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HYPOFIBRINOGENAEMIA

WITH SPECIAL REFERENCE TO SEVERE CONCEALED ACCIDENTAL HAEMORRHAGE

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One of the few major advances in the practice of obstetrics in the last decade has been the discovery of coagulation defects in pregnancy associated mainly with a reduction or lack of fibrinogen in the plasma.

As long ago as 1769 Morgani noticed that blood sometimes failed to clot at necropsy, and Hunter in 1794 observed that blood was deprived of its powers of coagulation in cases of sudden death. Early in the present century Blair Bell[1] found that menstrual blood contained neither fibrin ferment nor fibrinogen, but it was only in 1936 that Dieckmann[2] first indicated the true nature of the coagulation defect in association with abruptio placentae. Since then a similar coagulation defect has been described in many different circumstances.

In obstetric practice this hypofibrinogenaemia is most commonly associated with severe forms of accidental haemorrhage, less commonly following an intra-uterine foetal death of some standing, and rarely with amniotic-fluid embolism.

It has also been described following incompatible blood transfusions,[3] and ruptured uterus.[4] Recently Beischer[5] has described the condition occurring after apparently normal deliveries, and Winch and Bryans[6] have described one case associated with a retained intra-abdominal placenta after removal of an extra-uterine pregnancy.

Whilst it is not the purpose of this paper to discuss the exact mechanisms of the mode of production of this hypofibrinogenaemia, it is worth mentioning that three main theories exist, of which none is entirely satisfactory:

1. A thromboplastin theory, where it is postulated that thromboplastins are absorbed from the liquor amnii and uterine tissues, causing a widespread deposition of fibrin emboli in the vascular bed.
2. A fibrinolysin theory, which postulates the release of fibrinolysins from a damaged uterine muscle which inactivate or dissolve the available circulating fibrinogen.
3. A theory in which it is thought that a large portion of the available fibrinogen is used up at the site of the retroplacental clot, with perhaps a subsequent release of fibrinolysins.

THE PRESENT INVESTIGATION

70 patients with severe accidental haemorrhage (abruptio placentae) were found among 26,478 patients delivered in the Obstetric Unit of the University of Natal at King Edward VIII Hospital between 1 January 1958 and 31 December 1959. Only severe cases of accidental haemorrhage, where there was evidence of shock, intra-uterine death, and acute abdominal tenderness, were included.

Discussion of the Findings

The incidence of severe accidental haemorrhage was higher than described elsewhere in the literature, being no less than 0·3%. Similarly, the incidence of a serious clotting defect among the 70 patients in this series was high, being 62% (43 cases).

Naturally, the incidence of hypofibrinogenaemia associated with accidental haemorrhage will vary according to the criteria used in its diagnosis. Thus Barry *et al.*[7] in Dublin stated that 'the clotting defect is to be found in the majority of, if not all, cases of combined and concealed haemorrhages', whereas Beischer[5] found a clotting defect in 3·5% of patients with accidental haemorrhages, and Porter[8] an incidence of 42%.

Of our 46 cases of hypofibrinogenaemia, 44 were associated with abruptio placentae. One was associated with an intra-uterine death at 30-weeks period of gestation, and 1 was associated with a ruptured uterus which developed after a Caesarean hysterectomy had been performed. The incidence of hypofibrinogenaemia per total deliveries was 0·18%, which is 18 times higher than that found by Scott[9] in Liverpool.

Increasing parity appeared to predispose to hypofibrinogenaemia, for there were only 8·9% (4) primigravid, 63% (29) para 1 - 4, and as many as 28·2% (13) grande multiparous (5 or more pregnancies) patients in the present series, whereas the incidence of primiparae, multiparae and grande multiparae in the general run of deliveries was 29%, 56%, and 17% respectively.

Although it is traditional to associate hypertension or pre-eclampsia with abruptio placentae, the association is often impossible to establish in the presence of shock, and in many of our patients the hypertension did not become manifest until after resuscitation of the patient. Eastman[10] is of the opinion that 'with each passing hour abruptio conduces more and more to hypertension and albuminuria'.

It is not surprising, therefore, that the incidence of toxaemia in abruptio placentae is uncertain — being reported for instance by Kimbrough[11] as 8%, and as 66% by Adams.[12] In the present series definite evidence of hypertension with or without superimposed toxaemia was found in but 29% (13 cases), which contributes little to solve 'which is the horse and which is the wagon'.

Barry[7] has suggested that malnutrition and anaemia are important associated factors, and Kwaan *et al.*[13] have shown that an increased fibrolytic activity is associated with cirrhosis of the liver. Certainly in our patients hypoproteinaemia, an inverted albumin/globulin ratio, and

minor liver dysfunction are 'normal' findings, malnutrition being rife; but anaemia *per se* is comparatively rare in the African.

However, their fibrinogen levels are normal and their fibrinolytic activity is lowered during pregnancy.[14] The effect of this liver dysfunction on the clotting mechanism is at present undergoing investigation. These factors may possibly explain the relative frequency of hypofibrinogenaemia in our practice.

An important point lies in the previous history of accidental haemorrhage. Porter[6] found the incidence of abruptio placentae in a subsequent pregnancy was as high as 12% and Fyfe and Grant[16] describe a case of afibrinogenaemia in two successive pregnancies. Only one of our patients had a history of having had a previous antepartum haemorrhage.

A further important consideration is a history of a small antepartum haemorrhage at an earlier stage of the pregnancy. Two of our patients had been discharged following investigation for a small antepartum haemorrhage after placentography had demonstrated a normally situated placenta, only to be readmitted later, having had a severe accidental haemorrhage.

The Diagnosis of Hypofibrinogenaemia

The first prerequisite in the diagnosis of hypofibrinogenaemia is to be aware of its existence and suspect its presence in all patients with severe accidental haemorrhage and all patients with a bleeding tendency, either in pregnancy or immediately after delivery. Even then there may be a considerable delay in diagnosis.

Numerous qualitative and quantitative tests have been described in the investigation of the bleeding tendency. We have found Weiner's clot-observation test the most useful, and this is carried out as a routine in every patient with antepartum haemorrhage. This test has the advantage of simplicity and rapidity. However, Sharp *et al.*[16] consider that tests based on the reactivity of plasma to purified thrombin are the most reliable.

In every patient where a clinical possibility of a clotting defect existed or was suspected on the clot-observation test, a routine quantitative estimation of the fibrinogen level was performed, using the method described by Stirland in 1956.[17] Where doubt remained reliance was primarily placed on the bedside tests. A modified Schneider test was also performed in equivocal cases. These tests were repeated hourly, as necessary, during the treatment of the patient. Where error in diagnosis occurred, it resulted from failing to perform the tests rather than from any inaccuracy in the results.

Tests for a heparin-like factor and circulating fibrinolysins (other than the clot-observation test) have not been performed as a routine up to the present.

Treatment

The treatment of hypofibrinogenaemia varies greatly from centre to centre. We have found the following routine to give the most satisfactory results:

In the vast majority of patients with severe accidental haemorrhages of sudden onset we have found that there are at least 2 - 3 pints of retroplacental blood clot. We believe, therefore, that 2 - 3 pints of blood can be transfused rapidly in these cases with safety, to restore the blood volume and thus prevent the danger of renal arteriolar spasm with subsequent renal damage. Calcium gluconate is given with the blood as required, to counteract possible citrate effects.

The slow pulse often found, even in patients with severe accidental haemorrhage, tends to give the unwary a false sense of security, whereas these patients should nevertheless be treated along the routine lines. If hypovolaemia is not corrected, then a further small haemorrhage may easily precipitate a state of profound shock.

Additional defects in other sections of the clotting mechanism may also assume dominant rôles in recalcitrant cases, and 'fresh' blood, while not containing more fibrinogen than stored blood, may be beneficial.

At the same time as the blood volume is being restored, fibrinogen is replaced as required, either in the form of triple-strength plasma containing about 3 G. per unit, or as purified human fibrinogen. Of the two, our recent preference is for the purified fibrinogen since it requires less volume, weight for weight, and the fibrinogen content is more accurately known. Jeffcoate and Scott[18] have suggested that plasma may be more effective than fibrinogen. However, this has not been our experience; indeed, we are opposed to it since we have observed a tendency to hypervolaemia and subsequent pulmonary oedema with its use.

The hypovolaemia and the clotting defect should be corrected simultaneously, lest by raising the blood pressure without controlling the coagulation defect, further and possibly fatal haemorrhage may be precipitated.

We have found that certain patients require very large amounts of fibrinogen to restore the clotting mechanism to normal. In such patients intravenous cortisone may be helpful, according to Moore,[5] in order to speed the combination of plasmin (fibrinolysin) with an anti-plasmin, thus reducing fibrinolytic activity which may be increased in the presence of profound shock.

Our experience agrees with the leading article in the *British Medical Journal*[19] that defibrination is usually 'a once for all mechanism', but if the interval between the onset of haemorrhage and the delivery becomes prolonged, particularly in African patients, a recurrence of the clotting defect often occurs.

We have never found any evidence of an intravascular fibrin deposition of sufficient magnitude to produce any signs either during the delivery or in the puerperium, and so have not considered the use of heparin.

The amount of fibrinogen used depends on the progress of the clotting defect. Barnett and Cussen[20] have found very small doses of fibrinogen to be effective in some patients, but others give 4 - 8 G. empirically. We have found anything less than an initial dose of 3 G. inadequate in the type of patient under consideration.

Once the hypovolaemia and clotting defect have been corrected, then, and only then, is an effort made to expedite delivery, which is done by artificially rupturing the membranes. Immediate rupture of the membranes, as advocated by some authorities, is dangerous in serious cases.

If, one hour after rupture of the membranes, the patient shows no signs of going into labour, despite the presence of a cervix which is not too unfavourable, a pitocin infu-

sion of 1 part in 2,500 is given to stimulate labour. In the majority of patients these measures result in a rapid onset of labour. If, after 4 hours on a pitocin drip, labour is not well established and making good progress, the pregnancy is usually terminated by lower-segment Caesarean section, after again checking that the blood defect has remained corrected.

There are of course dangers in the use of pitocin and cases of high multiparity should be excluded. The theoretical danger of increasing the incidence of anuria has not been borne out in our series.

Obstetrical complications, such as malpresentation and cephalopelvic disproportion, are treated on their merits with early recourse to Caesarean section if there are signs of a difficult delivery ahead. Caesarean section is also performed in patients where there is evidence of a recurrence of the clotting defect, after again correcting this defect.

The one patient in whom intra-uterine death was associated with hypofibrinogenaemia was treated conservatively in this series by awaiting the spontaneous onset of labour and then rapidly correcting the coagulation defect. If, however, the bleeding tendency causes serious symptoms, then there may be a place for Caesarean section after correction of the clotting defect.

One of the practical difficulties in the management of these patients is the correlation of the clinical state, the serial investigations, and the progress being made, with the treatment given. To facilitate the management of these patients we have modified the 'flow sheet' (Caillouette *et al.*[21]) so that all necessary information is readily available.

The results obtained in the treatment of 45 patients with hypofibrinogenaemia associated with abruptio placentae are shown in Table I.

TABLE I. RESULTS OF TREATMENT

Vaginal Deliveries; Total 34	
(*i*) Without pitocin drip	24
(*ii*) With pitocin drip	9
(*iii*) With pitocin drip and low forceps extraction	1
Lower-segment Caesarean Section; Total 10	
(*i*) For obstetrical causes	5
(ii) For failure to respond to treatment	5
Caesarean Hysterectomy; Total 1	

The foetal mortality was 100% and 1 maternal death occurred in this series. This occurred in a para 3 aged 28 years, who sustained a ruptured uterus during the delivery of a hydrocephalic infant. The clotting defect appeared late in treatment after the Caesarean hysterectomy had been performed. She was given 18 pints of blood and 15 G. of fibrinogen before she died. At post-mortem examination the cause of death was found to be a slipped ligature on the uterine artery.

Two patients developed acute pulmonary oedema during treatment. This was ascribed in both to the excessive use of triple-strength plasma. Both patients responded to digitalization and venesection.

The complication of postpartum haemorrhage arose in 6 patients. In 4 of these, treatment of the clotting defect was inadequate, and in the other two insufficient time elapsed between admission and delivery for completion of adequate treatment.

Only in one patient severe oliguria occurred in association with hypofibrinogenaemia. It occurred in a hypertensive para 6, aged 26, who was admitted with revealed and concealed accidental haemorrhage, which had occurred 3 hours before admission. Her blood pressure was 170/120 mm.Hg on admission. Her lowest urinary output in 24 hours was 150 ml. and the highest blood-urea recording was 280 mg. per 100 ml. on the 9th day after delivery. She responded well to treatment and was discharged.

Until a few years ago severe accidental haemorrhage had always been associated with a high maternal mortality in which acute renal failure played a large part. In 1950, for instance, one of us (D.C., 1950[22]) found an anuria rate of 11·6% and a maternal mortality rate of 10·9% in a large series of patients treated at the Peninsula Maternity Hospital, Cape Town.

In the present series the single maternal death was mainly caused by factors other than the hypofibrinogenaemia, and the only case of observed oliguria occurred where there was probably already some predisposing renal arteriolar spasm with the hypertension associated with unpreventable delay in the onset of treatment.

We ascribe these results to 3 main principles of management: Firstly, the rapid correction of the hypovolaemia with blood; secondly, the rapid correction of the hypofibrinogenaemia with adequate quantities of fibrinogen as indicated by the clot-observation test and quantitative fibrinogen estimation; and finally, refraining from expediting vaginal delivery until the situation is well controlled, with Caesarean section occupying an important place in the treatment of patients with the complication of an unfavourable cervix, recurrence of hypofibrinogenaemia or shock, or a delayed onset of haemorrhage-delivery interval.

SUMMARY

1. A study of 46 patients with serious hypofibrinogenaemia is presented occurring among African and Indian patients. Of these 44 were associated with severe concealed accidental haemorrhage.

2. The frequency of liver dysfunction among the Africans was considered a possible aetiological factor in the high incidence of hypofibrinogenaemia found in accidental haemorrhage (62%) and among the total deliveries (0·18%). Grande multiparity was also found to predispose to hypofibrinogenaemia.

3. Both the hypovolaemia and the clotting defects were found to be complications in accidental haemorrhage which required correction as emergency measures — preferably within an hour of the admission of the patient. The use of fibrinogen was found to be preferable to that of triple-strength plasma in such circumstances.

4. Defibrinogenation is not always a 'once for all mechanism', and the most serious cases are prone to develop a recurrence of hypofibrinogenaemia following the initial correction (particularly among our African patients). Consequently Caesarean section plays an important rôle in the treatment of severe cases associated with a prolonged interval between the onset of accidental haemorrhage and the anticipated vaginal delivery.

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