Blood coagulation status of small-for-dates and postmature infants

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Blood coagulation status of small-for-dates and postmature infants. In a prospective study of blood coagulation status in small-for-dates and postmature infants there was often evidence of intravascular coagulation. Abnormal coagulation findings correlated with the degree of growth retardation and with the degree of postmaturity. Macroscopical placental infarction and neonatal polycythaemia were associated with coagulation abnormalities; asphyxia, however, was not. Intravascular coagulation may be an additional hazard to small-for-dates and postmature infants.

The material presented here is part of a broader prospective study of blood coagulation in term newborn infants. Described in the past as 'dysmature', two groups of infants, small-for-dates and postmature, are considered together as they have much in common, both during intrauterine life (fetal malnutrition, hypoxia, fetal distress, and polycythaemia), and postnatally (neonatal asphyxia, intracranial haemorrhage, and hypoglycaemia). Of these, asphyxia and polycythaemia are recognized causes of coagulopathies in infants. An additional aspect that we wished to explore was the possibility of preventing intracranial haemorrhage in neonates through early recognition and treatment of defects of blood coagulation.

Clinical material

Three groups of infants were studied; all were born at the Soroka Medical Centre between November 1971 and October 1972.

Normal controls. Normal infants of gestational age between 39 and 41 weeks and birthweight between

the 25th and 75th centiles (standards of Thomson, Billewicz, and Hytten, 1968).

Small-for-dates infants. Gestational age of more than 38 and less than 42 completed weeks, and birthweight less than the 5th centile for gestational age and sex. External signs were appropriate to gestational age.

Postmature infants. Gestational age of more than 42 completed weeks and appropriate external signs. The latter were graded according to Clifford (1954).

Infants with conditions predisposing to sepsis and with clinical evidence of infection were excluded. In addition, blood cultures taken at the time of blood sampling were negative in all infants. No selection was applied in relation to complications of pregnancy and parturition in the two study groups.

The cord was usually clamped 30-60 seconds after birth. The placenta was inspected macroscopically for gross pathology. Routine care included injection of 0.5 mg vitamin K within 2 hours of birth, and serial measurement of blood glucose in study group infants. Small-for-dates and postmature infants received a commercial milk preparation and/or breast feeding from the age of 6 hours, while control infants were breast fed from the age of 18-24 hours.

Definitions. Perinatal asphyxia: detection of the presence of fetal bradycardia and/or an Apgar score of less than 6 at one minute and less than 8 at 5 minutes. The placenta was considered abnormal when described in the labour ward record as extensively infarcted. Hypoglycaemia was defined by conventional criteria (Cornblath and Schwartz, 1966). Polycythaemia: capillary blood haematocrit exceeding 75%. Subarachnoid haemorrhage: consistent blood-staining of three

Abbreviations

PT: prothrombin time
TT: thrombin time
PTT: partial thromboplastin time
FDP: fibrin, fibrinogen degradation products

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consecutive samples of CSF, and the findings of crenated erythrocytes on microscopical examination of freshly drawn fluid.

Materials and methods

Blood samples were taken from the external jugular or femoral vein using a 19-gauge siliconized needle and plastic syringe. The mean age of blood sampling was 26 hours, range 1–72 h. The majority of infants had a single study only. Particular attention was paid to rapid sampling of free-flowing blood in order to avoid contamination by tissue thromboplastin and initiation of clotting *in vitro*.

The following parameters of blood coagulation were estimated by methods outlined in a previous publication (Dvilansky and Biran, 1973): PT, TT, PTT, fibrinogen, Factor V, Factor VIII, plasminogen, euglobulin lysis time, FDP, and platelets. Half volumes of blood were used. The microhaematocrit was measured in capillary blood. Tests were performed by the same technician within 0.5 hour of collection of blood in plastic tubes kept in crushed ice. All coagulation determinations were made with a BBL Fibrometer.

Results of blood coagulation studies as well as clinical data were processed and analysed with the aid of a CDC Control Data 6600 computer. Statistical significance was examined by Student's 't' test for small samples (Snedecor and Cochran, 1967).

Results

Clinical findings (Table I).

Normal controls. 17 males and 18 females were examined, their respective mean birthweights were 3445 and 3295 g. Mean head circumference was 35 cm for males and 34.1 cm for females.

Small-for-dates infants. 15 infants were male and 11 female; mean birthweight was 2320 g. In the majority the cause of the low birthweight was not clear. One mother suffered from chronic renal disease and 3 from pre-eclamptic toxæmia. 3 infants were the smaller of twins by a difference of 14 to 26% of the larger twin. 11 of 14 singleton infants who were the products of multiparous mothers had birthweights lower than their sibs. Evidence of perinatal asphyxia was found in 11 infants. The placenta was macroscopically abnormal in 5 cases.

No infants had evidence of haemostatic failure. 2 infants delivered by vacuum extractor had a large subaponeurotic cephalhaematoma which expanded the head circumference and was associated with a low haematocrit. Another infant with a bulging fontanelle had evidence of a subarachnoid haemorrhage. 2 infants had hypoglycaemia and 4 had polycythaemia. 4 infants had transient neurological findings including lethargy, hypotonia, weak cry, irritability, and depressed Moro reflex.

Postmature infants. Mean birthweight was lower and mean head circumference higher than in normal controls. The male to female sex ratio was 3 to 1; birthweight and head circumference data (Table I) indicated a male disadvantage. Pregnancy complications were rarely recognized in this group, but this may reflect self-selection of mothers who were relatively neglected from the point of view of antenatal care and hence the prolonged pregnancy. Evidence of perinatal asphyxia was common

TABLE I
Clinical data on control, small-for-dates, and postmature cases

	Control	Small-for-dates	Postmature	Total
No.	35	26	30	—
Gestational age (mean) (w)	40.3	39.6	42.7	—
Maternal toxæmia, hypertension	0	5	3	8
Ratio: male/female	17/18	15/11	27/9	—
Birthweight (mean) (g)				
Males	3445	2355	3225	—
Females	3295	2245	3365	—
Head circumference (mean) (cm)				
Males	35.0	33.0	35.0	—
Females	34.1	32.1	35.6	—
Fetal bradycardia	0	6	13	19
Severe meconium staining	0	6	12	18
Apgar score 7 at 5 min	0	4	8	12
Macroscopical placental infarction	0	4	9	13
Polycythaemia	0	5	3	8
Hypoglycaemia	0	2	2	4
Traumatic bleeding	0	2	6	8
Subarachnoid haemorrhage	0	1	3	4
Gastrointestinal bleeding	0	0	2	2
Neurological symptoms	0	4	13	17

TABLE II
Limited coagulation data comparing different grades of severity of small-for-dates and postmature cases

	Normal infants	Small-for-dates infants			Postmature infants	
		Stage I	Stage II	Stage III	Stage I	Stages II & III
No.	35	12	9	5	18	12
Haematocrit (%)	61.5 ± 7	67.6 ± 9.1*	65.7 ± 7.1	63.0 ± 10.1	68.0 ± 9*	68.6 ± 6.9†
Platelet count (× 10 ³ /mm ³)	169 ± 43	128.4 ± 38.4*	118.2 ± 46.1†	118.8 ± 53.6*	138.6 ± 31.8*	113.6 ± 70.4†
PT (s)	11.1 ± 0.7	12.6 ± 2.7*	11.1 ± 1.6	12.7 ± 1.5*	11.5 ± 1.8	11.6 ± 1.9
TT (s)	13.4 ± 1.3	13.6 ± 2.3	14.2 ± 2.4	15.7 ± 1.9*	14.3 ± 2.3*	15.4 ± 1.9†
PTT (s)	47.1 ± 7.9	63.2 ± 11.4†	53.3 ± 10.7*	60.0 ± 14.2*	52.5 ± 10.9*	45.8 ± 11.8
Fibrinogen (mg/dl)	184 ± 66	164.3 ± 42	155.8 ± 34.5	154.6 ± 53.5	179.9 ± 39	160 ± 46.6
FDP (μg/ml)	0.79 ± 0.81	3.5 ± 3.76†	3.26 ± 4.57*	6.1 ± 11.3*	0.96 ± 1.61	3.91 ± 7.76*

Values given as mean ± SD. *0.005 < P < 0.05. †P < 0.005.

(Table I). The placenta was macroscopically abnormal in 8 instances.

Two infants had gastrointestinal bleeding at the age of 1 and 4 days, respectively; 3 had evidence of subarachnoid haemorrhage. Hypoglycaemia was detected in 2 instances. 13 infants had neurological signs during the first postnatal days; 2 also had a convulsive disorder. Meconium aspiration pneumonia with bilateral pneumothoraces occurred in one infant.

Blood coagulation data (Tables II and III).

Normal controls. Values for Factors I, V, and VIII are similar to those reported by others

(Bleyer, Hakami, and Shepard, 1971). PT did not differ from adult values, while PTT was prolonged. The platelet count was lower than that reported in other studies (Sell and Corrigan, 1973), as is the normal range for platelets in adults in this laboratory (120 000—300 000/mm³). The highest value of FDP in a normal infant was 2.4 μg/ml. When postnatal age was related to the laboratory values including FDP, the relation was significant only for fibrinogen, the values of which rose during the first 48 postnatal hours, an observation which has been made by other workers (Ekelund, Hedner, and Nilsson, 1970).

Small-for-dates infants. Selected results ob-

TABLE III
Coagulation values in relation to

	Normal controls	Uncomplicated SFD and PM infants	Asphyxiated SFD and PM infants
No.	35	14	14
Haematocrit (%)	61.5 ± 7.0	68.0 ± 5.8*	64.2 ± 7.8
Platelets (× 10 ³ /mm ³)	169.1 ± 42.9	130.3 ± 43.9*	130.0 ± 34.5*
PT (s)	11.1 ± 0.7	11.8 ± 2.2*	11.4 ± 1.2
TT (s)	13.4 ± 1.3	14.7 ± 2.4*	13.9 ± 2.2
PTT (s)	47.1 ± 7.9	56.7 ± 11.8*	46.2 ± 10.2
Factor V (%)	98.0 ± 42.9	102.8 ± 45.8	108.3 ± 36.1
Factor VIII (%)	137.2 ± 83.8	115.7 ± 49.6	140.5 ± 38.9
Fibrinogen (mg/dl)	184.2 ± 65.7	158.2 ± 36.2	180.0 ± 40.6
Plasminogen units (min)	1.81 ± 0.81	1.44 ± 0.68	1.90 ± 0.54
Euglobulin lysis time (min)	140.2 ± 58.9	123.2 ± 67.8	163.6 ± 63.3
FDP (μg/ml)	0.79 ± 0.81	1.31 ± 1.21	1.55 ± 2.32
Haemoglobin (g/dl)	21.5 ± 2.6	23.1 ± 2.5*	20.7 ± 2.0

*0.005 < P < 0.05. †P < 0.005.

tained for the 26 infants are aggregated in groups by birthweight and summarized in Table II. Platelets were significantly diminished; PT, TT, and PTT increased, and the values of FDP were increased. In the case of platelets, TT, and FDP, the values were aberrant in proportion to the severity of the growth retardation (Table II). No significant alterations were observed in the levels of fibrinogen and Factors V and VIII.

Postmature infants. For the purpose of analysis of results this group was divided into two: (a) grade I (18 infants); (b) grades II and III (12 infants) (Clifford, 1954).

The clinical severity of the postmaturity was reflected in the abnormal laboratory values, particularly platelets, TT, fibrinogen, and FDP (Table II).

Uncomplicated small-for-dates and postmature infants. A control group of small-for-dates and postmature infants without prenatal or postnatal complications was selected for comparison (Table III). When compared with normal controls, uncomplicated small-for-dates and postmatures were associated with a raised haematocrit, diminished platelet count, and prolonged PT, TT, and PTT.

Other clinicopathological associations (Table III). The effect of a number of perinatal complications upon blood coagulation values was examined. Results for the two study groups were pooled for analysis.

Asphyxia was not associated with significant alterations of laboratory values. Gross placental infarction (13 cases), polycythaemia (8 cases), and

hypoglycaemia (4 cases) were each significantly correlated with thrombocytopenia, prolonged TT and PTT, and increased FDP values. 2 infants with spontaneous gastrointestinal bleeding had normal coagulation values. 4 infants with subarachnoid haemorrhage had a mean haematocrit of 70%. In addition, there was thrombocytopenia and increased FDP values but no evidence of bleeding tendency.

Examples are given in the Appendix to illustrate the various coagulation profiles observed in some of the more severely affected infants.

Discussion

Both categories of study group infants have been described as 'dysmature'. Small-for-dates and postmature infants have in common a high incidence of fetal hypoxia, malnutrition, polycythaemia (Humbert *et al.*, 1969; McKay, 1957), perinatal asphyxia, hypoglycaemia, and possibly of placental 'ageing' (Scott and Jordan, 1972). The clinical data in Table I highlight the increased immediate morbidity rate of both small-for-dates and premature infants and show the similarities between them. Of interest is the preponderance of males in both study groups and the greater tendency to low birthweight for gestational age in the postmature group.

The study provides evidence that intravascular coagulation frequently occurs in small-for-dates and premature infants. The significantly altered laboratory values were increased TT and PTT, decreased platelets, and increased FDP. Thrombocytopenia was the only evidence of a consumption coagulopathy, but values of fibrinogen and Factors

III

various perinatal complications

Placental pathology	Polycythaemia	Hypoglycaemia	Subarachnoid haemorrhage ?
13	8	5	4
65.0 ± 12.1	77.5 ± 2.4†	70.4 ± 5.2*	69.7 ± 3.9*
97.1 ± 43.9†	96.8 ± 39.2†	68.4 ± 40.1†	110.7 ± 42.4*
11.7 ± 1.5*	11.6 ± 1.6	12.0 ± 2.3	10.1 ± 1.1*
15.0 ± 2.7†	15.5 ± 2.7†	15.7 ± 1.7†	14.4 ± 3.1
55.7 ± 14.0*	59.4 ± 10.1†	60.3 ± 15.1†	48.4 ± 5.5
81.5 ± 33.4	101.0 ± 60.7	94.0 ± 41.9	115.1 ± 63.0
154.3 ± 70.3	178.6 ± 105.4	130.4 ± 84.9	160.0 ± 83.7
169.3 ± 52.2	183.3 ± 37.3	156.5 ± 54.6	152.0 ± 19.0
1.45 ± 0.51	1.49 ± 0.56	1.25 ± 0.54	1.66 ± 0.47
187.5 ± 134.5	98.8 ± 101.5	132.0 ± 54.8	130.0 ± 80.3
6.88 ± 10.08†	7.80 ± 9.77†	7.46 ± 10.98†	2.29 ± 2.83*
20.7 ± 3.0	24.8 ± 2.5†	21.5 ± 2.6	21.5 ± 3.5

V and VIII may be normal or increased in states of chronic or low-grade intravascular coagulation or during recovery (Cooper *et al.*, 1971).

Infants of mothers with uncomplicated pregnancies and labours and in whom no abnormality other than being small-for-dates or postmature was detected had lesser deviations from normal laboratory values than those with additional obstetric complications (Table III). Of major importance were the findings of gross placental pathology and of polycythaemia; asphyxia appeared to play no role in the observed changes (Table III). Infants with tissue bleeding had a low haematocrit and increased values of FDP. Neonatal hypoglycaemia was associated with particularly marked changes in the values of the haematocrit, platelet count, and FDP, and presumably represents the severity of the predisposing perinatal disturbances.

Owing to the presence of multiple pathogenetic factors in the majority of infants and the relatively small numbers studied it was not possible to evaluate the precise role of each factor in the production of the observed coagulation changes. However, three factors likely to be important are placental infarction, polycythaemia, and asphyxia.

The pivotal role of the placenta in blood coagulation is indicated from several lines of evidence. (1) Disseminated intravascular coagulation and consumption coagulopathy may occur as a result of placental abruption, in the neonate as well as in the mother (Nielsen, 1970; Leissring and Vorlicky, 1968). (2) Laboratory findings indicative of a hypercoagulable state have been detected in uterine venous blood taken during placental separation (Bonnar *et al.*, 1970). (3) Fibrin clots have been observed by microcirculation techniques in both uterine and umbilical veins of experimental animals during placental separation (Brown and Stalker, 1969). (4) In complicated pregnancies placental cushion lesions have been found to be associated with portal venous, pulmonary arterial, and systemic capillary thromboembolic phenomena (deSa, 1973). The high concentration of thromboplastin in the placenta (Schneider, 1947) is probably of central importance in the mechanism of the above phenomena. Though there appears to be no specific placental lesion(s) in the small-for-dates and postmature fetuses, there is probably an increased number of vascular lesions, ischaemic necrosis of villi, infarcts, and retroplacental haemorrhages (Scott and Jordan, 1972) in some instances. In the present study the correlation between placental infarction and blood coagulation changes consistent with intravascular coagulation suggests that the entry of placental

thromboplastin into the fetal circulation is facilitated in a proportion of small-for-dates and postmature infants.

Polycythaemia is associated with laboratory changes compatible with mild intravascular coagulation in cyanotic congenital heart disease, presumably mediated through hyperviscosity of the blood (Komp and Sparrow, 1970). In addition, polycythaemia is not infrequently associated with neurological symptoms in the neonate (Kontras, 1972), and has been invoked as a cause of irreversible brain damage (Baum, 1967). Polycythaemia was clearly associated both with neurological symptoms and with coagulation changes in the present series.

Asphyxia was not a predisposing cause of coagulopathies in our cases contrary to the findings of some investigators (Chadd *et al.*, 1971), but in agreement with others (Ekelund and Finnström, 1972). Anoxic tissue damage such as that possibly seen in Case 3 (Appendix) may have contributed to intravascular coagulation by releasing tissue thromboplastin into the circulation. The question arises as to whether the coagulation changes found in asphyxiated infants in other studies were not due to unrecognized asphyxia-associated factors such as polycythaemia or placental lesions.

Apart from consumption coagulopathy, the important implication of intravascular coagulation is tissue ischaemia and infarction. A placental mechanism, as suggested above, could result in embolization of fibrin clots via the fetal cardiovascular shunts to the brain and other organs. This may have more sinister implications than the observed pulmonary effects of fibrin embolization from the maternal side of the placenta in pre-eclamptic and eclamptic mothers (Birmingham Eclampsia Study Group, 1971). No evidence of necrotic pathological lesions was detected in the perinatal period in the infants studied; there was, however, a high incidence of neurological symptoms.

Although infants with subarachnoid haemorrhage had altered coagulation tests, the bleeding could not be attributed to a consumption coagulopathy. Necrotic pathological lesions due to intravascular coagulation, or, increased venous pressure due to polycythaemia, are possible alternative mechanisms.

The prevention of postnatal polycythaemia may be justified in infants at risk, by preventing the placental transfusion, or by phlebotomy or partial exchange transfusion with plasma. Ultimately, the early recognition of fetal distress and the establishment of criteria for obstetric intervention are probably more important approaches to the coagulation disorders of small-for-dates and postmature infants.

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Appendix

Case 1. A 23-year-old para-2 gravida-2 mother delivered a female infant spontaneously by breech presentation, after 296 postmenstrual days. Apart from meconium-stained liquor, the pregnancy and parturition were normal. Apgar score was 9 at one minute. The placenta was infarcted, calcified, and deeply meconium stained. Physical examination revealed signs of stage II postmaturity. Birthweight was 3150 g and head circumference 35 cm. Apart from asymmetry of the Moro reflex there were no abnormal physical findings.

At 28 hours the following abnormal tests of coagulation were documented: TT 15.7 s, FDP 14.4 µg/ml, and platelets 96 000/mm³. Other tests were normal.

On the fourth day a haematemesis occurred. At this time the only abnormalities in the coagulation profile were a platelet count of 86 000/mm³ with the FDP value still 14.4 µg/ml. Hb fell from 21.8 g/dl on the second day to 17.8 g on the fourth day. The initial tests could be attributed to mild intravascular coagulation. The gastrointestinal bleeding on the fourth day could not, however, be attributed to a consumption coagulopathy. The sustained high value of the FDP is unexplained.

Case 2. This infant was the product of an uncomplicated second pregnancy. During delivery, viscid meconium-stained liquor and fetal bradycardia were noted. Apgar score was zero at birth, but the infant responded to external cardiac massage, artificial ventilation, and alkali administration. Deep meconium staining of skin and cord were seen; birthweight was 3450 g and head circumference 35 cm.

After resuscitation, respiratory distress was noted and chest x-ray showed a picture of aspiration pneumonia and bilateral small pneumothoraces. At 30 min blood sugar was 4 mg/dl, this was corrected by infusion of 15% glucose. Subsequently convulsions occurred and the anterior fontanelle was noted to be tense. Lumbar puncture revealed evidence of a subarachnoid haemorrhage. There were residual neurological signs at the time of discharge at the age of 14 days.

Coagulation values on the fourth day were as follows: capillary haematocrit 80%, platelet count 12 000/mm³, TT 16.5 s, and FDP 28.8 µg/ml. After repeated phlebotomies totalling 60 ml, haematocrit and platelet count became normal. This complicated postmature infant had raised FDP on the fourth day postpartum, as well as severe thrombocytopenia. This may have been due to intravascular coagulation resulting from continuing tissue damage initiated by asphyxia, or to polycythemia.

Case 3. This male infant was born to a gravida-7 mother aged 36 years. Her third pregnancy had ended in a stillbirth after 42 weeks' gestation. She had no antenatal care in this pregnancy and spontaneous labour occurred at 303 days. Severe bradycardia occurred during the first stage and delivery was accomplished by caesarean section. Apgar score was 1, 3, and 6 at 1, 5, and 10 minutes. Birthweight was 3120 g

and head circumference 34.5 cm. Signs typical of stage III postmaturity were present. The subsequent course was complicated by convulsions with hypoglycaemia (blood glucose 12 mg/dl at 4 hours) and hypocalcaemia (7.1 mg/dl on day 1).

At 14 hours haematocrit was 76% and platelet count 30 000/mm³. At 38 hours the following abnormal laboratory tests were recorded: capillary haematocrit 77%, platelets 70 000/mm³, TT 18.2 s, fibrinogen 98 mg/dl, plasminogen 0.4 units, and FDP 7.2 µg/ml. 2 days later the capillary haematocrit was 68%, platelets 54 000/mm³, TT 14.5 s, and FDP 7.2 µg/ml. The plasminogen value had risen to 1.3 units and other tests were normal.

At birth the SGOT value was 440 units and SGPT 190 units and on the 4th postnatal day, 820 and 610 units, respectively. This stage III postmature infant with asphyxia and hypoglycaemia had a persistently raised value of FDP and thrombocytopenia. SGOT and SGPT values indicated continuing tissue damage which might have accounted for the persistent findings of low-grade intravascular coagulation.

Case 4. A male infant was delivered after 295 postmenstrual days to a gravida-5 mother aged 28 years. Pregnancy and parturition were uncomplicated and Apgar score was 9 at one minute. Birthweight was 3300g and head circumference 35 cm. External signs of postmaturity were noted but there was no meconium staining (stage I). At 48 hours a cyanotic spell occur-

red; blood glucose values were 3 and 5 mg/dl. Infusion of glucose 15% corrected the hypoglycaemia.

At 55 hours haematocrit was 71%, platelet count 64 000/mm³, TT 17.9 s, PTT 79 s, and fibrinogen 82 mg/dl. Euglobulin lysis time was 60 min. Lee-White silicone clotting time was 6 min. PT, Factors V and VIII, and FDP values were normal.

This hypoglycaemic postmature infant had some of the criteria required for the diagnosis of disseminated intravascular coagulation, with hypercoagulability rather than a bleeding tendency. The normal FDP value may have been due to rapid clearance of these products.

Case 5. This female infant was the product of a 37-year-old mother, para-3, gravida-3. The birthweights of the 2 previous children were 3200 and 3400 g. Gestation was 40 weeks, pregnancy and parturition were normal except for meconium staining of the liquor. Apgar score was 9 at one minute, birthweight 2600 g, and head circumference 33.5 cm. Apart from signs of malnutrition and gross meconium staining the infant appeared normal and the neonatal course was uncomplicated.

At 7 hours the capillary blood haematocrit was 80%; platelet count 122 000/mm³, TT 16.9s, PTT 68.2 s, euglobulin lysis time 40 min, and FDP 14.4 µg/ml. Other coagulation parameters were normal.

This small-for-dates infant had laboratory findings partially consistent with the diagnosis of intravascular coagulation. Polycythaemia appeared to be a likely pathogenetic factor here.