Evolution of Hemostasis in Neonates and Children

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Abstract

Children cannot be considered as miniature adults regarding to hemostatic balance. There is a great difference between neonatal, pediatric, and adult hemostatic systems. The concept of developmental hemostasis is now accepted on a wide range. It ensures accurate prevention, diagnosis, and treatment of thrombotic and hemorrhagic diseases in neonates and children. Developmental hemostasis could affect multiple physiological processes within the body other than hemostasis, such as angiogenesis, inflammation, and wound repair, as well as the interaction between different drugs and the coagulation system. “The Perinatal and Pediatric Hemostasis Subcommittee of the Scientific and Standardization Committee of the International Society on Thrombosis and Hemostasis (ISTH)” recommended for each laboratory to define reference ranges which are age-adjusted using its own technical conditions. Adding to that, accurate sampling techniques are mandatory for correct interpretation of laboratory results. New assays should be developed putting into consideration the fundamentals of developmental hemostasis.

Key words: developmental hemostasis; coagulation; thrombosis; neonates
The hemostatic system

Virchow’s triad of vessel wall, blood component and blood flow describes best the critical components of hemostasis. [1] On excluding the flow component, hemostasis can be considered as the interaction between the vessel wall, cellular component of blood and plasma proteins that maintain hemostatic balance. On a wider scale, hemostatic system is found to be important for normal angiogenesis, inflammatory responses, and wound repair through interacting with physiological systems facilitating these processes. [2] These interactions are still under investigation till now

Hemostasis can be subdivided into primary, secondary, and tertiary hemostasis. These three independent mechanisms combine to maintain hemostatic balance. Primary hemostasis is a process aiming at primary platelet plug formation that seals the site of injury, through the cellular interaction of platelets with sub-endothelium of the injured blood vessel. Secondary hemostasis depends on activation of the coagulation proteins sequentially, which is regulated by many feedback mechanisms. Tertiary hemostasis describes the fibrinolysis that breaks down blood clots to regain vascular integrity after healing. [2] So, many parameters take part in the equation of hemostasis, such as platelets, clotting factors and inhibitors.

Hemostasis is a complex mechanism depending on a very delicate balance of hemostasis of both pro-coagulant and anticoagulant factors. These factors are essential in maintaining blood fluidity in intact blood vessels and promoting effective blood clotting upon vascular injury. They are also essential for limiting the clot to the site of injury and avoiding its propagation to other non-injured parts of the blood vessel. [3]

The hemostatic balance differs in neonates and children than adults, as, hemostasis is in continues evolution and maturation starting since early intra-
uterine fetal life till adulthood, this evolution is marked especially during the first few months of prenatal life. At birth, plasma coagulation proteins were found to be about half their levels in adults. They are even lower in preterm than in full-term newborns, and increase postnatally to reach adult values after few months in some and up to 16 years in others. [4]

**Developmental hemostasis**

Children cannot be considered as miniature adults regarding to hemostatic balance. There is a great difference between pediatric and adult hemostatic systems. [3] In the 1980s, Maureen Andrews introduced the term ‘developmental hemostasis’ to describe the changes occurring in the coagulation system as it develops progressively over time from early intra-uterine fetal, then postnatal and pediatric life till adulthood and then into geriatric systems. [5,6] Clinical interpretation and coagulation studies in neonates and children has changed by turning point papers published in Blood journal in 1987, 1988 and 1992. [5, 6]

The maternal coagulation factors do not cross the placenta [7, 8], and the fetus starts synthesis of coagulation proteins by the fifth week of intra-uterine life [9], its blood can clot by 11 weeks of gestation. [10] The coagulation factors reference ranges were found to be ten to thirty percent of adult values, depending on the factor, at gestational age between 19 - 23 weeks and progressively increase to levels between 10% - 50% at gestational age between 30 - 38 weeks. [11, 12]

The importance of developmental hemostasis is that understanding it prevents wrong diagnosis, and treatment of hemostatic problems in neonates and children and explains the pathophysiological basis of hemorrhagic and thrombotic complications of all ages. [1]
Difficulties to interpret the hemostatic system in neonates and children

There are limited data about the physiology of hemostasis in neonates and children when compared to data available about the adult hemostatic system. There are many factors augmenting this limitation in neonates and children such as multiple reference ranges are required that go with the age-related evolution of the hemostatic system which requires many patients to establish a normative data [2,7,13,14]; in addition to difficult blood sampling in the young age-groups. [15]

- **Sample acquisition problems**

  The sampling is a problematic process in neonates and young infants than in adult, which is a key point to consider. Blood samples obtained are often contaminated by heparin from central vascular access devices, or pre-heparinized syringes, this gives inaccurate results. Moreover, neonatal polycythemia, which is common, result in disturbance of the citrate-to-blood ratio (9:1), and collection into an adjusted tube is required. Under-filled tubes may not affect the results of a chemistry panel or a full blood examination, unlike the coagulation results. [1]

- **Defining reference ranges**

  The lack of use of appropriate reference ranges remains the most common obstacle in the interpretation of pediatric coagulation assays. [1]

  One problem in defining age-appropriate-reference ranges is that the coagulation proteins functional levels change with age. [13] These changes are reflected on the results of some coagulation tests, such as the activated partial thromboplastin time. Other tests are less affected by age-related changes in hemostatic factors, such as thromboelastography. [16] Using the international normalized ratio (INR) minimizes the variations in prothrombin time (PT) results. [17] Thrombin time in neonates is prolonged due to the absence of calcium during performing it, because
fibrinogen is present in the “fetal form” at birth, which depends on calcium to polymerize. [5, 7, 13]

Another problem is that age-related reference ranges, which are specific for analyzer-reagent combinations of many clinical laboratories, have not been determined. Adding to that in aPTT interpretation - due to missed published age-related references ranges of aPTT reagents – may lead to unnecessary referral to hematologists, multiple investigations, and misdiagnoses, and cancellations of surgeries or overtreatment of the child during the procedure. [1]

Accordingly, ISTH, ‘the Subcommittee of the Scientific and Standardization Committee of the International Society on Thrombosis and Hemostasis’, recommended to define age-dependent reference ranges for each laboratory according to technical conditions. [18]

- **New diagnostic tests**

New assays should be introduced into clinical use in children based on understanding the fundamentals of developmental hemostasis and on pediatric clinical studies, confirming their predictive values. The Endogenous Thrombin Potential (ETP) is one of the new assays that measures, in vitro, the overall ability of the hemostatic system to generate thrombin. [19]

**Age-related changes in the hemostatic system**

There is a transient increase in platelet count at birth, reaching adult values within 1 year. [20] Even though platelet functions are depressed in the neonatal period, [20-25], the bleeding time and the platelet closure time (PFA-100) were found to be shortened in newborns till the end of the first month of life. (21, 22, 25) Von Willebrand factor was reported to be elevated in newborns and to decrease reaching adult levels after 1 year of age. [26]

**Changes in coagulation proteins**

Coagulation proteins, as was mentioned before, are synthesized during fetal life and are not able to cross the placental
barrier. (2) By ten weeks of intra-uterine life, coagulation proteins have measurable plasma concentrations, that continue to increase gradually with progression of gestation. [27]

Prothrombin, FVII, FIX, and FX are reported in many studies to be physiologically low at birth and increasing gradually afterwards to reach adult levels. The last to reach adult level is FVII, which may not reach adult level till 16 years. [5, 7, 13, 28, 29]

The levels of FXI, FXII and the contact factors (pre-kallikrein, and high molecular weight kininogen) gradually increase to near-adult levels by 6 months of age. [5, 7, 13] The low contact factor levels are the cause of prolonged aPTT during the first months of life. [30]

The high basal metabolic rate in infants and children may accentuate the low level of the plasma proteins through accelerating the rate of their clearance. [31]

Levels of fibrinogen, FV, FVIII, FXIII, and von Willebrand factor (vWF) are not decreased at birth. On the contrary, plasma levels of FVIII may be raised beyond adult levels, necessitating an adjustment of the lower limit of normal. Also, level of vWF is increased at birth and for the first 3 months of life. [5]

Regarding fibrinogen levels, not only fibrinogen is found to be low at birth, but it has also been reported to exist in a ‘fetal form’, in cord blood of term infants. (32) This ‘fetal form’ of fibrinogen has high sialic acid and phosphorus content than adult fibrinogen. [33, 34] Sialic acid in fibrinogen directly binds to Ca$^{+2}$ leading to decreased repulsion between fibrinogen chains facilitating fibrin polymerization. [35]

Prolonged thrombin time in newborns may be attributed to different polymerization of fetal fibrinogen from adult fibrinogen [36], which had led to claims that infants have ‘dysfunctional fibrinogen’. [37]

**Changes in natural anti-coagulants**

- **Antithrombin**
Thrombin is inhibited by many anticoagulants present in cord blood, such as antithrombin, α2-macroglobulin, dermatan sulphate like anticoagulants and heparin cofactor II. [38] α2-macroglobulin is found to be a more potent inhibitor of thrombin in neonates than it is in adults [39,40], which compensates for the low levels of antithrombin in neonates. Despite the potency of neonatal α2-macroglobulin, thrombin inhibition is still slower in neonates than it is in adults. [2]

- **Protein C, protein S and Thrombomodulin**

At birth, plasma concentrations of both protein C and protein S are very low. Protein C levels remain low during the first 6 months of life. [7, 13] The low level of protein S is compensated by an increase in its functional activity. All protein S is present in an active form due to the absence of C4 binding protein in newborns. [41, 42] Moreover, the increased levels of α2-macroglobulin facilitate the interaction of protein S with activated protein C in newborn plasma. [43] While, thrombomodulin plasma levels are increased in early childhood, decreasing to adult values by reaching adolescence. [44-47]

- **Tissue Factor inhibitor Pathway (TFIP)**

Free TFPI is found to be low in neonate than adults, yet, the total TFPI levels are reported as being comparable to levels in adults. [48]

**Clinical importance of developmental hemostasis**

Even though the concentration of individual procoagulant and anticoagulant proteins, and coagulation tests are different in neonates and children than adults, hemostasis in neonates and children does not seem to be ‘disadvantaged’ compared to the ‘normal’ hemostasis in adults. Prolongation of coagulation tests, such as the aPTT, are not associated with bleeding tendency, despite that considerably prolonged aPTT in adults with von Willebrand disease (vWD) is
associated with clinical manifestations. [32]

On the contrary, the neonatal hemostatic system was found to be more protective against stimuli that might cause adult hemostatic disorders, such as bleeding or thrombosis. Furthermore, the neonatal hemostatic system was considered ‘the ideal system’ that is affected by aging leading to deterioration in its function despite the increase in level of most of its components. [1]

But the age-related changes occurring in developmental hemostasis represent a challenge, as they could affect the interaction between drugs, such as anticoagulants and the coagulation system, which could explain the discrepancy between anticoagulation in adults and in children. Another challenge is the low levels of proteins involved in the coagulation that add to the difficulty of diagnosis and treatment of thrombotic or hemorrhagic diseases in neonates and children. [4] Also, from studying developmental hemostasis, the currently available coagulation factor assays cannot determine the clinical phenotype of their relevant factor deficiency, and further research is remained to be performed for better understanding the relationships between plasma levels of pro-coagulant and anticoagulant proteins and the functional outcome of their deficiency. [1]

For example, anti-thrombin levels during the first three months of life are normally lower than their levels in adults with recurrent thrombosis due to heterozygous anti-thrombin deficiency; however no clinical evidence of thrombotic manifestations was reported in neonates and infants. [32] Similarly, factor IX levels are below thirty percent of adult levels in neonates and infants and yet there are no clinical manifestations of bleeding tendency. [1]

An alternative view is that the differences in the hemostatic system of neonates and children are related to other non-hemostatic functions the hemostatic system is involved in. The hemostatic
proteins were found to be involved in multiple physiological processes within the body, such as inflammation, wound repair, and angiogenesis. One theory suggested that these physiological systems that drive the developmental changes in the hemostatic system. [1]

Recently, anti-thrombin has been shown to have powerful anti-angiogenic functions, in addition to its potent anticoagulant activity. [49] Anti-thrombin levels in neonates are less than 50% of their adult levels, and gradually increase during the first 6 months of life. [32] This might enable prolific angiogenesis that is increased during fetal and early neonatal life than any later stage of life. So, anti-thrombin replacement therapy during neonatal life, like present in fresh frozen plasma transfusions, may have deleterious effects on normal angiogenesis. [2]

Hence, understanding developmental hemostasis may enable us to avoid non-hematological complications in neonates and children.

**Conclusions**

Understanding developmental hemostasis is crucial for reaching diagnosis of bleeding and thrombotic disorders in neonates and children, as well as avoiding hematological and non-hematological complications. Proper sampling techniques and age-appropriate, analyzer and reagent specific reference ranges are crucial to avoid misdiagnoses and over-treatment. Finally, new assays should be developed putting into consideration the fundamentals of developmental hemostasis.

**Clinical Practice points**

1. Proper Sampling is a necessity in pediatric coagulation studies, attention to details and repeated sampling are important to avoid wrong results.

2. Age-appropriate reference ranges are crucial for accurate diagnosis and management of coagulation disorders in neonates and children, as the levels of the hemostatic proteins change
rapidly over the first few months of life.

3. Each laboratory should determine its own specific reference ranges depending on their technical conditions.

4. Adult plasma products or drugs may have unintended effects on the neonate due to the multiple non-hemostatic functions of hemostatic proteins

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References


8. Cade JF, Hirsh J, Martin M. Placental barrier to coagulation factors: its relevance to the coagulation defect at birth and to


31. Ahlsten G, Ewald U, Tuvemo T. Arachidonic acid-induced aggregation of


