Regular review

Neonatal haemostasis

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The newborn baby's haemostatic mechanism is immature and does not develop fully until the age of 6 months. This does not seem to cause clinical problems for the healthy neonate, but may contribute to morbidity in the sick and premature infant.

Platelets

Platelets have been identified in the fetal circulation at 11 weeks' gestation,¹ and fetoscopy has shown their numbers to be within the adult range from 15 weeks' gestation onwards.² On the basis of this and other information³ healthy infants, both premature and born at term, should be considered thrombocytopenic if they have platelet counts below $150 \times 10^9/l$, regardless of their period of gestation. Thrombocytopenia is, however, common among sick infants. A unique set of conditions surrounds the newborn infant causing an unusual susceptibility to thrombocytopenia—for example, maternal antibodies, congenitally acquired infections, and hypoxia. The incidence of thrombocytopenia has been variably reported. A prospective study of 807 consecutive infants admitted to a neonatal intensive care unit found platelet counts below $150 \times 10^9/l$ in 174 (22%) infants, and below $100 \times 10^9/l$ in 97 (12%).⁴ In three quarters of the thrombocytopenic infants the lowest platelet count was on day 4 and the thrombocytopenia had resolved by day 10. Investigations suggested that increased consumption of platelets was the underlying mechanism. Only 21% of the markedly thrombocytopenic infants (platelet count $<100 \times 10^9/l$) had evidence of disseminated intravascular coagulation and 12% had had exchange transfusions. Of the risk factors assessed, birth asphyxia correlated most closely with the subsequent development of a low platelet count. It is difficult to assess the clinical impact of thrombocytopenia on the newborn because thrombocytopenic infants are usually sick, or premature, or both, and have a variety of medical complications that by themselves can contribute to morbidity and mortality. The same study reported that thrombocytopenic

infants (platelet count $<100 \times 10^9/l$) weighing less than 1500 g at birth had three and a half times the risk of intraventricular haemorrhage of infants who were not thrombocytopenic, and who were matched for age, weight, and disease, even when infants with disseminated intravascular coagulation were excluded from analysis.⁵

Defective platelet aggregation in response to stimulation by adrenaline, collagen, and adenosine diphosphate has been reported in both premature infants and those born at term.⁶ The response to adrenaline is particularly impaired, and this may be related to a deficiency of α -adrenergic receptor sites on the neonatal platelet membrane. In contrast, aggregation in response to ristocetin is increased and this may be explained by the raised concentration of von Willebrand factor in the newborn. Despite impaired platelet function, newborn babies have bleeding times that are normal or shorter than that of the adult.^{5,7} This may be due to either raised concentrations of von Willebrand factor⁵ or to reduced prostaglandin I_2 -like regenerating activity,⁸ both of which are present in the newborn. Although impaired platelet function does not cause a bleeding tendency, newborn babies are more susceptible to inhibition of platelet aggregation by aspirin and promethazine taken by the mothers.

Procoagulants

Clotting factors in the circulation of the newborn have been synthesised by the fetus and do not cross the placenta. Fetoscopy has provided valuable data about coagulation factors at various gestational ages. The information suggests that factors I,⁹ V,¹⁰ and VIII³ are within the normal adult range from the beginning of the third trimester onwards. All other factors are variably reduced at birth, being lower in the preterm infants, and dependent on the gestational age. Infants from 24 weeks' gestation onwards have mean fibrinogen concentrations within the adult range, suggesting that a fibrinogen concentration of 1.5 g/l at birth should be regarded

as the lower limit of normal in both premature infants and those born at term.^{9 10} Fetal fibrinogen is comparatively insensitive to thrombin induced proteolysis and has an increased sialic acid content compared with adult fibrinogen; this varies with the degree of prematurity and correlates with the prolongation of the thrombin clotting time. Although the role of sialic acid in the conversion of fibrinogen to fibrin is controversial, its removal from the fibrinogen molecule enhances clot formation by thrombin. There is no firm evidence that fetal fibrinogen is comparable with fetal haemoglobin and coded for by a specific gene. Because similar abnormalities of fibrin formation are encountered in liver disease in adults, fetal fibrinogen may represent a postsynthetic modification of a basic fibrinogen protein in which hypersialation occurs in the fetal liver.

The procoagulants that are dependent on gestational age include the vitamin K dependent factors (factors II, VII, IX, and X), the contact factors (factors XI, XII, prekallikrein, and high molecular weight kininogen), and factor XIII.

At term the vitamin K dependent factors are about 50% of adult values, and at 24 weeks' gestation are about half that concentration.¹¹ Factor XIII concentrations are in a similar range at term. As only small quantities of factor XIII are required for clot stabilisation, the decreased activity in the newborn infant is unlikely to have any clinical relevance. Concentrations of contact factors have been reported to be 20–30%, and 30–50%, of adult values in preterm and term infants, respectively.

Anticoagulants

Four principal anticoagulants have been identified that act as inhibitors in different parts of the coagulation cascade. Antithrombin III, protein C, and protein S are dependent on gestational age; α_2 macroglobulin is not. Antithrombin III concentrations in the infant born at term are about 60% of the adult values, and further reduced in the preterm infant. Antithrombin III inhibits factors II and X. As concentrations parallel these vitamin K dependent coagulation proteins, a balance of procoagulants and anticoagulants exists.¹¹

Protein C and protein S are vitamin K dependent factors and reduced to concentrations similar to those of other vitamin K dependent proteins. Protein S acts as a cofactor for protein C, which in its activated form inhibits activated factors V and VIII. Unlike protein C and protein S, factors V and VIII are not reduced at birth and consequently an imbalance in favour of thrombosis exists.¹¹ This physiological imbalance does not seem to lead to

thrombosis. In the adult, protein S exists in a free active form (40%), and in an inactive form complexed to C4b-binding protein (60%). Newborn babies have low or undetectable concentrations of C4b-binding protein, which results in most of their protein S being in the free active form.¹² This comparatively high concentration of active protein S may enhance the potential of the protein C pathway, and consequently compensate in part for the low concentrations of other inhibitors.¹² α_2 Macroglobulin concentrations are raised above the adult range in both the term and preterm infant,¹¹ and likewise this inhibitor may have a protective role against thrombosis at a time when concentrations of the other principal anticoagulants are low.

Although plasminogen concentrations are about 50% of adults values at term, and do not reach adult concentrations until about 6 months of age, fibrinolytic activity seems to be increased in the newborn.¹³

A recent study of healthy infants born at term confirms that coagulation tests vary with the postnatal age, and that different coagulation factors show different postnatal patterns of maturation, but that most coagulation factors achieve near adult values by 6 months of age.¹⁴

Specific inherited coagulation defects

Although haemorrhage is usually due to an acquired coagulation defect in the newborn period, inherited coagulation defects may also present at this time and a family history is not always available. Isolated haemorrhage in an otherwise healthy infant is particularly suggestive, especially if the infant has been bottle fed. Factor deficiencies associated with neonatal haemorrhage include those of factors VIII, IX, XIII, VII, X, and afibrinogenemia. It is generally only severely affected infants (<1%) who present at this age. Haemophilia A and B and von Willebrand's disease account for more than 90% of inherited clotting factor deficiencies, and between 5–10% of affected infants will present in the neonatal period.

Thrombosis

The peak incidence of thrombosis in the paediatric age group is in the neonatal period, when it is most frequently iatrogenic and associated with indwelling catheters, although not exclusively so.¹⁵ There is no real evidence that the physiological reduction of anticoagulants in the newborn contributes to thrombosis. Although infants have plasma concentrations of antithrombin III and protein C (which would be associated with thrombotic episodes in adults), even

in congenital antithrombin III and protein C deficiency thrombosis is exceptional in childhood. Other physiological changes may compensate for the low concentrations of these inhibitors. Raised values of the other inhibitors, in particular α_2 macroglobulin, free active protein S, C1-esterase inhibitor, and heparin cofactor II, have been proposed. A profound reduction of either antithrombin III or protein C, however, does cause disease. Newborn infants with homozygous protein C deficiency have been reported with fatal fulminant thrombosis.¹⁶⁻¹⁸ A small number of infants born to mothers with congenital antithrombin III deficiency have died of thrombotic complications in the neonatal period.^{19, 20} Congenital antithrombin III deficiency was suspected but not verified by assay.

Homozygous antithrombin III and protein C deficiencies are probably incompatible with life. Infants born to mothers with antithrombin III deficiency should have their antithrombin III concentrations measured at birth. It has been advocated that affected infants should receive prophylactic antithrombin III concentrate to maintain values appropriate for the newborn until the infant's own concentration has risen to about 50%.²¹ The risk of viral transmission by the blood product, however, must be balanced against the risk of thrombosis and a more conservative approach may be indicated. A few cases of homozygous protein C deficiency have been diagnosed early and treatment instigated. Initial treatment should always be with fresh frozen plasma, with or without anticoagulation. The half life of protein C is about seven hours, and to maintain adequate concentrations treatment would have to be given at such frequent intervals that it is not a practical long term solution. Factor IX concentrate has been used successfully for administering protein C.²² The factor IX concentrate should be selected with care to minimise its thrombotic risk.²³ Infusions of 50-75 U/kg of protein C every other day seem sufficient to stop thrombotic episodes, although concentrations approach zero by the end of 48 hours. Warfarin has also been used with some success. It is difficult, however, to achieve a stable therapeutic dose in the newborn, and this treatment does nothing to raise the concentration of protein C or correct the imbalance between protein C and its procoagulants.

Haemorrhagic disease of the newborn

Vitamin K₁ is safe and virtually no infant who is given it develops classic haemorrhagic disease of the newborn.²⁴ McNinch *et al* reported an incidence of local recurrence of haemorrhagic disease of the newborn of 1:1200 live births in an area in which

prophylactic vitamin K₁ was not given routinely.²⁵ All infants were breast fed and had not received vitamin K₁ at birth. Three of the infants died. This highlights the need for vitamin K prophylaxis for all newborn babies, especially in a society in which breast feeding is becoming increasingly popular. Oral administration seems an attractive alternative to the parenteral route. There is little information on the intestinal absorption of vitamin K in the newborn, but one study that compared oral with parenteral administration of 1 mg vitamin K₁ reported that neonates receiving oral vitamin K₁ achieved median peak plasma concentrations of 73 ng/ml at four hours compared with 1781 ng/ml at 12 hours with parenteral administration.²⁶ Although the concentration after oral administration was considerably lower than that after parenteral administration, it was still some 300 times the adult median, and nearly 4000 times the estimated maximum cord plasma concentration. No infant in the study developed haemorrhagic disease of the newborn. It is clear that vitamin K prophylaxis should be given to all newborn infants.

Should infants who are exclusively breast fed receive further vitamin K supplementation after the immediate neonatal period? Late haemorrhagic disease of the newborn has been reported in a small number of breast fed infants who had received vitamin K at birth. This, however, seems to be a rare finding. At particular risk are breast fed infants who develop diarrhoea and infants who are treated with antibiotics. The American Academy of Pediatrics stated in 1979 'Breast-fed infants who develop diarrhea of longer than several days duration should be given one intramuscular injection of vitamin K (1.0 mg). Infants at continued risk of vitamin K deficiency (eg, malabsorption, biliary atresia) should be given supplements of vitamin K at regular intervals'.²⁷

Conclusion

Newborn infants are at particular risk of both thrombotic and haemorrhagic problems. These conditions are under investigated because of the difficulty of obtaining adequate volumes of blood for analysis, and this often means that the infants are inappropriately treated. It is important that a laboratory serving a neonatal unit establishes specialised standardised microtechniques that are reproducible with respect to the reagents, methods, and volumes used for routine coagulation screening.

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