacking in precision for depicting cellular and enzymatic coagulation components' mutual reliance [57]. Hence, there is neither an accurate interpretation of the hemostatic mechanisms *in vivo* nor clinical accuracy in providing hemostatic profile and patient's bleeding diathesis [58]. Although aPTT, PT and PLT do not completely represent the pathophysiology of the clot formation *in vivo*, they are of paramount importance in the laboratory workup of blood coagulation.

The cell-based model, which is based on the idea that hemostasis involves both cellular components and coagulation proteins, mirrors more qualitative hemostasis *in vivo* [56]. The viscoelastic teststhromboelastography/rotation-thromboelastometry (TEG/ROTEM®), by measuring multiple parameters of clot formation and dissolution, better reflects the blood cells and coagulation proteins interdependence and thus more effectively interprets the hemostasis *in vivo* [58]. The obtained measurements lie on the dynamics of clot development, stabilization, and dissolution, and the gained information concerns coagulation elements' functionality [59].

Although the viscoelastic tests have not been used in the diagnosis and management of bleeding disorders in the neonatal population, they seem to be promising. The published thresholds of ROTEM® parameters for the diagnosis of coagulopathy are mainly derived from adult studies. Even more, there is no strong evidence in the current literature supporting diagnostic reference values [60]. Regarding neonates, available data are limited and are mainly extrapolated from even more restricted studies, including neonates undergoing cardiac surgery or suffering from neonatal complications such as sepsis, IVH, and hypoxic-ischemic encephalopathy undergoing therapeutic hypothermia [58, 61].

Conclusions

Even though the hemorrhagic events are relatively rare in the neonatal period, accurate and prompt diagnosis is crucial. Guided, individualized management results in unnecessary blood products

reduction, whose adverse effects are considerable. So far, dealing with a bleeding disorder, neonatologists should first distinguish whether the neonate is sick or not. Ruling out DIC or thrombocytopenia should be the next step. Treating physicians should be aware of the existence and prevalence of rare bleeding disorders. The laboratory values interpretation should be placed in parallel with the age-related reference ranges evaluation for neonates. Optimal management/treatment requires multidisciplinary approach from Obstetricians/Gynecologists, Pediatricians/Neonatologists and Hematologists.

Declaration of interest

The Authors declare that no conflict of interest exists. Funding: there was no funding.

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