COAGULATION DEFECTS IN OBSTETRICS

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Coagulation defects are only rarely met with in obstetrics. It is probable that the complication is nowadays being diagnosed with increasing frequency, owing mainly to a greater awareness of the condition. In Mulago Hospital where the author practises, it occurred 11 times in about 33,500 deliveries in the period 1964-66. This gives an incidence of about 0.03%. In cases of concealed accidental hæmorrhage the incidence is however higher; it appears to occur in some 5% of cases.

Historical background

The first reported case dates back to 1901 when De Lee (1901) described death in a patient from post partum hæmorrhage as being due to a "Hæmophilia-like phenomenon" which followed concealed accidental hæmorrhage. In 1936 Dieckmann (1936) was the first to suggest that such bleeding might be caused by a marked

decrease in fibrinogen. Maloney *et al.* (1949) reported the first case successfully treated with intravenous fibrinogen and blood transfusion.

The Clotting Mechanism

In blood clotting very many co-ordinated reactions take place by which two recognized end-products are formed: these are *thrombin* and *fibrin*. Thrombin is essentially an enzyme which converts fibrinogen into fibrin.

Figure I shows three distinct steps in the process of coagulation. The first is the making of thromboplastin from the interaction of a platelet factor and several substances found in the plasma — thromboplastinogen complex. The second step is the conversion of prothrombin into thrombin by the action of thromboplastin in the presence of calcium and in some way assisted by other plasma substances. The third step is the formation of fibrin by the action of thrombin on fibrinogen. Fibrinogen itself is a protein of high molecular weight which is synthetized in the liver;

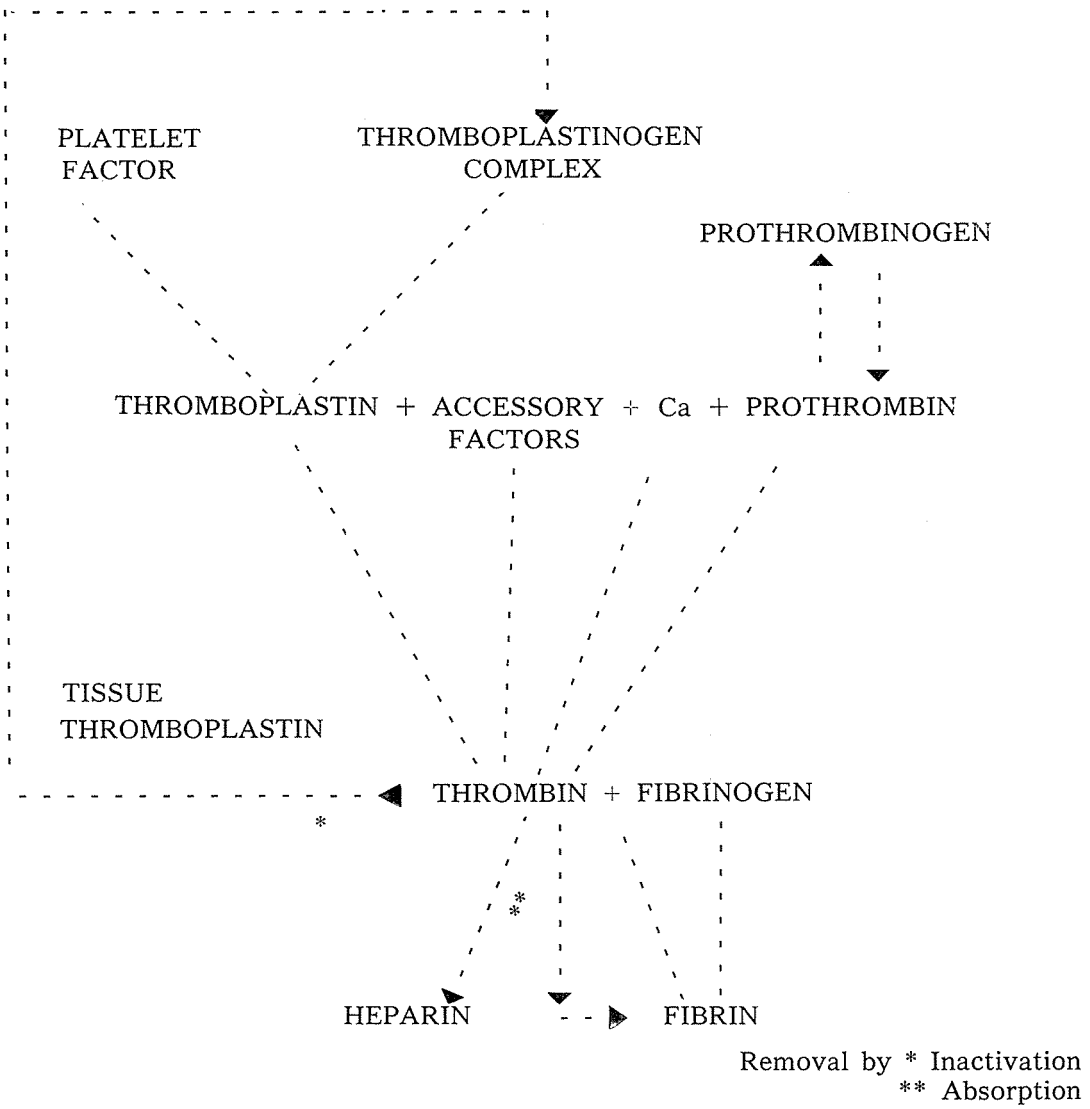

Figure I shows diagrammatically the mechanism of normal clotting.

the normal blood fibrinogen level being 325-400 mg. per 100 ml. It is constantly being converted in small amounts into fibrin all over the body. But this fibrin production, is, again constantly, counteracted by a circulating fibrinolysin. This, coupled with the normal absence of thromboplastins, prevents intravascular clotting.

Mechanism of Production of Hypo or Afibrinogenæmia

The exact methods of production of coagulation defects in various hæmarrhagic states are, even now, not clearly understood. The placenta, decidua and to a lesser extent the liquor amnii, are potent sources of thromboplastins and in abnormal conditions can liberate thromboplastin into the blood stream.

Figure 2 shows that the usual mechanism by which coagulation failure is produced is probably a bi-phasic one as suggested by Schneider (1951). The first phase is one of increased coagulability whereby fibrin is deposited extensively, especially in the pulmonary and hepatic capillary

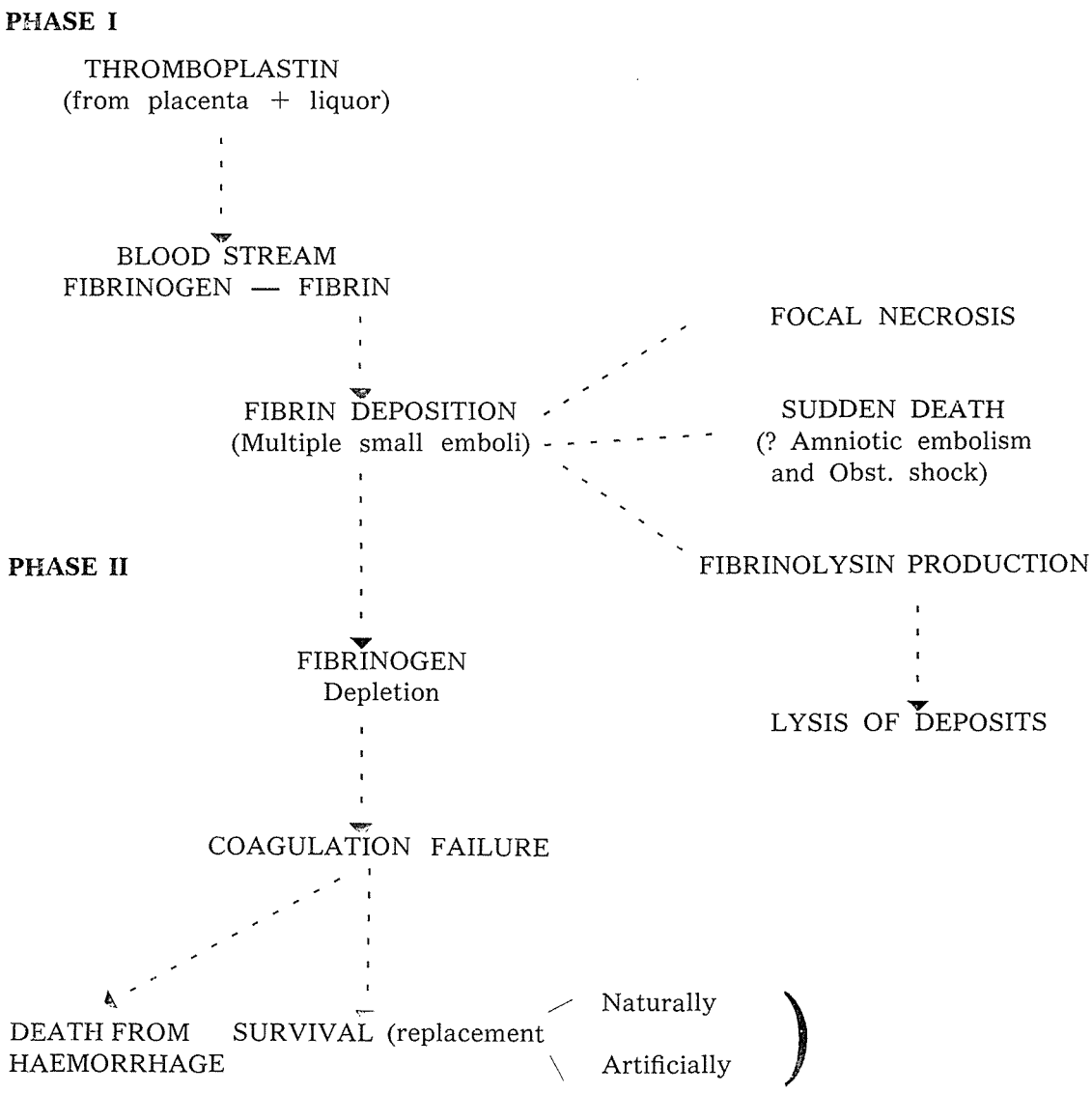

Fig. 2. Diagram to show the mechanism by which coagulation failure is produced.

beds. Progressive defibrinogenation follows, with consequent disruption of the clotting mechanism, but probably the actual mechanism of fibrinogen depletion varies in different patients. So far good evidence has been produced to show that one of three processes can occur:

(a) Excessive intra-uterine fibrinogen utilization;

(b) Intravascular micro-coagulation (Beisher 1961);

(c) Fibrinolysis and fibrinogenolysis (Albrechtseu *et al.* 1955).

There is disagreement as to which of these processes is the primary or most frequent mechanism. The argument is however no longer academic since potent therapeutic agents are now available which can correct or inhibit coagulation derangements.

A recent study by Willoughby (1966) suggests that the type of coagulation defect is primarily determined by the precipitating obstetric cause. In most instances it is easier to determine this than to distinguish between the different coagulation disturbances. This is important as it helps towards simplification in the management.

Clinical Conditions Associated with Failure of the Blood to Clot

1. *Concealed Accidental Hœmorrhage*

Abruptio placentæ is the commonest underlying cause of afibrinogenæmia. It has been shown that the fibrinogen deficit in these cases is due to conversion of fibrinogen to fibrin locally in the retroplacenta hæmatoma. There is usually a striking uniform response to fibrinogen administration, with immediate and permanent correction of the circulating fibrinogen levels and the thrombin time. There is hardly ever post-partum hæmorrhage in these cases after giving fibrinogen.

2. *Prolonged Retention of a Macerated Fœtus in Utero*

The incidence of hypofibrinogenæmia in cases of intra-uterine fœtal death of more than 2 weeks duration is quoted as 1-2%. Serial fibrinogen studies often demonstrate a significant fibrinogen depression that is not clinically apparent. When the fœtus is retained for more than 5 weeks the incidence has been quoted to be as high as 25-40%.

It is thought that in these cases the cause of fibrinogen deficiency is intravascular micro-coagulation with no evidence of fibrinogenolysis contributing to the coagulation defect. Experiments have shown that the fibrinogen level and thrombin time are not corrected by giving fibrinogen infusion when the dead fœtus is still in utero.

It is of interest that the onset of this type of hypofibrinogenæmia is of a quite different time-sequence from that of abruptio placentæ, the fibrinogen falling slowly and steadily over a period of 5 or more weeks. The reason for this delayed onset is possibly due to the more gradual absorption of liquor.

When the diagnosis of intra-uterine death is confirmed the patient should be followed each week with serial fibrinogen estimation. Labour should be induced by Pitocin drip. A more recent method is that of intra-uterine injection of hypertonic saline after withdrawing 200-300 mls. of liquor amnii,but 2 or 3 cases of maternal deaths have been reported from this method. Artificial rupture of the membranes in an effort to induce labour is condemned when a dead fœtus is present because of the risk of gas grangrene.

3. *Amniotic Fluid Embolism*

This can sometimes occur in a labour of sudden onset and rapid course. Labour in such cases may be followed by severe post-partum hæmorrhage due to hypofibrinogenæmia. It is highly probable that deficiency of fibrinogen is here caused by fibrinogenolysis due to a hyperplasminæmic state precipitated by infusion of amniotic fluid. The same mechanism has been reported in ruptured uterus and septic induced abortion.

These cases are usually fatal since there is hardly any time to institute treatment. Skjodt (1965) reported a success-

fully treated case by giving 2.5 g. Epsilon Amino-caproic acid (E.A.C.A.) and 12 g. of Fibrinogen.

4. Placenta Prævia

There is no obvious reason why hypofibrinogenæmia should not occur with placenta prævia. The low incidence could be due to the fact that routine laboratory investigations of coagulation defences are not always requested. On the other hand, the free escape of blood draws attention to the placenta prævia and demands urgent treatment.

5. The Use of Macromolecular Solutions

Solutions such as dextran may in themselves cause a coagulation failure. There is strong evidence to suggest that they may increase hypofibrinogenæmia should it be present. Scott (1955) suggests that they act by both simple dilution of the already lowered fibrinogen level and also by encouraging precipitation of fibrinogen as fibrin.

Analysis of Cases at Mulago Hospital

Associated Obstetric Abnormality

Accidental hæmorrhage	7
Placenta Prævia	1
Precipitate labour	1
Retained placenta + P.P.H.	1
P.P.H.	1
I.U.D.	—

Mortality

Mother		*Infant*	
Alive	6	Alive	4
Dead	5	S.B.	6
		N.N.D.	1
Parity		*Age*	
Primigravida	1	14—18	1
Gravide 1	—	19—23	—
,, 2	—	24—28	3
,, 3	1	29—33	4
,, 4	1	34—38	1
,, 5	—	38+	—
,, 5+	5	Unknown	2
Unknown	3		

Diagnosis

This is primarily clinical and consists in verifying the suspicion that a clotting defect is present when uterine or other bleeding persists. In such cases it may be noticed that the blood is not coagulating.

A minimal scheme of investigations should be performed bearing in mind that a case is usually one of considerable urgency and may occur at times when full laboratory facilities are not available. A practical list of investigations is that suggested by Willoughby (1966). *(Table 1).*

Treatment

A. Preventive

Since severe accidental hæmorrhage provides the greater number of cases of hypofibrinogenæmia attention is mostly focused on this.

Table I showing minimal scheme of investigation.

Before Treatment	*Immediately after giving Fibrinogen before Obst. Abn. resolved*	*Subsequently, before or after Obst. Abn. resolved*
Thrombin Time	Thrombin Time	Thrombin Time
Thrombin Time (control)	—	—
Fibrinogen Estimation	Fibrinogen Estimation	Fibrinogen Estimation
Test for Active Clot Lysis	Test for Active Clot Lysis	Test for Active Clot Lysis
Platelet Count	—	—

1. Early rupture of membranes — this lowers the intra-uterine pressure, thus minimising the chance of absorption of thromboplastins into the maternal circulation.

2. Effecting delivery as soon as possible — this not only stops the absorption of thromboplastins but also removes the precipitating factor, and thus allows the blood fibrinogen to return to normal spontaneously. Pitocin should only be used if labour does not start within a reasonable interval of rupturing the membranes.

3. Induction of labour in cases of intra-uterine fœtal death if the fœtus is retained for more than 2-3 weeks or earlier if the fibrinogen estimation warrants it.

4. Avoiding the use of dextran or other macromolecular solutions.

B. Curative

Early recognition of the disorder is important. All cases of antepartum hœmorrhage and intra-uterine fœtal death should be investigated. Treatment consists mainly in:

1. Maintaining an effective blood volume through the administration of fresh blood transfusions in sufficient number to replace blood loss.

2. Administration of fibrinogen only when it is really needed. It is expensive and can cause viral hepatitis. Two grams of fibrinogen should be administered and the clotting test repeated. If clotting remains inadequate, another 2 grams of fibrinogen should be administered. In most cases, 4 gms. of fibrinogen should be sufficent to elevate the blood fibrinogen to a therapeutic level.

In cases where fibrinolysis or fibrinogenolysis is suspected fibrinolytic inhibitors such as Epsilon-amino-caproic acid should be given at the same time as fibrinogen. Epsilon-amino-caproic acid is a 6-amino-hexanoic acid. It is administered intravenously, starting with 4 gms. in the first half hour and then 1 gm. per hour for at least 12 hours.

In cases with intra-vascular coagulation the use of Heparin may be considered. This will stop intra-vascular coagulation and at the same time inhibit additional depletion of fibrinogen. However, as most coagulation defects in obstetrics may be treated by fibrinogen alone, Heparin is rarely indicated. It's use is permissible in special cases and only when its effects can be monitored by special laboratory tests. When used, Heparin may be readily antagonized by Protamine Sulphate if bleeding is found to increase.

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