# La paradoja de la trombosis neonatal

## The neonatal thrombosis paradox

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There is no better example of the nuances and short comings of our laboratory assays to predict bleeding, than neonatal coagulation. Paradoxically, very prolonged partial thromboplastin time and protime assays are the "norm" for a term neonate and maybe even further prolonged in the premature infant, and yet these, our very youngest patients, are considered more likely to experience a thrombotic event, rather than bleed[1,2]. Indeed, based on the most recent registries, the rate of thrombosis in this age group is 10 fold that of a child 12 months or greater, with coagulation studies in normal range[3]. Understanding the shifts from fetal/newborn production of both clotting factors and those factors responsible for slowing the rate of thrombus formation, along with the equally challenging developmental alterations in platelet function, is key in the proper evaluation of the high-risk neonate and in determination of optimal therapy.

It does not take long to surmise how this unique state of coagulation might have evolved for the neonatal mammal when one considers the birth event outside of a sterile and well-equipped obstetric suite. The newborn would need to survive blood loss through immediate vasoconstriction of large vessels leading to a detached placenta, perhaps protracted exposure to bacterial pathogens in lieu of antibiotics, and inevitable trauma to fragile head and limbs. In many respects, it is a finely tuned system to be admired and respected in its balance and efficacy over the millennia. In summary, hematologists quickly realized that the neonate has a highly evolved, transient

state of hypercoagulability which is protective and well controlled in the healthy newborn.

## Neonatal hemostasis

### Clotting factors

For over several decades, hematologists have recognized that it is the low levels of pro-coagulant factors that result in prolongation of the standard activated partial thromboplastin time (aPTT) and protime. Notable exceptions are factor VIII, von Willebrand factor (VWF), FXIII and fibrinogen, which are actually normal to elevated in the neonatal period[1]. This challenged conventional wisdom in light of the hypercoagulable state of the newborn, until work in the 1980's which demonstrated that the natural anti-coagulants, such as antithrombin, protein C and protein S are reduced as well[4]. In balance, the decrease in these factors appear to tip the scale toward a more hypercoagulable state *in vivo*. Helping to sustain the clots that do form, the activity of the plasmin/plasminogen system is decreased as well in order to reduce fibrinolysis[5].

Only one anti-coagulant protein, alpha-2-macroglobulin, remains at normal to super normal levels in the neonate. Monagle and colleagues hypothesize that the anti-angiogenic properties of antithrombin would negatively impact the developing fetus where vascular development is critical even through the first months of life[5,6]. In addition, antithrombin's role in downregulation of the complement system and other anti-inflammatory effects might negatively impact the newborns whose immune system is still quite immature. As alpha-2-macroglobulin has none of these effects, it appears to be the major protein serving to slow down the propagation of clot in these early months of life.

### Neonatal platelets

Platelet production and circulating platelet numbers are normal in the healthy term infant and premature infants > 22 weeks gestation[7]. Early work in the study of neonatal platelet function was performed on platelet rich plasma (PRP) samples from cord blood and term infants using light transmission aggregation[8-10]. Using this system most investigators concluded that the neonatal platelet was dysfunctional in all categories apart from ristocetin induced agglutination, where newborn platelets appeared to be better than the adult control samples. Alternative assays, such as the platelet function analyzer (PFA-100) and thromboelastography performed with whole blood rather than PRP, demonstrated a quite different profile for neonatal platelets, suggesting that they are relatively hypercoagulable in response to ADP and epinephrine as agonists in these assays[11-14].

Was it simply the presence of other blood components making the difference in platelet function or a reflection of limitations of our assays in the past and present? Likely both, it would seem, pointing to the fact that we still have much work to do in truly understanding the functional capacity of the perinatal platelet and the changes that occur with development in the first weeks and months of life. Understanding the nuances that influence platelet function in this period is particularly important in the critically ill patient where transfused platelets and plasma factors may predispose the patient to a more thrombotic state.

Many subsequent studies, point to the impact of the red cell on platelet function in whole blood assays, such as the PFA-100 and thromboelastography, as the newborn hematocrit is much higher than normal[15,16]. Sixma et al demonstrated that it is not just the hematocrit, but also red cell size that shortens the PFA-100 closure times in neonates whose mean cellular volume (MCV) is 110-130 cu/mu compared to that of the adult red cell (MCV 85-95 cu/mu)[15]. In both of these assays, platelets are particularly sensitive to elevated levels of the von Willebrand high molecular multimers present in the newborn[17-19]. Of note, there is certainly a very brisk and strong response to both ADP and epinephrine agonists in the PFA-100 system as compared to the weak or absent response in light transmitted aggregation studies, likely due to the presence of collagen in the PFA-100 cartridges and elevated shear rate. This combination optimizes the VWF-collagen platelet initiation step, and shortens closure time in the neonate compared to older children or adults. Perhaps, similar to the clotting protein paradox, the relative decrease responsiveness to isolated agonists, like ADP or epinephrine, measured *in vitro* with plasma rich platelets, reflects a mild hypo-responsiveness that offsets the very pro-thrombotic effects of elevated hematocrit and von Willebrand multimers in whole blood for the neonate.

In the past 40 years since the initial studies were

performed on neonates, we have learned much more about ADP receptor diversity, the G-protein and signaling pathways in adult platelets. There is very little literature examining these receptors or pathways in the neonatal platelet, and even less looking at platelet RNA and protein expression with inflammation. The advances being made in microfluidics and scaling down of volumes needed to study these pathways should open the way today for investigators to expand our knowledge of platelet function and regulation in the newborn.

**Vascular and endothelial function**

As the major role of the endothelial cell is to maintain circulation, thrombomodulin expression is critical in the inactivation of thrombin in areas of local platelet activation or trauma. Piecing together our knowledge of neonatal endothelial cell function *in vitro,* suggests that elevated tissue factor production, paired with decreased thrombomodulin expression and decreased fibrinolysis would once again favor a prothrombotic state[4-7]. Tissue factor production is markedly increased in areas of endothelial damage or disruption, while its inhibitor, tissue factor pathway inhibitor (TFPI) is reduced. The term neonate plasminogen levels are 60% of the normal adult range, while tissue plasminogen activator (TPA) and plasminogen activator inhibitor (PAI) are more than double that of a normal adult. At the same time, inhibitors such as $\alpha_2$-antiplasmin ($\alpha_2$AP) are reduced[1,4,20].

Endothelial production of nitric oxide is a critical regulator of vasodilation, especially in highly vascular areas like the lung and intestine. In the newborn, under steady state conditions, the balance favors vasodilation due to an increased constitutive and stimulated production of NO, decreasing vascular resistance in the newborn lung and gastrointestinal tract[21-23]. In steady state this guarantees increased rate of blood flow and oxygen delivery to the newborn gut and other highly vascular areas. In pathologic states, the damaged endothelium may increase the release of endothelin (ET-1), a vasoactive peptide promoting vasoconstriction. This combined with the neonatal prothrombotic state can precipitate tissue necrosis with associated microthrombi and platelet consumption characteristic of necrotizing enterocolitis (NEC) that is frequently seen in premature infants.

In summary, the newborn infant has a unique balance of regulatory interactions in the coagulation system, in particular when one examines the clotting factors, endothelium and platelet interactions in totality, using a cell based model of clot formation[24]. Given the high risk of hemorrhage, infection and trauma surrounding birth itself, it is not surprising that the balance favors thrombosis in most pathologic states. Further elucidation of the unique pathways and regulators of cell based coagulation in full-term and premature neonates needed to optimize treatment for these small infants in our intensive care units and cardiac surgery centers.

**Evaluation and treatment of thrombosis in the neonate**

Although the rate of thrombosis is 20-40 times higher than any other pediatric age group, it is still a relatively rare event, 2.4 per 1000 neonatal admissions, when compared to adults[3,25,26]. The majority of the neonatal pathologic thromboses are linked to catheters, which are critical for the survival and alimentation of sick neonates, but often result in occlusion due to endothelial disruption on placement and decreased flow and vasoconstriction in small veins. The incidence of thrombosis associated with line placement alone has been estimated to be between 0.9% - 12% in the neonatal and premature infant. Umbilical venous catheters (UVCs) and peripherally inserted central catheters constitute over 80% of all catheters placed. Size of the catheter placed as well as increased number of lumens elevate the risk of thrombosis as does earlier gestational age. Factors which are associated with inflammation, such as infection or surgery, CNS trauma, infused medications or hyperalimentation that damage fragile vessels, also increases the likelihood of catheter related clot formation.

Use of low-dose heparin as a continuous infusion has been used with some success to extend the catheter patency and decrease clot formation, but reports are mixed as to the efficacy of this approach in different centers[27-29]. All agree that sterility and attention to detail in line care, is the most important feature for the prevention of large propagating catheter related thrombi and end organ damage[27-30]. Many ask if prospective monitoring of the catheters would be helpful. In an interesting prospective study of monitoring catheters with ultrasound to detect

early thrombosis, out of 1333 catheters screened, 10.7% had thrombi which were non-occlusive and not propagating[31]. Only 8 catheters (1%) had a change in management due to thrombi detected in the study, whereas an average of 14 ultrasounds were performed to monitor the thrombi identified in the 10.7%. Costs were $951 per CVC with thrombus and $8106 per case of CVC-related thrombi with a change in treatment. The final conclusion for this study was that ultrasound monitoring added significant costs, but resulted in infrequent changes to patient management.

As mentioned above in previous sections, the decrease in circulating levels of natural anticoagulant factors that would limit clot propagation results in larger thrombi, and also limit the use of heparin without dose escalation or supplementation with antithrombin. Several excellent very detailed reviews have been published in recent years on the topic of treatment of catheter related thrombosis in the neonate[29,30,32]. If clots cannot be prevented and result in full occlusion, intervention is needed to prevent limb and organ damage. In the case of umbilical or large vessel catheters, thrombotic embolization to the lungs is possible, or worse to the brain, given that most neonates still have a patent foramen ovale (PFO) and increased pulmonary artery pressures due to elevated ventilator settings.

When presented with a catheter-related occlusion and extensive thrombosis, initial evaluation and treatment decisions usually are tempered by the risks of hemorrhage versus the need to maintain life-sustaining venous or arterial access in a sick infant. If the catheter is in a small or large vessel, and other sites are available, the line should be removed, although when the risk is low, some centers would consider a low dose continuous infusion of rTPA for a short period of time to facilitate local clot breakdown[30,35] prior to starting heparin. When limb or organ viability is at risk, site directed thrombolysis or even surgical thrombectomy should be considered in close collaboration with the interventional and surgical teams. Any intervention involving anticoagulation or fibrinolysis, should only be undertaken in the absence of active or recent bleeding, especially in the brain or gastrointestinal track. In addition, prior to starting treatment one should assess the current status of other major arms of the clotting system by confirming that the patient has adequate platelet numbers and clotting factors as measured by aPTT, protime and fibrinogen. Specific regimens for the assessment, and treatment of these catheter-related thrombosis, including those associated with right atrial clots with central lines or following major cardiac surgery, are listed in detail in the comprehensive reviews by Saxonhouse[30] and Monagle[35]. Overall the response to therapy is quite good even with extensive and more established catheter related clots, as long as there is close monitoring of clotting proteins, platelets, and for evidence of occult bleeding, in stool, urine or CNS.

**Inherited risk factors and thrombophilia in the neonate**

Given that levels of our natural inhibitors of coagulation are already significantly reduced at birth, inherited deficiency of antithrombin, protein C or protein S would seem to surely result in major systemic thrombosis. Indeed, purpura fulminans or spontaneous diffuse thrombosis may be the initial presentation in neonates with homozygous inheritance and profound deficiency of any one of these three major anticoagulants. Purpura fulminans in the neonate is a life threatening emergency and may be observed in patients with homozygous factor V G1691A variant[36,37]. Skin necrosis, particularly in distal or less well perfused areas, is the hallmark of protein C and S deficiency requiring emergent infusion of fresh frozen plasma and initiation of anticoagulation[36].

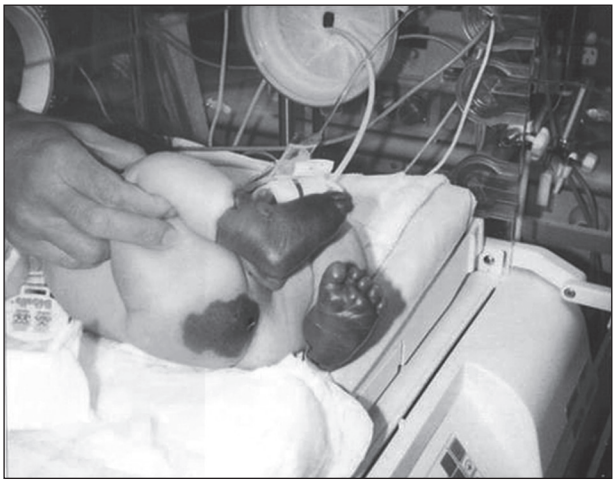


***Figura 1.*** *Typical skin lesions of neonatal purpura fulminans, courtesy Dr. Paul Monagle.*

There are now plasma derived and recombinant protein concentrates to treat patients with protein C and antithrombin deficiencies, but hospitals rarely car-

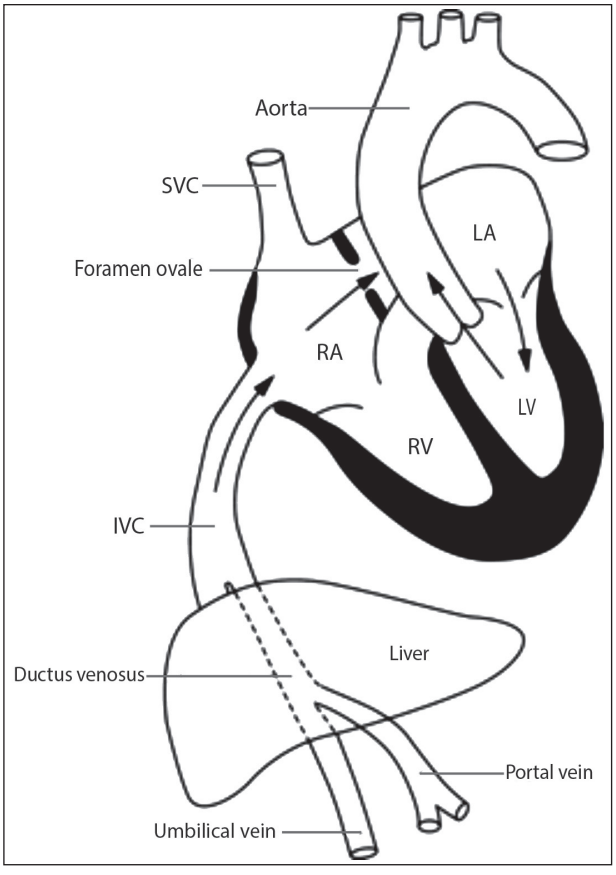
ry these in their formulary, so fresh frozen plasma should be used for replacement until these products can be obtained by the pharmacy. Fresh frozen plasma is the only replacement available for protein S deficiency[37].

Deficiencies in protein C, protein S and antithrombin confer significant additional risk to all forms of thrombosis in the neonate, but the role of other inherited molecular risk factors, such as MTHFR, prothrombin, and factor V Leiden variants, are less clear. Extensive studies and registries have examined the significance of these molecular variants and others in both risk of thrombosis and recurrence[30,35,38-40]. Although it remains controversial whether neonates should be prospectively screened for these genetic risk factors without a strong family history, significant thrombosis such as purpura fulminans, neonatal stroke or central sinus venous thrombosis (CSVT), recurrent line obstruction or portal or mesenteric venous thrombosis would trigger a work-up in most centers. As mentioned above, severe deficiencies of antithrombin, protein C and protein S require replacement and ongoing anticoagulation, but response to the molecular risk factors is mixed. Most meta-analysis would confirm that having more than 1 risk factor does increase likelihood of thrombosis, as does the homozygous or compound heterozygous state for any one particular variant[40]. Even so this would not prompt any change in therapy unless a pattern of recurrent thrombosis is present. In that setting, centers might add a low dose continuous infusion of heparin through critical central access lines or prophylactic dosing of enoxaparin to decrease the rate of catheter related thrombosis.

As the vast majority of patients with molecular risk factors do not experience clinically significant thrombosis, infants are not screened prospectively unless there is a strong family history[38-40]. One study did show a higher incidence of one molecular risk factor in *asymptomatic*, *non-occlusive* catheter related clots, but for clinically significant occlusive catheter related thrombosis, only patients with ≥ 2 genetic variants showed increased risk of occurrence[39]. Even in the presence of acute ischemic stroke, the presence of a molecular risk factor does not predict recurrence unless there are ≥ 2 risk factors present. For these reasons, the Subcommittee for Perinatal and Pediatric Thrombosis of the Scientific and Standardization Committee of the International Society of Thrombosis and Haemostasis (ISTH) only recommends screening in the setting of clinically significant thrombosis or strong family history[41].

**Acute ischemic stroke (AIS) and central venous sinus thrombosis (CSVT)**

When one examines the perinatal events and circulatory changes that occur during birth, it is amazing that the incidence of neonatal stroke and central sinus thrombosis is as low as it is. Thrombotic risk factors appear to play no role in the likelihood of embolic events causing AIS. Maternal hypertension, sepsis, or protracted labor and delivery result in a very high risk factor for neonatal stroke, which primarily presents with seizures (82%), focal findings, or changes in tone. Source of these emboli often is unclear by day 1 or so after birth when the seizures are noted. Parker et al suggest that it is the unique feature of the prenatal circulation that may provide a route for emboli from the large abdominal vessels to the cerebral vessels in the fetus and newborn[41].




As seen in the upper figure, emboli from the portal or umbilical veins can pass through the ductus veno-

sus, into the inferior vena cava, and across the patent foramen ovale (PFO), which accounts for about 27% of fetal cardiac output in utero. Importantly, the ductus venous does not close until just after birth, so this may explain some of the "idiopathic" cerebral infarction seen in term infants. In sick neonates on ventilators, the increased right sided pressures in the heart due to ongoing lung disease may also continue to divert some portion of the right atrial blood flow through the PFO. The foramen ovale may remain permanently patent and 20-34% of adults from the third to ninth decades of life have at least a small patent foramen ovale[43]. The authors suggest that careful investigation of the portal vein and other remaining large vessels in the abdomen would prove informative in these patients with no clear etiology of their stroke. There is no increased rate of AIS in patients with molecular risk factors alone and, of note, these factors when present do not appear to increase risk of recurrence either[39,41,44].

Central sinus venous thrombosis presents with seizures, changes in tone and/or poor feeding in the first week of life as well, but the etiology of this process appears to be quite different from the embolic process we see with AIS[45-53]. In this instance, there is a much higher association with maternal and neonatal factors such as diabetes, pre-eclampsia, oligohydramnios, hyper-viscosity with polycythemia, premature rupture of membranes and inherited or acquired prothrombotic states such as infection or antiphospholipid syndromes. The most common site of thrombosis are the superior sagittal sinus, transverse (lateral) sinuses of the superficial venous system and the straight sinus of the deep system. Yang et al point out that increase in venous pressure may result in secondary hemorrhage which is observed in 50% of initial imaging. Intraventricular or thalamic bleeds in term infants should prompt a closer look for CSVT as an etiology[52]. Treatment with unfractionated or low molecular weight heparin is recommended as long as there is no associated intracranial bleeding, antithrombin if levels are decreased and addressing any of the inciting problems such as infection or elevated hematocrit in the infant[45-53]. Survival ranges from 2-24%, and long term disability associated with epilepsy, cognitive impairment or cerebral palsy is listed as 10-80%[52].

In summary, the unique biologic and anatomical features of the newborn infant have created a transient alteration in the usual checks and balances that maintain our coagulation and the integrity of our vascular circulation. In the healthy term infant this has resulted in excellent hemostasis and optimization of the vascular angiogenesis needed in a rapidly growing neonate. In the sick infant, the very pathways that are prothrombotic and protective in one scenario may predispose to venous or arterial obstruction placing vital organs and limbs at risk. Treatment options are still quite limited to anti-coagulation with heparin, localized or systemic thrombolysis, anti-platelet agents, and surgical removal of large life threatening clots. Much more work is needed to find treatment which is targeted to the neonatal coagulation system and its regulatory elements, to improve long term outcomes and minimize morbidity.

**Conflicts of interest:**
I serverd on advirsory commitees for Bayer and Novonordisk this year as specialist in rare blood disorders.

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