Coagulation Studies in Severe Birth Asphyxia

J. M. CHESSELLS* and J. S. WIGGLESWORTH

From the Departments of Haematology and Child Health, Hammersmith Hospital

Chessells, J. M., and Wigglesworth, J. S. (1971). *Archives of Disease in Childhood*, 46, 253. **Coagulation studies in severe birth asphyxia.** Coagulation studies have been performed in 9 infants who were so severely asphyxiated at birth as to require assisted ventilation for at least 10 minutes. Four of the infants died, though none suffered from any bleeding tendency in life. In 2 fatal cases and 1 survivor the laboratory findings of circulating fibrin degradation products, low plasma fibrinogen, and low or rising platelet count indicated that disseminated intravascular coagulation had occurred in the first few hours of life. Fibrin thromboemboli were found in the liver and adrenals of the 2 such babies that died.

One baby had a low level of vitamin K dependent factors associated with fetal growth retardation.

Clinical factors common to the cases with evidence of disseminated intravascular coagulation were the need for mechanical ventilation, and the occurrence of hypothermia.

Though haemostatic failure due to disseminated intravascular coagulation is likely to develop only in a small minority of birth asphyxiated infants, the possibility should be considered in any that become hypothermic within a few hours of birth.

There have been a number of case reports of haemostatic failure in infants with severe birth asphyxia. Valentine (1958) and Reerink-Brongers and De Koningh (1964) reported low plasma fibrinogen levels in these infants and a similar case has been reported more recently by Skyberg and Jacobsen (1969).

In theory, asphyxia could influence haemostasis in the newborn in one of two ways: either by promoting consumption of platelets and coagulation factors as a consequence of disseminated intravascular coagulation, thus resulting in a fall in platelet count, fibrinogen, factors V and VIII, and the formation of fibrin degradation products, or, by causing an exaggerated fall in the level of vitamin K dependent factors II, VII, IX, and X. A further possibility is that conditions with a high risk of birth asphyxia (e.g. fetal growth retardation) might also be associated with coagulation defects.

Hathaway and Henderson (1968) investigated this problem in newborn puppies and concluded that asphyxia depressed the level of vitamin K dependent factors, but they did not measure the

platelet count or plasma fibrinogen level. Hardaway *et al.* (1964) have suggested that a fall in pH accelerates the clotting time and may tend to promote disseminated intravascular coagulation.

We have performed coagulation studies on a small group of babies who were severely asphyxiated at birth to find out if any haemostatic abnormality occurs regularly in such infants.

Materials and Methods

The infants studied were all admitted to the neonatal ward at the Hammersmith Hospital for supervision following severe birth asphyxia which had necessitated resuscitation with intubation and intermittent positive pressure ventilation. Samples of blood for study were aspirated from the umbilical cord before delivery of the placenta; follow-up samples were taken from an umbilical arterial catheter or from a peripheral vein.

Blood was taken into a 1 in 10 dilution of Na citrate with the addition of 1/10th volume of 10% epsilon amino caproic acid to those samples intended for estimation of plasma fibrinogen and fibrin degradation products (FDP). The following tests were performed, based on those described in Dacie and Lewis (1968): a platelet count, plasma fibrinogen, thrombin-fibrinogen time expressed as a ratio patient/adult normal, Thrombotest, and thromboplastin generation screening test.

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* Present address: Applied Sciences Laboratory, University of Sussex, Falmer, Brighton.

TABLE I
Clinical Data on Infants

Case No.	Birthweight (g)	Gestation (wk)	Delivery	Apgar Score 1 min	IPPR Duration (min)	Minimum Temperature (°C)	Outcome
1	3300	40	Forceps	2	10	36.1	Lived
2	3100	40	LSCS	1	10	36.1	Lived
3	2540	36	Vertex	0	30	35.0	Lived
4	2600	40	LSCS	1	15	36.1	Lived
5	2000	34	Vertex	0	Ventilator	33.9	Lived
6	2240	38	LSCS	0	19	32.8	Died 43 hr
7	2560	34	LSCS	0	Ventilator	34.7	Died 4 dy
8	2000	34	Forceps	0	Ventilator	33.9	Died 21 hr
9	3250	40	Breech	1	Ventilator	30.6	Died 30 hr

LSCS = lower segment caesarean section.

FDP were measured on thrombin-treated plasma by the method of Merskey, Lalezari, and Johnson (1969). The methods used and the results obtained in normal infants are described in detail elsewhere (Chessells, 1971).

The postmortem material was stained with phosphotungstic acid haematoxylin and examined for the presence of fibrin thromboemboli.

Results

Clinical data on the 9 infants are presented in Table I. All infants required assisted ventilation; the length of time for which this was necessary is noted in the Table. Cases 5, 7, 8, and 9 were unable to maintain spontaneous respirations. Case 1 responded to stimulation at birth; in

Cases 2, 4, and 9 the only sign of life was an apex beat; in the other 5 infants no apex beat was detectable at delivery. Body temperature was recorded on all infants on admission to the ward: in 4 it was under 34 °C. All the infants were fed with milk from the time of admission, and only one (Case 4) was given vitamin K. No infant in the series showed any clinical evidence of a bleeding tendency.

Laboratory results are given in Table II. In Cases 1-3 there was no detectable disturbance of haemostasis apart from the low thrombotest and prolongation of the thromboplastin generation screening test which reflect the reduced level of vitamin K dependent coagulation factors always present in the newborn infant. Case 4 was born

TABLE II
Laboratory Findings

Case No.	Age (hr)	Platelets (10 ³ /mm ³)	Fibrinogen (mg/100 ml)	FDP Titre	Thrombin/Fibrinogen Ratio	Thrombotest (%)	TGST (sec)†
1	0*	225	151	0	1.4	17	12
	24	246	178	0	1.6	21	13
2	0	154	141	0	1.4	26	16
	24	171	186	0	—	23	11
3	2	192	173	0	1.5	16	15
	0	250	149	0	1.4	9	30
4	23	220	198	0	—	34	9
	2	167	97	2	1.6	20	—
5	16	252	125	0	—	—	—
	72	238	252	0	—	—	—
6	2	236	112	0	1.9	20	15
	18	258	164	0	—	—	—
7	1	209	100	0	1.8	20	19
	24	219	126	0	1.5	22	17
8	8	—	—	4	—	—	—
	18	112	134	2	1.3	11	12
9	3	335	21	64	—	26	—
	10	251	102	16	2.6	26	11
Normal infant	Day 1	168-378	123-280	0	1-2	16-50	8-25

* Age 0 = cord blood sample.

† TGST = thromboplastin generation screening test.

TABLE III
Necropsy Findings

Case No.	Macroscopic	Histology	Fibrin Thrombi		
			Liver	Adrenals	Other Organs
6	Congested lungs with surface petechiae*	Hyaline membrane disease and pneumonia	—	—	—
7	Congested oedematous lungs with surface petechiae; subarachnoid haemorrhage	Hyaline membrane disease with early O ₂ toxicity changes	—	—	—
8	Haemorrhages over heart and lungs; pulmonary haemorrhage and oedema	Haemorrhage and oedema of lungs with inhaled epithelial squames	+	+	—
9	Tentorial tear with subdural and subarachnoid haemorrhage; midshaft fracture of right humerus; haemorrhagic infarction of adrenals; early segmental infarction of small gut	Inhaled squames in lungs	+	+	—

* Lungs stable on pressure-volume determination.

at term but was small for dates weighing only 2600 g. The cord blood showed a very low thrombotest 9% and thromboplastin generation screening test (30 sec), and the infant was given 1 mg vitamin K. At 23 hours the Thrombotest had risen to 34% and the thromboplastin generation screening test was 9 sec.

Case 5, a premature infant, remained on the ventilator for 5 days. Her initial coagulation studies revealed a low plasma fibrinogen level (97 mg/100 ml) and FDP in serum diluted 1 in 2; at follow-up no FDP were detected and the plasma fibrinogen had risen to 125 mg/100 ml; the platelet count rose to a maximum of $478 \times 10^3/\text{mm}^3$ by day 6.

Cases 6 and 7 showed low normal initial plasma fibrinogen levels (112 and 100 mg/100 ml), but normal platelet counts and screening tests for coagulation factors, and no FDP were detected. In Case 8 a low platelet count ($112 \times 10^3/\text{mm}^3$) was accompanied by the presence of FDP to a maximum titre of serum diluted 1 in 4. Case 9, an undiagnosed breech, was profoundly hypothermic on admission and had a very low plasma fibrinogen level (21 mg/100 ml) with FDP in high titre (1 in 64) and an increased thrombin ratio (2.6). The initial platelet count of $335 \times 10^3/\text{mm}^3$ had fallen to $251 \times 10^3/\text{mm}^3$ by the age of 10 hours but the Thrombotest and thromboplastin generation screening test were not grossly abnormal.

Necropsy findings on the 4 infants who died are detailed in Table III. The lesions were compatible with severe asphyxia and Case 9 had a tentorial tear and fractured humerus resulting from birth trauma. Intravascular fibrin thrombi were found in the liver and adrenals in Cases 8 and 9.

Discussion

In this series of 9 babies who suffered severe birth asphyxia necessitating positive pressure ventilation for at least 10 minutes there was laboratory evidence of disordered haemostasis in 4, of whom 2 died, but none showed a clinically detectable bleeding tendency. If this series is typical of birth asphyxiated babies in general, haemostatic failure is unlikely to be a problem in the majority of such cases.

In 3 of the babies with abnormal laboratory findings (Cases 5, 8, and 9), there was evidence that a disturbance of haemostasis had occurred as a consequence of disseminated intravascular coagulation. Fibrin degradation products were detected in all 3 infants and were present with low plasma fibrinogen levels in 2, and in association with mild thrombocytopenia or a sharply rising platelet count in one case each. Confirmation of this diagnosis was provided by the presence of fibrin thromboemboli in the sinusoids of liver and adrenals at necropsy in the 2 babies who died. In all 3 infants the maximum disturbance was present in the first few hours of life. As platelet counts in these infants were always above $100 \times 10^3/\text{mm}^3$ they would not be expected to show any bleeding tendency.

One small-for-dates infant (Case 4) had a low level of vitamin K dependent factors at birth, which was corrected by administration of the vitamin. In no case was there evidence of a postnatal drop in vitamin K dependent factors. The policy of early feeding of asphyxiated infants is probably responsible for maintaining the levels (Gellis and Lyon, 1941). The single low level mentioned above may well be related to the baby being small

for dates rather than to birth asphyxia, as we do have evidence of low levels of vitamin K dependent factors in small-for-dates infants.

Our studies indicate that disseminated intravascular coagulation is the most frequent cause of haemostatic abnormality in the asphyxiated infant, and it seems worth looking for common clinical factors in the 3 cases where this had occurred.

All 3 infants were so severely asphyxiated as to require treatment on the mechanical ventilator, 2 of them died, and the third required artificial ventilation for 5 days. Only one other infant required mechanical ventilation. It seems that these infants must have been subjected to more severe hypoxia, and more prolonged acidosis than the rest of the group. Another factor common to the infants with evidence of disseminated intravascular coagulation was the occurrence of hypothermia; all 3 babies had a minimum temperature below 34 °C. Only one other baby in the series had a similarly low temperature.

The combination of ventilator therapy and a body temperature below 34 °C was seen only in the 3 infants with disseminated intravascular coagulation.

We have previously pointed out the association of severe hypothermia with haemostatic failure in the newborn (Chessells and Wigglesworth, 1970).

If acidosis and hypothermia have a synergistic action in causing disseminated intravascular coagulation, the newborn baby with acidosis of any cause who becomes hypothermic may be at particular risk to this form of haemostatic failure. However, as birth asphyxia can impair a baby's ability to maintain its body temperature, the hypothermia in our babies is perhaps only a further measure of the severity of the asphyxial episode.

The precise mechanism by which coagulation is triggered off in these circumstances remains a matter for debate. Stagnation of blood in the peripheral circulation is a possible factor: Gaynor, Bouvier, and Spaet (1968) have suggested as an alternative that anoxic damage to small blood vessels may form a basis for intravascular fibrin deposition.

From the clinical point of view the most important measure available for prevention of disseminated intravascular coagulation may well be to keep newborn babies warm.

Haemostatic failure due to disseminated intravascular coagulation is most likely to be evident within the first few hours after birth, and the possibility should be considered in any sick or premature newborn infant who becomes hypothermic at that time.

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Correspondence to Dr. J. S. Wigglesworth, Department of Child Health, Hammersmith Hospital, Du Cane Road, London W.12.

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