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Review

Thromboembolism and anticoagulation management in the preterm infant

Revathi Rajagopal [a], Fook-Choe Cheah [b], Paul Monagle [c, *]

[a] Pediatric Hemato-Oncology, Department of Pediatrics, University of Malaya, Kuala Lumpur, Malaysia
[b] Faculty of Medicine, Universiti Kebangsaan Malaysia Medical Centre, Kuala Lumpur, Malaysia
[c] Department of Clinical Hematology, Department of Pediatrics, Royal Children's Hospital, University of Melbourne, Parkville, Victoria, Australia

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SUMMARY

The incidence of preterm thromboembolism has been increasing due to advances in diagnostic imaging which allow better detection of thrombi in sick preterm infants. At the same time, improvement in neonatal intensive care unit supportive care has increased the number of surviving and living preterm infants with thromboembolic risk factors. Disruption in the fine balance of hemostasis with potential risk factors, specifically septicemia and indwelling catheters, increase the occurrence of thromboembolic events. Treatment strategies in preterm infants are challenging due to limited data.

1. Introduction

Preterm infants (PIs) are at greater risk than older children for thrombosis and thromboembolic complications [1]. Their hemostatic system is very dynamic and different from children and adults [2,3]. Whereas some have reported that the evolution of hemostatic cascade in utero places PIs in a relative pro-thrombotic state, they in fact appear to be in relative hemostatic balance as they rarely suffer spontaneous thrombosis (Fig. 1) [2,4,5]. When the balance is disrupted, in particular with vascular access devices and septicemia, the risk of developing thromboembolism increases significantly [4]. Dehydration, polycythemia, fluctuations in blood pressure and maternal risks such as pre-eclampsia, diabetes mellitus (DM), autoimmune disorders, chorioamnionitis are other potential contributors to the development of thrombosis in PIs [1,3]. Postnatally, the coagulation proteins in PIs continue to change substantially over the subsequent six months of age [1,2,6,7].

The Canadian and German registries have reported incidences of thromboembolism in 2.4 per 1000 and 5.1 per 100,000 live births respectively [1–3,8,9]. A review of 4734 neonates in The Netherlands (January 2004 to July 2010) recorded an incidence of 6.8 per 1000 neonatal intensive care unit (NICU) admissions with 63% of the neonates at <32 weeks of gestation. This rate is higher than the previous reported incidences [10]. The distribution of events and imaging techniques in these three neonatal registries were similar. All symptomatic venous and arterial thrombotic episodes were included but central nervous system (CNS) events were excluded in the Canadian registry [1,2].

The lack of clinical data related to preterm thromboembolism forces extrapolation of treatment strategies from adult data [2]. Furthermore, heterogeneity in gestational age of PIs with different maturational stages of coagulation system poses a challenge to develop a "one-size-fits-all" treatment strategy. This review article focuses on hemostasis, types of thrombosis, risk factors, diagnosis, management, and outcome of thrombosis in PIs.

2. Evolution of fetal and neonatal hemostasis

Components of hemostasis change throughout fetal life and these components do not cross the placenta [11]. The development of the hemostasis system is incomplete at birth [2,11]. Platelets are the first component that appears in fetuses at five weeks of conception and reaches the normal adult range of 150 to 450×10^9/L by 22 weeks of gestation [12]. Platelet aggregation in PIs has been reported to be hypo-reactive and impaired due to deficiency of α-adrenergic receptors on the platelet membrane. These findings are more evident in PIs <30 weeks of gestation. However, this intrinsic platelet dysfunction seems to be balanced by elevated von Willebrand factor (vWF) levels, resulting in overall normal platelet function [12]. Limited blood volumes for platelet aggregation

* Corresponding author. Address: Department of Clinical Hematology, Department of Pediatrics, Royal Children's Hospital, University of Melbourne, 50 Flemington Road, Parkville, 3052 Victoria, Australia. Tel.: +61 393455161; fax: +61 393491819.
E-mail address: Paul.Monagle@rch.org.au (P. Monagle).

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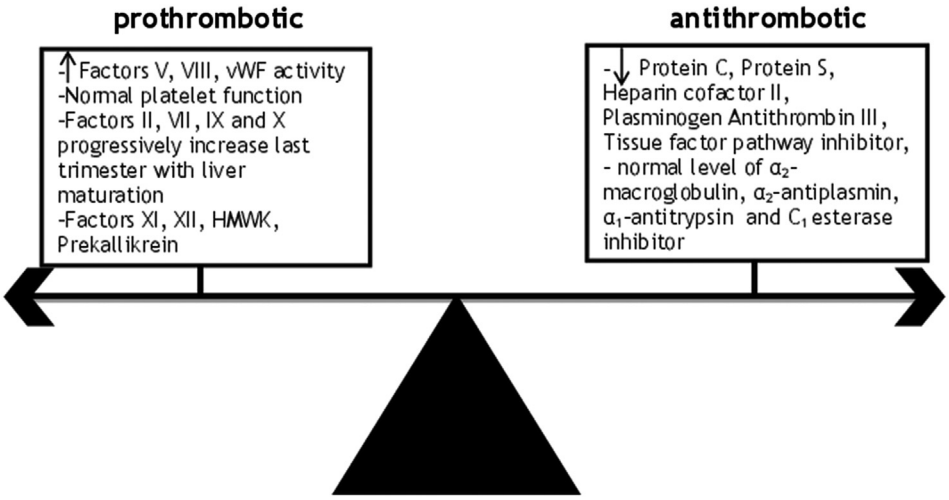

Fig. 1. Components of the hemostatic system in preterm infants compared with adults. The overall outcome appears to be balanced as spontaneous thrombosis or bleeding are rare in the absence of blood flow or vessel wall disturbances. vWF, von Willebrand factor; HMWK, high-molecular-weight kininogen.

studies are a major challenge in the analysis of platelet function in PIs [11]. Flow cytometry methods should enhance our knowledge of platelet function in PIs over the coming years. In addition, data on the role of vascular endothelium in the initiation of hemostasis in PIs are limited.

Coagulation proteins are detectable as early as 10 weeks of gestation in the fetal plasma and increase gradually with gestational age [2]. Coagulation reference values in extreme PIs are not easy to generate because of blood sampling difficulties; furthermore, sampling technique and handling of specimens may influence the reliability of the results [11,13]. Most of the reference ranges for PIs born before 28 weeks of gestation were obtained from fetuses [13]. Reverdiau-Moalic et al. reported the first data on procoagulant and anticoagulant activities during intrauterine fetal life from fetal cord blood [7]. In fetuses between 19 and 29 weeks of gestation, vitamin K-dependent factors (II, VII, IX, X), contact factors (XI, XII, prekallikrein, high-molecular-weight kininogen), factor V, factor VIII, fibrinogen, and coagulation inhibitors [antithrombin III (ATIII), heparin cofactor II (HCII), protein C (PC), protein S (PS)] were significantly low. Procoagulant factors in fetuses between 30 and 38 weeks of gestation, especially factors V, VII and VIII, progressively increased up to 45% to 50% of adult values. At the same time, inhibitors remained low at 20% of adult values until end of pregnancy [7]. In another prospective study by Salonvaara et al., coagulation levels of factors II, V, VI and X in extreme PIs between 24 and 27 weeks of gestation were reported to be significantly lower than in those born at 34–36 weeks of gestation [13]. Andrew and colleagues found that the mean values of vitamin K-dependent factors, contact factors, and inhibitors in 137 healthy PIs between 30 and 36 weeks of gestation were lower, with a range between 25% and 70% of adult values. In contrast, fibrinogen, factors V, VIII, XIII, vWF and inhibitors α_2-macroglobulin (α_2-M), α_2-antiplasmin (α_2-AP), α_1-antitrypsin (α_1-AT) and C_1 esterase inhibitor (C_1INH) were relatively spared with reference levels between 70% and 140% of adult values [2,6]. These physiological changes of coagulation factors during the last month of intrauterine life are related to hepatic maturation [7]. Comparison of fetal results from 30 to 34 weeks to neonates of same gestational age showed lower values in fetuses. Thus hemostatic changes ex utero are different from those in utero [7].

Normal pregnancy is characterized by increased in-vivo thrombin generation. Human placenta is rich in dermatan sulphate (DS) proteoglycan and it is capable of catalyzing the inhibition of thrombin by HCII. It has been speculated that DS is released into fetal and maternal circulation to reduce the incidence of thrombosis [14]. This evidence is consistent with the detection of its anticoagulant activity in cord blood term infants. The presence of DS in PIs has not been investigated so far. Hence, the role of placental DS in local regulation of thrombin in placenta among PIs warrants further study.

In summary, fetal and neonatal hemostasis studies are difficult to compare because of differences in the route of sampling (cord blood versus venepuncture), timing of blood sampling (pre-vitamin K versus post-vitamin K injection) and changes in the specimen volume for analysis.

3. Hemostastic dysregulation in septic preterm infants

Sepsis continues to be a significant cause of mortality and morbidity in PIs. Activation of procoagulant pathways, consumption of clotting factors, alterations in fibrinolysis and reduced anticoagulant activity are factors that contribute to dysfunction of the coagulation cascade in sepsis [15]. Initiation of coagulation is triggered by pro-inflammatory cytokines with amplification of thrombin generation and inhibition of the fibrinolytic system. This mechanism causes fibrin deposition in the microvasculature. Low level of ATIII, PS, PC, elevated plasminogen activator inhibitor type 1 (PAI-1) and platelet activation cause a net procoagulant situation. Alternatively, severe bleeding might be the leading symptom with coexisting thrombosis [15]. Recent studies have shown that certain genetic polymorphism hemostasis genes (factor XIII-Val34Leu polymorphism, PAI-1 mutation gene 4G/5G polymorphism) are associated with higher incidence of sepsis and longer hospital stay [16]. These are additional and indirect contributing factors for thrombogenesis in PIs [15,16].

4. Types of thrombosis

4.1. Umbilical vein catheter-related thrombosis

4.1.1. Overview and incidence

Vascular access is a major challenge in PIs [11]. Umbilical venous catheter (UVC) is necessary to provide vascular access for hemodynamic monitoring, intravenous fluids, medication and frequent blood sampling. However, it carries an additional risk for thrombosis and is the commonest cause of thrombosis in PIs. Incidence of UVC thromboembolic event varies between 21% and 71% in