Developmental Hemostasis

Clinical Implications From the Fetus to the Adolescent

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KEYWORDS

• Developmental hemostasis • Neonatal • Children • Coagulation

KEY POINTS

- Developmental hemostasis is the evolution of the coagulation system from a fetus to an adolescent.
- The levels of procoagulant and anticoagulant protein levels differ substantially between infants and adults, and these differences affect both the ability to accurately diagnose and treat infants and children with hemostatic and thrombotic diseases.

INTRODUCTION

Hemostasis refers to the process by which ruptures in the wall of blood vessels are occluded by a fibrin clot and involves the interaction of the blood vessel wall, platelets, and coagulation proteins. In addition to preventing excessive bleeding, the fibrin clot provides the structure for wound repair. Developmental hemostasis describes the evolution of the coagulation system from fetal life to adolescence. The coagulation system, which includes both procoagulant and anticoagulant proteins, forms early in utero, although the levels of many of these proteins are different than those seen in normal adults. Many of these proteins exhibit levels that are far less than those seen in adults, although a few are, in fact, more than adult levels. Although much of the evolution to normal adult levels takes place within the first 6 months, some proteins do not reach normal adult levels until adolescence. The evolving changes in the functional level of the coagulation proteins lead to several challenges for the clinician. First,

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Pediatr Clin N Am 60 (2013) 1407–1417
http://dx.doi.org/10.1016/j.pcl.2013.08.003 **pediatric.theclinics.com**
0031-3955/13/$ – see front matter

the changes make it more difficult to correctly diagnose a child with a disorder of coagulation. Second, the particularly rapid changes that occur during the neonatal period can affect the choice and monitoring of anticoagulant agents. Third, the changes create significant challenges for the clinical coagulation laboratory as it relates to establishing normal ranges for various laboratory assays. This article reviews the current data on the development of the coagulation system as it matures from early fetal life into the teenage years and explains how these changes impact the diagnosis and treatment of pediatric coagulation disorders.

HEMOSTASIS PHYSIOLOGY

A basic overview of the coagulation cascade is crucial to understanding developmental hemostasis. Damaged endothelium exposes tissue factor (TF) present in the subendothelium, which then activates the coagulation cascade,[1] consisting of multiple procoagulant proteins that interact together to lead to the formation of a fibrin clot. The procoagulant proteins, mostly known as factors, include fibrinogen and factors (F) II, V, VII, VIII, IX, X, XI, and XIII. Of note, there are several factors (FXIII, prekallikrein, and high-molecular-weight kininogen) in the so-called contact activation system that are not currently considered to be involved in hemostasis, although abnormal levels will result in an abnormal activated partial thromboplastin time (aPTT). In order to prevent excessive clotting, there exist several natural inhibitors to the procoagulant factors (also known as *natural anticoagulants*), including antithrombin (AT), α_2-macroglobulin (α_2-M), heparin cofactor II (HCII), protein C, protein S, and TF pathway inhibitor (TFPI).

The activation of the coagulation cascade results in the formation of large quantities of thrombin (FIIa) at the site of bleeding. Thrombin plays a pivotal role in the formation of the fibrin clot. It activates FV and FVIII, which are the main catalysts of the coagulation cascade resulting in the generation of even more thrombin. This large amount of thrombin leads to the conversion of the soluble protein fibrinogen into its insoluble form, fibrin, which forms the structure of the clot (**Fig. 1**). Thrombin also activates 2 proteins, FXIII and thrombin-activatable fibrinolysis inhibitor, both of which are critical to the formation of a stable clot that is resistant to fibrinolysis. Lastly, thrombin also activates platelets at the site of bleeding.

Thrombin plays the key role in its own downregulation by forming a complex with thrombomodulin that serves to activate protein C,[2,3] which, along with its cofactor, protein S, inactivates the catalysts FV and FVIII. The prohemostatic effect of thrombin remains local to the site of endothelial damage because any thrombin that remains in the circulation is quenched by AT.

HEMOSTASIS IN THE INFANT AND CHILD

At birth, an infant's coagulation system differs significantly from that of an adult. The levels of many of their procoagulant and natural anticoagulants are low; as a result, the screening coagulation tests, the aPTT and the prothrombin time (PT), are prolonged compared with adults. Some of the components of the hemostatic system even have fetal forms whose actions vary from the adult forms, such as protein C and fibrinogen.[4,5] These fetal forms have been shown to generate and regulate thrombin differently or to be synthesized at a different rate.

All coagulation factors are present at birth; but most coagulation factors do not reach typical adult levels until 6 months of age and some not until adolescence.[6–9] **Fig. 2** shows the evolution of the components of the coagulation system throughout fetal life. Because coagulation factors cannot cross the placenta,[10] the fetus starts