HYPOFIBRINOGENAEMIA IN OBSTETRICS

BY

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Introduction.

For long it has been known that women suffering from antepartum haemorrhage, no matter whether it be unavoidable or accidental, sometimes die from postpartum haemorrhage. The standard explanation of this has been failure of the uterus to retract during and after the third stage. This probably is true for placenta praevia but, in regard to concealed accidental haemorrhage, there is some doubt. At least very few obstetricians (and these do not include us) have seen a uterus so damaged by extravasated blood that it failed completely to contract during and after labour, and there is now another more acceptable explanation of postpartum haemorrhage in these cases.

In 1901, De Lee called attention to a case of abruptio placentae in which the circulating blood lost its power to coagulate. This observation passed relatively unnoticed, and remained so even when Dieckman described the condition again in 1936 and went so far as to suggest that the coagulation failure was the result of lowering of the fibrinogen level in the blood, a suggestion confirmed by Weiner et al and by Schneider. Indeed, there were few cases described, if seen, until the last 5 years when a spate of articles on the subject, and accounts of many fatal and near fatal cases have appeared in the literature.

Sir Arcot Mudaliar lecture presented by T.N.A. Jeffcoate at the University of Madras, August 1955.

Clinical Features.

The typical picture of coagulation failure is seen in concealed accidental haemorrhage. In this the patient first presents in a state of shock, shock out of proportion to the blood loss, shock characterised by cyanosis. Assuming the shock is not fatal, labour usually supervenes and, once the delivery of the foetus and placenta is complete, the general condition improves. In the meantime, however, the delivery of the placenta is followed by persistent or recurrent uterine haemorrhage from a reasonably well retracted uterus. Any tears also bleed. These bleedings persist despite oxytocic drugs, uterine packing, uterine compression and other measures. Indeed, after a time uterine retraction fails and the haemorrhage

becomes more severe. If, in desperation, the obstetrician resorts to heroic measures such as hysterectomy, bleeding occurs from all suture lines. If the patient is kept alive by adequate blood transfusion, the condition passes off after several hours when the blood commences to coagulate again. If the patient dies, postmortem examination reveals that the circulating blood is incoagulable and, in keeping with this, there is extravasation of blood into the uterus, sub peritoneally, and into various viscera.

The condition can be further illustrated by two less typical cases selected from 7 which we have seen in recent years.

1. H. R. Aged 38. Gravida 9. This patient was admitted suffering from moderately severe concealed and revealed accidental antepartum haemorrhage at the 32nd week of the 9th pregnancy. The degree of shock was not gross and, soon after admission, she rapidly and easily delivered a still-born premature child. The amount of revealed bleeding during labour was estimated at 20 ozs., and 16 ozs. of clot was delivered with the placenta. When the third stage of labour was complete, and despite the administration of oxytocics intravenously and intramuscularly, there was a steady trickle of blood from the uterus which soon began to relax intermittently. Bleeding continued on and off for 5 hours during which time 3 pints of plasma substitute ("Dextran") and 7 pints of blood were transfused. At the end of 5 hours, bleeding gradually ceased and the patient recovered.

2. F. D. Aged 43. Gravida 8. Blood group A. Rh. -ve. and Rh. antibodies present The 5th and the 6th children had been lost as a result of erythroblastosis. This patient was admitted in labour at term and there was no evidence of toxaemia or antepartum haemorrhage. Rupture of the membranes revealed yellow brown liquor. After 16 hours in the first stage and 1 hour in the second stage of labour, the patient became distressed and flushed so low forceps delivery was carried out under local analgesia. Foetal ascites caused difficulty in delivering the trunk and the foetus was stillborn as the result of erythroblastosis. Ergometrine 0.5 mgms. was given intravenously at the end of the second stage of labour and oxytocin 5 units was given intramuscularly immediately after delivery of the placenta. All went well until 15 minutes after the end of the third stage when the patient complained of pain in the chest and her respirations became laboured. Soon after, bleeding occurred from the uterus although it remained well retracted. The ensuing state of collapse was treated by means of morphine and an intravenous drip infusion, first of 3 pints of Dextran and then of 2 pints of cross matched blood. At the end of 2 hours bleeding continued and was made worse by uterine relaxation. It was not controlled even by intrauterine packing and the woman died three hours after delivery. Postmortem examination revealed incoagulable blood and haemorrhagic extravasations in the uterine wall, in the pelvic cellular tissue, sub-peritoneally, in the liver and various organs.

Conditions in which Clotting Failure Occurs.

The last case emphasizes that coagulation failure can occur in conditions other than accidental antepartum haemorrhage although this is the disease in which it is most common. It has now been described as a complication of:—

Obstetric conditions.	Accidental antepartum haemorrhage.
	Intrauterine death of the foetus.
	Amniotic embolism.
	Abortion and hydatidiform mole.
	Paravaginal and vulval haematoma.

Non-obstetric conditions.	Operations on the lung. Acute pancreatitis. Chronic wasting diseases. Hepatic diseases. Acute infections. Inherent defect in the blood.

This second group need not concern us here; suffice it to say that in each one hypofibrinogenaemia can be explained on the basis of failure of the liver to produce fibrinogen or on a mechanism similar to that to be described for antepartum haemorrhage.

Mechanism of Coagulation Failure.

A blood clot consists essentially of a network of fibrin which is formed from normally circulating fibrinogen. This change occurs under the influence of thrombin which is in turn formed from prothrombin, a normal constituent of blood. The conversion of prothrombin requires thromboplastin (thrombokinase) acting in the presence of calcium. Thromboplastin is derived from blood platelets and various tissues when damaged. The process can be represented by the traditional equations:

Prothrombin+Ca+Thromboplastin =Thrombin;

Thrombin+Fibrinogen=Fibrin.

This description is an over simplification of a more elaborate process in which other factors are concerned—particularly in the formation of thromboplastin. It is, nevertheless, essentially true and is adequate for our purpose.

Failure of the blood to coagulate as in the cases described above is proved to be associated with a deficiency of fibrinogen in the blood (Dieckman, Weiner et al, Schneider). The reason for this deficiency remains, however, a matter of theories of which the two most popular are·

1. The mechanism suggested by Schneider and illustrated diagramatically in Fig. 1 is biphasic. An initial state of increased coagulability (Phase I) is induced by the release of thromboplastic material into the maternal circulation from the placental site or as liquor amnii. This leads to precipitation of fibrinogen as fibrin which is deposited as multiple tiny emboli in the pulmonary and other capillary beds. In certain circumstances the plugging of the blood vessels may lead to focal necrosis in various organs (McKay et al) and, if the lungs are extensively involved, can cause sudden death. Deposition of fibrin leads to depletion of circulating fibrinogen (Phase II) and, if sufficiently severe, results in failure of blood clotting. In non-fatal cases the fibrinogen is replaced by its manufacture in the liver, but this may take 12 to 24 hours (Feeney).

This concept is supported by experiments in animals in which injection of thrombokinase produces a similar haemorrhagic state (Schneider Hartman, Conley and Krevans and others). One of the difficulties about accepting it is that in only a small number of human cases have fibrin emboli been demonstrated histologically. This, however, may be explained by antemortem and postmortem fibrinolysis (see later).

Enthusiasts for this theory even argue that necrosis occurring in the anterior pituitary and in the renal cortex as a complication of accidental

antepartum haemorrhage with shock is caused by fibrin embolism. This, however, is unlikely for many reasons set out in detail by Moore. Cortical necrosis of the kidneys at least is the result of vasospasm associated with severe shock.

A variant of this theory sponsored by Feeney suggests that the fibrin deposit may be confined almost entirely to the uterine wall but this is not generally accepted.

2. A view put forward by Weiner et al is that the disappearance of fibrinogen from the blood is caused by fibrinogenolysis. The blood normally contains a globulin fraction (plasminogen) which, under conditions of shock, tissue injury and the like, can become activated by fibrokinase to form an enzyme (plasmin or fibrinolysin) which destroys fibrin and prevents fibrinogen from being converted to fibrin. Ordinarily a certain amount of fibrinolysis is physiological in that it promotes the resolution of inflammatory processes and the results of tissue damage. According to this theory, an exaggeration of this normal protective function becomes pathological to the extent of destroying or inactivating fibrinogen.

There is abundant evidence that both fibrinolysin and fibrinogenolysins are often produced at some stage in the condition of hypofibrinogenaemia as it occurs in obstetrics, but the finding is not constant so this mechanism is not generally accepted as the primary or the essential one concerned. Nevertheless it may well play a secondary part in the process and proteolysis possibly has an important practical bearing on the problem, for instability of a blood clot will contribute to haemorrhage and difficulty in controlling it. Antemortem and postmortem fibrinolysis may also explain why the fibrin emboli described in the first mechanism are fleeting and difficult to demonstrate.

Implications of the Hypofibrinogenaemia Mechanism.

The recognition of the occurrence of hypofibrinogenaemia and the foregoing comments on the mechanism of its production have immediate practical implications.

1. *Accidental Antepartum Haemorrhage.*

In this condition it is established that the fall in the fibrinogen level does not occur *before* the retroplacental haemorrhage and therefore it does not cause it. It is an immediate result of the injury to the placenta and to the opening up of maternal vessels. Although it does not account for the chorio-decidual haemorrhage it may well explain the secondary haemorrhages, those in the uterine wall (Couvelaire uterus), in the broad ligament, outside the peritoneum as well as those in other organs such as the brain and liver.

These internal haemorrhages probably do not require such a serious lowering of the fibrinogen level as is necessary to produce obvious external bleeding. The level of fibrinogen in the blood of normal women in labour at term, according to our observations, averages 0.45 *G.* per cent (range 0.35 *G.*—0.55 *G.*), but this can be reduced to as low as 0.1 *G.* per cent in cases of abruptio placentae without the patient showing *external* clinical evidence of coagulation failure. The critical level at which

coagulation fails to the extent that uncontrollable uterine haemorrhage is liable to occur is between 0.07 *G.* and 0.1 *G.* per cent. Even then, it is not inevitable and we have seen women in whom no fibrinogen was demonstrable in the blood who did not suffer postpartum haemorrhage (see later). So far as internal haemorrhages are concerned Feeney says that they are likely when the level reaches 0.15 *G.* per cent or less.

The failure of the uterus to retract which appears to be a late manifestation of hypofibrinogenaemia is not explained but it is possible that it is essential for fatal uterine haemorrhage. For if uterine retraction is good, haemorrhagic states (e.g. purpura) do not usually cause postpartum haemorrhage.

Although fibrin embolism probably does not cause renal cortical and pituitary necrosis, it may explain the cyanosis which accompanies the shock in the early stages of concealed accidental haemorrhage.

The source of the thromboplastin (and possibly of the activator for fibrinolysis) is the placenta and the damaged tissues behind it. So long as the placenta is in the uterus the patient is therefore not safe. This is in conformity with long established clinical observations.

2. *Abortion, Hydatidiform Mole*

In these conditions it is again the placenta which is the source of the noxious agent and the situation is similar to that in accidental antepartum haemorrhage.

3. *Intra-uterine Death of the Foetus*

Here again it is presumably the degenerating placenta which liberates thromboplastin.

4. *Amniotic Embolism*

The amniotic fluid is rich in thromboplastin so amniotic embolism can produce a clinical picture of either Stage I or II of the hypofibrinogenaemia mechanism.

5. *Vaginal and Vulval Haematoma*

Here again there is widespread tissue damage and opening up of blood channels with opportunity for the entry of thromboplastin and fibrolysins into the circulation.

Frequency of Hypofibrinogenaemia in Abruptio Placentae

Several workers have now studied the blood in cases of accidental antepartum haemorrhage and, according to laboratory findings, hypofibrinogenaemia is a common complication. Thus Feeney found a clotting defect in 2 out of 50 cases of "toxic" accidental haemorrhage. We recently studied 20 consecutive cases of severe and moderate accidental antepartum haemorrhage with the following results:—

No haematological or clinical evidence of coagulation defect	12 cases
(Placental separation was sufficient to kill the foetus in 7 of these cases)	
Clinical evidence of coagulation failure	2 cases
Afibrinogenaemia without postpartum haemorrhage	2 cases
Haematological evidence of hypofibrinogenaemia but no postpartum haemorrhage	4 cases

It is probably fair to say that if blood studies are made, significant lowering of the fibrinogen content is demonstrable in not less than 30 per cent cases of concealed accidental haemorrhage yet clinical evidence of coagulation failure by way of postpartum haemorrhage is not common. In attempting to assess its incidence, old hospital records are of little value except in regard to fatal cases. In this respect the findings at the Liverpool Maternity Hospital for the years 1932—1951 are of interest. During the 20 years 44,920 women were delivered or died undelivered and there were 730 cases of accidental antepartum haemorrhage, 21 being fatal. The causes of death were as follows:—

Shock	11
(all of these cases were prior to 1938, before the provision of blood banks)	
Renal cortical necrosis ..	8
Postpartum haemorrhage ..	2
(a) Retained cotyledon of placenta.	
(b) "Traumatic" haemorrhage from cervical tear.	

It will be seen that during those years there was no case of fatal postpartum haemorrhage which could be directly attributed to hypofibrinogenaemia although such a state might have contributed to the bleeding from a deep cervical laceration.

Another piece of evidence comes from Sheehan and Moore who studied 67 *fatal* cases of accidental haemorrhage. Amongst these, severe or moderate postpartum haemorrhage occurred in only 8 and was not necessarily the cause of death. In some of these cases, coagulation failure undoubtedly played a part but it is uncertain in how many (Moore).

One of us (J.S.) also analysed in detail 85,130 deliveries occurring at the Birmingham Maternity Hospital, 1937-53; Queen Charlotte's Hospital, London, 1946-51; Mill Road Maternity Hospital, Liverpool, 1948-54; the Liverpool Maternity Hospital, 1948-54. Eight cases of coagulation failure were discovered, 7 of them serious and 4 fatal. In 5 the condition complicated accidental antepartum haemorrhage. One of the most interesting findings of the enquiry was that only one of the cases occurred prior to 1951, the remainder being encountered during the period 1951-55. This is in keeping with the observation made earlier, that although coagulation failure in association with accidental haemorrhage was described almost 50 years ago, very few cases were recorded until the last 5 years and most of the older obstetricians can only recall isolated cases which, on reflection, might have qualified as hypofibrinogenaemia.

Indeed, such evidence as is available strongly suggests that although hypofibrinogenaemia no doubt occurred in the past it has only become a real clinical problem as a cause of severe postpartum haemorrhage in recent years.

Plasma Substitutes as a Cause of Hypofibrinogenaemia

The immediate conclusion from the above is that the incidence of serious degrees of hypofibrinogenaemia has suddenly increased and the question

arises as to why this should be. In searching for an answer the 7 recent cases mentioned above were studied and it was at once noticeable that 6 of the patients had received an infusion of Dextran, the average amount per case being 3½ pints. Moreover, in one of these cases serial haematological studies revealed a striking deterioration in the quality of the clot formation within a period of 15 minutes during which 1 pint of Dextran was administered. In another of our patients 5 pints of Dextran were given as part of the treatment of atonic postpartum haemorrhage and this appeared to precipitate coagulation failure which had not been present previously. The clotting function in this case was not properly restored until 12 hours later, by which time 6 pints of blood had been transfused.

In the one case when a plasma substitute was not used the coagulation defect was transient and never serious, the situation being quickly controlled when 2 pints of whole blood were transfused.

These observations receive support from the published accounts of other cases. McKay et al described a case in which coagulation failure developed rapidly after the administration of Dextran, the basic coagulation defect being hypofibrinogenaemia, while Soulier et al and Lepage et al described cases which followed the administration of polyvinylpyrrolidone, a similar type of large molecular plasma substitute. Hodgkinson et al in a recent extensive review of coagulation defects in obstetrics also commented on the possible association between the coagulation disorder and the use of "plasma expanders" of the dextran type.

Apart from clinical data such as the above, there is experimental evidence (Ricketts, Fletcher et al, Laurell, Adant, Carbone et al) to support the view that Dextran can exercise an adverse effect on the coagulation mechanism. By itself it may not often be sufficient to result in clinical manifestations of coagulation failure, but, in the patient already suffering from hypofibrinogenaemia (as are approximately 30 per cent of patients with moderate or severe accidental antepartum haemorrhage) it can tip the scales, converting a subclinical blood change into a state of uncontrollable bleeding.

Dextran exerts this effect (a) by simple dilution of the already decreased fibrinogen content and (b) by encouraging precipitation of fibrinogen as fibrin or by forming a fibrinogen-dextran compound and thus acting as a contributory factor to Phase I of the coagulation disorder (Fig. 1). The second effect is possibly not operative in all cases, its occurrence depending on (a) the relative concentrations of Dextran and fibrinogen and (b) the molecular weight of the Dextran employed.

In view of these considerations it would appear that Dextran or similar

Dextran is a complex polysaccharide of large and variable molecular size. Commercial preparations vary but in the one used in most of these cases 63 per cent of the molecules fell within the weight range of 130,000—250,000. It was administered as a 6 per cent solution in normal saline. This and similar macro-molecular substitutes for plasma have only been in general use since 1950 or 1951.

preparations should never be used in any condition in which hypofibrinogenaemia may occur, and never, in any circumstances, in amounts exceeding 2 pints.

The Recognition of Hypofibrinogenaemia

The persistent escape of incoagulable blood from the placental site or from obstetrical and surgical wounds, provides obvious clinical evidence of the final stage of the blood disturbance. It is clearly desirable, however, to have means of recognising fibrinogen depletion before it reaches a dangerous level, especially as we have evidence that such a level can be present for some time before frank haemorrhage develops.

In the course of our investigations the fibrinogen content of blood was estimated by the method described by Biggs and Macfarlane using the micro-Kjeldahl distillation apparatus. This method takes several hours so it is obviously of little practical value. Other less accurate methods such as serial dilution clotting (Schneider); clot observation (Weiner) and micro-electrophoresis (Barnett and Cussen) are described but none of these are sufficiently rapid, nor can they be easily performed at the bed side.

A modified form of the test recently described in the advertisement of "Fibrindex" (Ortho Pharmaceutical) is, on the other hand, an eminently practical, if rough, method for assaying fibrinogen in the delivery room. To 0.2 ml. of citrated blood in a small test tube is added 0.2 ml. of thrombin solution, freshly prepared by dissolving 50 N.I.H. units of dried thrombin in 1.0 ml. of saline, both these being obtainable in ampoules. If the fibrinogen level is normal, clotting is evident within 5-10 seconds and the clot is firm and stable at 60 seconds. Thereafter it contracts with the extrusion of serum. Delay of the initial clotting beyond 15-20 seconds and liquefaction or disintegration of most of the clot at 60 seconds indicate that the fibrinogen level is considerably reduced while absence of clot formation during 60 seconds is evidence of afibrinogenaemia. The interpretation of the test is greatly facilitated for the occasional user by setting up a control tube with blood from a normal patient; the amount of thrombin solution prepared allows for this. The great advantage of this method is that a result is obtained within one minute and this can be vital in certain circumstances. Fig. II gives a photographic illustration of a series of tests performed by this method in a case of accidental antepartum haemorrhage.

The Treatment of Hypofibrinogenaemia

I. *Prevention*

This is here considered in relation to the treatment of accidental antepartum haemorrhage in which the fibrinogen level is reduced to a significant degree in 30 to 40 per cent of moderate and severe cases. The main object is to prevent further lowering and to avoid hypofibrinogenaemia becoming afibrinogenaemia.

1. *Artificial Rupture of the Membranes*

This should be done as a matter of urgency in all cases of antepartum

haemorrhage for it reduces intrauterine pressure and limits the entry of thromboplastin into the circulation. It can be demonstrated by blood studies that rupture of the membranes has an almost immediate good effect on coagulation. It moreover brings on and quickens labour and helps to control the amount of retroplacental bleeding. The old fear that the uterus may fail to retract and thus allow more bleeding is ill founded.

2. *Rapid Emptying of the Uterus*

One of the objects of rupturing the membranes is to ensure rapid delivery of the placenta. Oxytocin is often given in these cases and there are arguments for and against. It is advantageous in that it quickens delivery; it is disadvantageous in that by raising intrauterine pressure it may drive thromboplastin into the circulation. If the uterus is not contracting well the advantage generally outweighs the disadvantage.

Caesarean section has the merit of ensuring even more rapid delivery and, in certain cases, it may save the life of the baby. If coagulation failure is already present however, it is dangerous as is any operation. Caesarean hysterectomy is probably never necessary.

3. *Resuscitation.* When the patient is shocked and the condition calls for intravenous fluids the important consideration is *never* to administer an artificial blood substitute of the polysaccharide type. Whole blood or plasma are essential if the fibrinogen level is not to be reduced further. The amount of blood to be given depends on the amount of blood loss, a matter difficult to estimate when some of it occurs into tissue spaces.

II. *Curative*

If coagulation failure does develop, or if blood studies indicate that it is likely, fibrinogen replacement is urgently indicated. The transfusion of whole blood will contribute a little (0.4 *G.* per cent) if the blood is fresh and 0.3 *G.* per cent if it is stored 7-14 days. The ideal is to administer intravenously the fibrinogen fraction isolated from human plasma (Weiner et al, Reid et al) in a dose of up to 8-12 *G.* although there is no need to give more than is required to render the blood coagulable. Fibrinogen preparations, however, are difficult to obtain and they are not really necessary if dried plasma is available. This retains a high fibrinogen content even if stored for as long as 3 years and, if it is reconstituted to *double strength*, it provides a solution containing approximately 0.7 *G.* per cent of fibrinogen. One or two pints of this is sufficient to enable the patient to survive the crisis in the majority of cases. Indeed, it appears doubtful if there is any advantage in using isolated fibrinogen because it carries the same hepatitis risk as does plasma* and the latter may in addition contribute other coagulation factors.

If, in the meantime, active bleeding takes place after the delivery is complete it should be controlled as far as possible by the standard remedies. Hysterectomy, so often advised, is contraindicated. It cannot help

* The risk of hepatitis when "small pool" plasma is used is no greater than when whole blood is transfused (Lehane et al).

and it only provides further sources of bleeding from all the lines of incision and suture.

Conclusion

From the evidence it is difficult not to conclude that the problem of severe hypofibrinogenaemia and of persistent postpartum haemorrhage complicating abruptio placentae which has come to the forefront in recent years is to some extent one of our own making. Nevertheless, good may come of it for it has resulted in the partial if not complete elucidation of a phenomenon previously unrecognised, and which can only be recognised often by blood coagulation studies. If these are done, however, in all cases of antepartum haemorrhage, and if hypofibrinogenaemia is immediately corrected, it may be possible to limit the extent of the common internal extravasations as well as to prevent the more obvious external haemorrhages.

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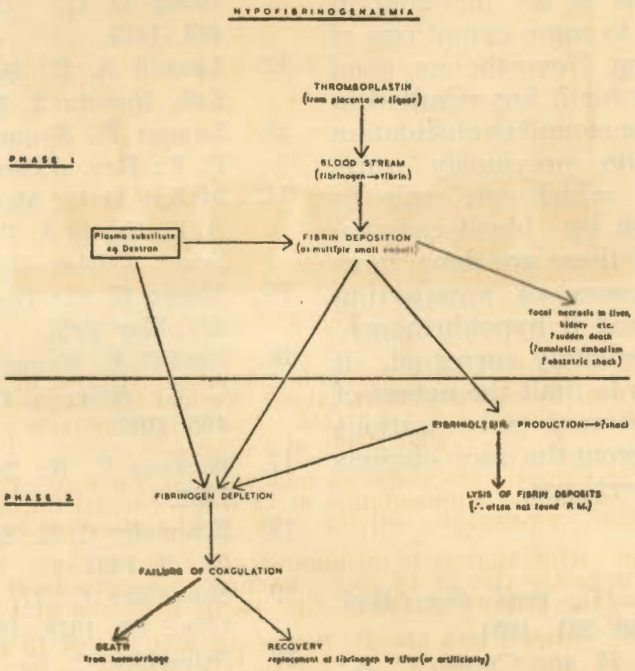

Fig. 1

Two Phase Mechanism of hypofibrinogenaemia as suggested by Schneider, also showing how artificial plasma substitutes may make the condition worse.

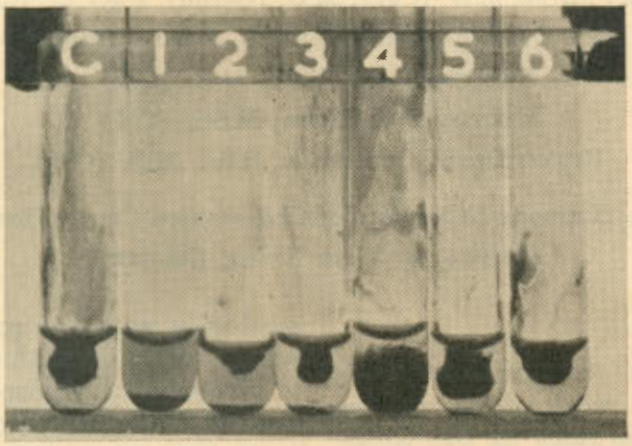

Fig. 2

Rapid fibrinogen assay by adding thrombin solution to citrated blood (see text).
C. Control Tube. Normal patient in labour. Normal clot formed in 7 secs. (Actual fibrinogen level = 0.35G.%. Fibrinolytic activity = Nil). Clot stable at 1 hour.

1. Case of abruptio placentae on admission at 7.0 a.m. Poor clot with much serum and sedimentation in 15 secs. (Actual fibrinogen level = 0.175G.%. Fibrinolytic activity = 79%). Clot dissolved in 1 hour.
2. 8.0 a.m. After rupture of membranes and ½ pint plasma. Poor although slightly better clot at 15 secs. (Actual fibrinogen level = 0.237G.%. Fibrinolytic activity = 13%). Clot partly dissolved at 1 hour.
3. 9.0 a.m. After ½ pint blood. Better clot and this at 10 secs. (Actual fibrinogen level = 0.237G.%. Fibrinolytic activity = 26%). Clot fairly stable.
4. 10.0 a.m. After ½ pint more blood. Good clot at 10 secs. (Actual fibrinogen level not determined). Clot stable at 1 hour.
5. 11.50 a.m. After 1 more pint blood. Baby just delivered. Normal clot at 10 secs. (Actual fibrinogen level — 0.306G.%. Fibrinolytic activity = 14%). Clot stable at 1 hour.
6. 2.0 p.m. Patient in good condition, no haemorrhage. Normal clot at 10 secs. (Actual fibrinogen level = 0.237G.%. Fibrinolytic activity = 8%). Clot stable at 1 hour.