HYPOFIBRINOGENAEMIA IN OBSTETRICS*

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'. . . that there are alterations in the blood or blood vessels of a temporary nature which prevent its clotting and this, during labour and operations, causes death.' *De Lee* 1901.[9]

Maternal deaths from uncontrollable haemorrhage due to a clotting defect must have occurred and are still occurring since the above words were spoken.

Animal experiments[1, 5, 20] had shown that by the intravenous injection of placental extracts the animals could be defibrinated sufficiently to cause a 'haemorrhagic diathesis', but only in 1936 did Dieckmann[4] attribute the bleeding tendency in the obstetric patient to a depletion of plasma fibrinogen. This depletion, he thought, was due to a large haemorrhage and the mobilization of fibrinogen at the site of the haemorrhage. In 1947 Schneider[1] propounded a theory, the most widely accepted today, that the fibrinogen was mobilized in the circulation by absorption of thromboplastin from the uterus and its contents, which caused intravascular thrombosis. The fibrinogen could be lowered sufficiently to cause a bleeding state. 2 years later Maloney[20] first treated patients suffering from depleted plasma fibrinogen with blood and human fibrinogen infusion. Since the beginning of this decade, many cases have been reported,

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particularly in the American literature, of hypofibrinogenaemia and its associated obstetric conditions.

THE CLOTTING MECHANISM OF BLOOD

Prothrombin (*globulin*) + calcium + thromboplastins (*from damaged tissue, blood platelets and plasma*) = thrombin (*albumin*).
Thrombin + fibrinogen = fibrin.

The foregoing schema (after Samson Wright) shows the three basic reactions, which are as follows:

(*a*) Thromboplastin is formed from precursors in the platelets, plasma and damaged tissue; this takes place only when blood is shed or tissue damaged.

(*b*) The enzyme thrombin is formed from its precursor prothrombin, which itself is formed in the liver.

(*c*) The soluble substance fibrinogen, also formed in the liver is converted to insoluble fibrin by the enzyme thrombin.

Certain factors in the liver may prevent the formation of both prothrombin and fibrinogen, e.g. necrosis or anoxia.

The normal plasma-fibrinogen level is 250 mg. per 100 c.c. (range 190-330)[24] but from the 3rd month of pregnancy this rises to 325 mg. per 100 c.c. (range 220-450)[12, 8, 21] at term. The total fibrinogen content of the average individual is about 18 g.

Normally all clotting factors are available in excess; they must be reduced by about 25-50% before the mechanism fails 7( )—in the case of fibrinogen to below 100 mg. per 100 c.c., though a value between 100[13] and 150 mg. per 100 c.c. is thought to be dangerous.

AETIOLOGY

The following are obstetrical conditions known to be associated with hypofibrinogenaemia:

Accidental Haemorrhage. The majority of cases of the condition occur with the concealed type of accidental haemorrhage, when marked shock, severe extravasation of blood and tissue damage are present. In 94 cases of all types of accidental haemorrhage at Baragwanath Hospital, 60 were the less severe forms and of these none showed a bleeding tendency, whereas in the 34 cases of the concealed type there were 14 cases of hypofibrinogenaemia. The one exception was a case of accidental haemorrhage due to a circumvallate placenta (the only case from this cause reported) in which the serum fibrinogen was 96 mg. per 100 c.c. (case 2). Whether the accidental haemorrhage was toxic (6 cases) or non-toxic (8 cases) did not appear to be of significance except in one case (case 8), in which the lowered fibrinogen appeared 28 hours *post partum*. In this case liver damage can only be presumed, for liver function tests were not carried out.

Amniotic Fluid Embolism. This frequently causes death from cardio-pulmonary failure, but should the patient survive, she will almost certainly develop a bleeding tendency from defibrination. Even the cases that die from cardio-pulmonary failure bleed abnormally before death or fluid blood is found at necropsy.

Missed Abortion and Retained Dead Foetus. As the method of production of hypofibrinogenaemia is the same, these can be grouped together. Thromboplastins absorbed from the dead conceptus over a period of at least 4 weeks[16] lower the plasma fibrinogen sufficiently to cause a bleeding diathesis (case 6).

The *Rhesus factor* was at one stage thought to be a direct cause of hypofibrogenaemia, but it is now realized that it is a common cause of intra-uterine death, with frequently a fairly long period of retention of the macerated foetus, and is only an indirect cause of the haemorrhagic condition.

Dextran and other similar substances are associated contributory causes in lowering an already low plasma fibrinogen, possibly below the critical level and causing uncontrollable haemorrhage.[21]

Pitocin. Tumultuous contractions, in many instances caused by the injudicious use of Pitocin, may force thromboplastins into the circulation, and if in sufficient quantity, cause an amniotic-fluid embolism. Because of this association in those cases where fibrinogen is reduced caution should be exercised in the use of Pitocin.

Clotting Factors

Though all clotting factors fall secondarily to a greater or lesser degree,[7] the fall in the level of plasma fibrinogen seems to be the most important.[2-4, 18, 23] MacKay *et al.*[15] think that a drop in all factors is important, especially a thrombocytopaenia.[3] They hold that if thrombocytopenia is not present abnormal bleeding will not occur,[12] but that if it is present it is of grave significance.[16] This was not confirmed in our series.

The aetiology is still unsettled and much of it is based on theory. Phillip and Larkin[18] have classified it into 4 main theories:

Group A. Theories of plasma-fibrinogen depletion: (1) *actual loss of fibrinogen,* (2) *Increased Utilization and* (3) *Failure of Production.*

A sudden large haemorrhage may seriously deplete the fibrinogen content of the plasma—a 6-pint blood loss may completely defibrinate the body.[20]

Fibrinogen might be mobilized at the site of tissue damage, such as the uterus in an accidental haemorrhage or the lungs in the inhalation of vomitus or pneumonia.

Failure of production of fibrinogen as the result of liver damage has not been proved except in extirpation of a liver, in carcinoma of the liver and in chloroform necrosis, and in these conditions the prothrombin level usually falls first. In pre-eclampsia liver function tests are usually normal and hypofibrinogenaemia is not seen unless there is an associated accidental haemorrhage.[13] Prolonged hypotension in severe shock may cause liver anoxia and a failure to produce fibrinogen,[20] or the liver may not synthesize fibrinogen sufficiently rapidly to replace a rapid loss.

Group B. Thromboplastin Theory

This is most widely accepted today.[1, 3, 6, 7a, 8, 10, 12, 21, 23] The protein thromboplastins[23] from the uterus and its contents (confirmed by animal experiment) gain access to the maternal circulation *via* the sinusoids[20, 12, 19] and cervical veins,[19] where they cause intravascular thrombosis and embolism, chiefly in the lungs, liver and kidneys.[12] They may be forced into the circulation by increased intra-uterine pressure, as in concealed accidental haemorrhage or tumultuous labour, and the rate of fibrinogen utilization depends on the amount present[19] and on its rate of absorption.

Group C. Anaphylactoid Theory

That 'fibrin thrombosis' is the common factor in such conditions as eclampsia, premature separation of the placenta, bilateral renal cortical necrosis, and pituitary necrosis, seems to be evident from work done by MacKay *et al.*,[14] and also

that these conditions and a general Shwartzman reaction seem to be related; but, as fibrinogen estimations were not done, it may well be that other factors come into play.

Group D. Fibrinolysin Theory

Fibrinolysins are enzymes present in minute quantities, which are normally protective and are formed from precursors in the endothelium. They are only released in very shocked patients.[6, 7, 10, 15, 23] Some[6, 9] think they do not play any part, because they are not found when specifically sought after and also do not account for the drop in all elements of coagulation. The disintegration of the clot *in vitro* may be due to a fibrinogen level too low to form a strong clot and not to fibrinolysis.[22, 23]

INCIDENCE AND CLINICAL MANIFESTATIONS

In 90% of cases of accidental haemorrhage, hypofibrinogenaemia most probably exists in a sub-clinical form. In the other 10% of cases, e.g. severe forms (50-100% placental separation), it may be present in a definite clinical form.[7a, 23] In 85,000 deliveries in 3 large centres in Britain, 8 cases of hypofibrinogenaemia were proved.[21]

In 94 Bantu cases of accidental haemorrhage at Baragwanath Hospital, 34 being severe, 14 cases of hypofibrinogenaemia were found, an incidence of 14·9% and 41·2% respectively. It was only looked for in 60% of the 94 cases by one or more diagnostic tests. It was not sought in any other condition. These 14 cases are included in the series of 15 which are recorded in this article. Clinical summaries of the series are set out at the end of the article.

Clinical Manifestations

Not all patients who bleed severely develop a coagulation defect and not all with a coagulation defect such as hypofibrinogenaemia bleed severely[9] (cases 2 and 14). In general, it is only found when specifically sought after, as it was in 14 of the cases in this series.

Prolonged or uncontrollable vaginal bleeding, with no apparent reason, particularly if the blood does not clot and is associated with one of the conditions enumerated above, should make the diagnosis suspect at once. It must be remembered that uncontrollable haemorrhage can be caused by severe birth trauma which can exsanguinate a patient sufficiently to cause hypofibrinogenaemia, and trauma must be excluded.

There are 3 main clinical types, depending on the amount of thromboplastin present and its rate of absorption viz. hyper-acute, acute and chronic:

Hyper-acute. This is seen in amniotic-fluid embolism and the signs of defibrination are usually overshadowed by the signs of cardio-pulmonary failure. Shock is out of proportion to the blood loss until the latter becomes prominent after the clotting mechanism has failed. Death in these patients, unless caused by cardio-respiratory failure, is not inevitable if prompt treatment is instituted.

Acute. The signs and symptoms of the associated obstetric emergency are present as well as severe haemorrhage and shock. Hypofibrinogenaemia may be forgotten if not specifically looked for, because its signs may be overshadowed by those of the primary obstetric condition.

Chronic. The onset of defibrination is insidious, and is manifested by purpuric phenomena such as ecchymoses, bleeding gums, etc. The history of a missed abortion or retained dead foetus is usually obtained. Shock is not seen unless associated with a large secondary haemorrhage. The massive bleeding associated frequently with evacuation of a missed abortion may be due to hypofibrinogenaemia and the plasma fibrinogen level should be estimated before operation and corrected if it is low.

It should be remember that there may be no signs present, but as long as the clotting defect is there the patient is in potential danger.

DIAGNOSIS

The diagnosis depends on a full understanding of the pathological situation. Apart from the gravity of the condition accurate diagnosis is called for by the expensiveness of the methods of treatment (human fibrinogen at £9 a gram, plasma at £4 a pint and blood at £2 10s. a pint). The following tests are useful aids:

(*a*) *A blood count, including platelet count*. The presence of thrombocytopenia is regarded as of grave import.[16]

(*b*) *The Lee-White test for coagulation time* (normal 4-10 minutes). If no clot forms the plasma fibrinogen is definitely below the critical level.

(*c*) *Weiner's clot-observation test*[19, 23] is usually carried out in conjunction with the coagulation-time test, and for gauging purposes is repeated at frequent intervals. Of the cases here recorded, all those showing abnormal clotting time or clot formation, or clot dissolution, were found to have plasma-fibrinogen levels below 100 mg. per 100 c.c. except 2 cases, one just above 140 mg. and one of 140 mg. which later went well below the critical level. Confirmatory fibrinogen tests showed one case with a clotting time of 2½ minutes in which the plasma fibrinogen was 100 mg. per 100 c.c.; 2 cases with plasma fibrinogen below 150 mg., and the remainder well above 200 mg. In 4 cases no further investigation was made because bleeding ceased; and one patient died. In one case a normal clotting time changed to abnormal, but bleeding ceased after treatment.

(*d*) *In the topical thrombin test*, Topical Thrombin (Parke Davis) is diluted in 20 c.c. of normal saline to make a solution of 50 mg. per c.c. Of this solution 0·5 c.c. is further diluted in 10 c.c. of normal saline, and 0·1 c.c. of this final dilution is added to 1 c.c. of the patient's serum. This is incubated at 37°C for 15 minutes and examined for clotting, and then observed for 1 hour more for dissolution of the clot, as in the clot-observation test. Normally all factors are present on addition of the thrombin, and if no clot forms, or an unstable clot, this is an indication of a deficiency in serum fibrinogen.

(*e*) *Prothrombin time and prothrombin index*. This test was performed in 12 of the 15 cases. Of the patients with serum fibrinogen below the critical level, 8 showed a prothrombin time greater than 2 minutes. In 4 patients in whom the prothrombin time, though increased, was below 2 minutes, the fibrinogen level was below 150 mg. per 100 c.c., and in one of them it was below the critical level. It appears, then, that a greatly increased prothrombin time may indicate plasma-fibrinogen levels below the critical level.

(*f*) *Plasma fibrinogen*. There are two main methods of estimating fibrinogen, viz. (1) the turbidimetric method, which gives an approximate reading, and (2) the Kjeldahl method, which though accurate takes a longer time. Both methods were used in this series. The critical plasma-fibrinogen level

is 100 mg. per 100 c.c.; below this the clotting mechanism fails.

In the present series 4 main tests were used in the diagnosis, viz. the clotting time, the clot-observation test, the topical thrombin test and the prothrombin time, confirmed by the plasma-fibrinogen level. The results usually arrived 24 hours after the blood had been taken. The first three of these tests are valuable ward procedures and, as regards the fourth, most laboratories can estimate the prothrombin time rapidly. If it is greater than 2 minutes it is diagnostic of a serious clotting defect.

Retained cotyledons, obstetric trauma etc. must be borne in mind and excluded.

Thrombocytopenic purpura. Thrombocytopenia accompanying hypofibrinogenaemia may confuse the diagnosis (case 15). Thrombocytopenic purpura is rare in pregnancy.[25] The history of previous purpuric attacks, or retention of a dead foetus, may suggest either thrombocytopenia or hypofibrinogenaemia. The Lee-White coagulation-time test will differentiate the two.[26]

TREATMENT

Early detection and prompt correction of a low plasma fibrinogen is the aim in treatment, for the untreated case, whether delivered by the abdominal or vaginal route, may end in disaster[23]. The treatment of shock, restoring of blood volume, and raising of plasma-fibrinogen level are all important.[6]

The policy of ultra-conservatism in the treatment of missed abortion and a retained dead foetus might have to be reviewed,[2, 15] particularly if the retention is longer than 4 weeks; and if a waiting policy is practised, plasma-fibrinogen levels must be estimated twice a week.[12] If the level is found to be falling, evacuation of the uterus becomes necessary.

Pitocin must be used with care, so as not to cause tumultuous contractions, and should not be used to hasten normal labour.[7a]

Blood Transfusion

The blood loss in accidental haemorrhage is frequently under-estimated. A liberal amount of blood—2-4 pints in the first hour[23]—should be used to combat shock and restore blood volume. Fresh blood,[12, 20] as it restores all clotting factors, is better than bank blood, but even multiple transfusions will not raise the fibrinogen to effective levels in the severely defibrinated patient.[23] It might, however, be all that is necessary in the less severe types. Sibthorpe[22] states that 1 pint of fresh blood raises the plasma fibrinogen by 5-10 mg. per 100 c.c. One must remember to give 10 c.c. of 10% calcium lactate for every 2,000 c.c. of blood administered, to counter the anti-coagulant effect of sodium citrate.

In 7 of our cases, although blood transfusion alone stopped bleeding in 4, the results as shown by the known fibrinogen values were not entirely satisfactory because they could have been raised to higher levels. In the other 3, blood transfusions alone were inadequate and fibrinogen had to be given.

The whole series of cases were under-transfused, the average transfusion being 1,600 c.c. per patient, as compared with Reid, Weiner and Roby's series with 2,600 c.c. per patient, Jackson's series with 2,000 c.c. and Barry's with 2,500 c.c. In the above 7, only 3 patients received 2,000 c.c. or more.

Plasma Infusion

This is beneficial for two reasons—firstly because by restoring the blood volume it combats shock, and secondly because it has a high fibrinogen content (0·29 mg. per 100 c.c. or 1·45 g. per pint). When blood is available it may be given in double or quadruple strengths and in the one patient of the series who received 750 c.c. of quadruple-strength plasma (8 g. of fibrinogen) and 1,000 c.c. of blood, the fibrinogen was raised from 75 mg. per 100 c.c. to 316 mg. If fibrinogen is not available, plasma is the finest substitute, and it has the advantage of costing less.

Human Fibrinogen

Blood transfusion and fibrinogen are essential in the severely affected patient,[1, 2, 5, 7a, 8, 9, 12, 13, 21, 23] especially if fibrinolysins are present.

Theoretically, as all factors are lowered, fibrinogen alone should not be sufficient to correct the coagulation defect, but in practice this does not appear to be the case. As soon as the clotting defect has been discovered, give fibrinogen and do not await the laboratory findings.

In the cases treated with fibrinogen in the present series, the fibrinogen levels were raised adequately in 4 cases (to 324, 175, 298 and 201 mg. per 100 c.c.), satisfactorily but not adequately in 2 (134 and 140), satisfactorily but not measured in 2, unsatisfactory in 1 (100), and inadequately in 1 (88). Sufficient fibrinogen to restore the clotting mechanism[26] appears to be adequate in most cases, as fibrinogen seems to stimulate the body to produce more,[18] but massive doses are occasionally necessary.[23] The amount to be given varies with the severity of the case and amounts of 4-6 g. have been given as empirical doses[1, 2, 12, 13, 19] and some cases require as much as 10 g. or more. All institutions practising obstetrics should have fibrinogen readily available for emergency use.

Induction of Labour

Once the uterus is evacuated, spontaneous fibrinogen recovery is rapid, so that early artificial rupture of the membranes to induce labour may be advisable. Rupture of the membranes also prevents a fall in serum fibrinogen, by reducing the intra-uterine pressure.[5] The clotting mechanism if defective should be corrected first. This was practised in 9 of the present series and after rupture, though no serial fibrinogen estimations were made, failure of coagulation did no recur.

A recent idea that the patient must be delivered by Caesarean section immediately, failing which clotting will be defective, is wrong.[23] Artificial rupture of the membranes, as well as improving many, will bring the majority into labour and prevent an unnecessary Caesarean section being performed upon a shocked patient. Seven out of the 9 patients whose labours were induced were delivered spontaneously within 9 hours of induction, and the other 2 (who might have had Caesarean sections) in 31½ and 57 hours respectively. In 2, induction was unnecessary as delivery was imminent. In the 3 not induced, the labours were 10, 12 and 15½ hours respectively. One Caesarean section was performed for placenta praevia.

Caesarean Section and Hysterectomy

The indications for Caesarean section in this type of patient remain controversial. It would appear, from the cases presented, that Caesarean section should only be done

after a preliminary trial by rupturing the membranes. It is, however, unjustifiable[7] and dangerous[12] to rupture the membranes if the coagulation defect is not corrected first. As the operation of Caesarean section is only done in the interests of the mother, 6-12 hours[12, 23] should elapse after rupturing of the membranes, before surgery is undertaken, provided the maternal condition remains satisfactory and labour has not started.

In this series only one case was treated by Caesarean section (6·6%). It was done for type-III placenta praevia. If a prolonged induction delivery interval is accepted as an indication, 2 more could have been done and one for prolapse of the cord, had it been discovered earlier.

Indications for a hysterectomy seldom occur, and this procedure should be reserved for cases in which the uterus fails to contract and continues to bleed actively, despite more conservative haemostatic measures. The more extensive operation may have been lethal in Case 15. If the coagulation defect is corrected before surgery, hysterectomy should be a very rare necessity.

CASE REPORTS

Case 1

A 36-year-old unbooked Para 8 was admitted at 36-weeks gestation. She had had severe abdominal pain and profuse vaginal haemorrhage of 5 hours' duration. She was pale and shocked. BP 130/90 mm. Hg. The uterus was that of a patient with concealed accidental haemorrhage and she was passing fluid blood per vaginam.

Blood Examination. Hb. 11·4 g.%. PT: failed to clot 2 mins. Pl scanty. CT: 10 min., clot dissolved. TT: 15 minutes—dissolved. F: 75 mg. 100 c.c.

Patient received 1,000 c.c. of bank blood and 750 c.c. of quadruple-strength plasma.

Repeat Blood Examination. CT: 5 min., stable. PI: 76%. TT: clot formed, stable. Pl 175,000/c.mm. F: 316 mg./100 c.c.

3 hours 25 minutes after surgical induction delivered of a 7 lb. 13 oz. stillborn infant. There was a 32 oz. retroplacental clot and no fresh bleeding. Recovery uneventful.

Case 2

A 41-year-old Para 7 was admitted in labour from District in her 34th week of gestation. She had experienced abdominal pain and moderate vaginal bleeding for 4½ hours. She was pale and slightly shocked. BP 112/64 mm. Hg. The foetus was vertex LOL: foetal heart rate 132/min. Blood transfusion was started.

Blood Examination. CT: 7 min., clot friable and retraction poor. PI: 58%. F: 96 mg./100 c.c.

12 hours after admission she was delivered of a live 5 lb. 5 oz. child. There was a large retroplacental haematoma and 15 oz. of fresh blood. The placenta was circumvallate. Only 500 c.c. of blood had been given.

Repeat Blood Examination at Delivery. Hb. 9·5 g.%. PI: 62%. Pl: normal. Repeated after 12 hours: Hb. 7·4 g.%. PI: 83%. F: 118 mg./100 c.c.

Recovery uneventful.

Case 3

A 26-year-old unbooked Para 3 was admitted 3½ hours after having bled painlessly, fairly severely per vaginam. Her period of amenorrhoea was unknown. She was pale. BP 150/110 mm. Hg. The uterus showed all the signs of a concealed accidental haemorrhage. She was bleeding per vaginam.

Blood Examination. CT: no clot after 1 hour. PT: failed to clot in 2 mins. F: 96 mg./100 c.c.

She received 1,750 c.c. of bank blood and 2 g. of fibrinogen.

Repeat Blood Examination. CT: 4½ min., stable. TT: clot formed, stable. F: 324 mg./100 c.c.

She was delivered 57 hours after surgical rupture of the membranes of a macerated 4 lb. infant. The clotting time repeated during this period never exceeded 7 min., the clots formed being stable. There was a 10 oz. retroplacental clot and no fresh blood.

Tests Repeated at Delivery. CT: 2 min., stable. F: 282 mg./100 c.c.

The puerperium was complicated by a uterine infection treated with penicillin. She was discharged on the 6th day after delivery.

Case 4

This 32-year-old Para 3 was admitted from the District. The expected date of delivery was unknown. She had had backache and vaginal bleeding for 3 hours before admission. She was pale. BP 140/70 mm. Hg. The uterus showed all the signs of a concealed accidental haemorrhage.

Blood Tests. Hb. 5·9 g.%. CT: 2½ min., stable clot. PI: 64%. F: 132 mg./100 c.c.

After 5 hours in hospital patient was more shocked, BP 104/70. 800 c.c. of normal saline and 1,000 c.c. of bank blood were infused. After a further 5 hours macerated twins weighing 2 lb. 12 oz. and 3 lb. were delivered. The second of the two placentae was covered over half its surface by blood clot, and 10 oz. of fresh blood accompanied delivery. Despite the uterus being well contracted the patient lost a further 25 oz. of blood as an ooze.

Repeat Tests. CT: 5 min., retraction poor. TT: very poor clot formed.

1,000 c.c. of blood and 2 g. of fibrinogen were infused and abnormal bleeding ceased. F: 175 mg./100 c.c. at this time. Recovery was uneventful.

Case 5

An unbooked 27-year-old Para 4, whose expected delivery date was unknown, was admitted 2 hours after vaginal bleeding caused by coitus had started. She was very shocked and pale. BP 90/60 mm./Hg. All the signs of concealed accidental haemorrhage were present.

Blood Tests. CT: 7-8 min., clot dissolved ½ hour. PI: failed clot 2 min. F: less than 100 mg./100 c.c.

Haematoma and bleeding were noticed at the site of previous venipuncture when transfusion was started. She received 1,000 c.c. of blood and 2 g. of fibrinogen.

Repeat Tests. CT: 2½ min., stable. F: 100 mg./100 c.c.

An early macerated infant weiging 6 lb. 6 oz. was delivered, followed by 8 oz. blood loss, and placenta completely covered by clot.

There was no further bleeding and recovery was uneventful.

Case 6

An unbooked 36-year-old Para 8 at 36-weeks gestation was admitted after 3 hours of vaginal bleeding and pain. 3-4 weeks before admission the patient had fallen on her abdomen and since that time had not felt foetal movements. She was pale, moderately shocked. BP 110/60 mm. Hg. The foetus could be felt presenting vertex L.O.L. but no foetal heart could be heard. Vaginal bleeding was slight.

Blood Tests. Hb. 4·1 g.%. CT: Small clot 6 min., dissolved. PI: Failed clot 2 min. F: less than 50 mg./100 c.c.

1,000 c.c. of blood and 1 g. of fibrinogen were given.

Repeat Tests. CT: 3 min., unstable clot. TT: No clot in 1 hour. F: 80 mg./100 c.c.

A further 500 c.c. of blood and 2 g. of fibrinogen were given.

Tests Repeated. CT: 1½ min., stable clot. Hb. 9·2 g.%. PI: 75%. F: 298 mg./100 c.c.

Three hours after surgical induction she was delivered of markedly macerated infant, and 20 oz. of retroplacental clot with placenta. Progress was uneventful.

Case 7

A 38-year-old Para 8 was admitted from District having been bleeding per vaginam for 3¾ hours. She was 34 weeks pregnant. She was very pale, extremely shocked. BP 50/30 mm. Hg and the uterus was that of a patient with a concealed accidental haemorrhage. Fluid blood was seen at the vulva.

Blood Tests. CT: 20 min., dissolved in ½ hour. PI: Failed to clot in 2 mins. F: less than 50 mg./100 c.c.

600 c.c. of normal saline and 500 c.c. of bank blood were infused rapidly and then a further 500 c.c. of blood and 2 g. of fibrinogen. BP 140/60 mm. Hg. During next 2 hours a further 1,500 c.c. of blood and 2 g. of fibrinogen were given. Abnormal bleeding ceased.

Repeat Tests. CT: 3½ min., stable. PI: 70%. F: 135 mg./100 c.c.

Two hours after surgical induction a macerated 4 lb. foetus was delivered. The placenta and 28 oz. of clot followed with no fresh bleeding. Progress thereafter was uneventful.

Case 8

An unbooked 20-year-old Para 2 was admitted in her 'seventh month' of pregnancy. She had had earache 3 days before delivery, followed by right-sided facial paralysis. No foetal movements had been felt for 24 hours and vaginal bleeding had been present for 2 hours before admission. She had a right-sided facial paralysis and herpes of the lip. BP 228/130 mm. Hg and the urine 'boiled solid' on examination. Fundi showed all the signs of Grade-IV retinitis.

Blood Tests. CT: 20 min., unstable clot. F: 140/mg./100 c.c.

One hour after admission delivered of a 3 lb. 5 oz. stillborn infant. Fresh bleeding and retroplacental clot amounted to 20 oz. and then bleeding ceased. 28 hours after delivery the patient felt dizzy and started to ooze per vaginam. She was shocked. BP 130/70 mm. Hg and further examination, including lumbar puncture, was negative.

Repeat Tests. Hb. 7·4 g.%. F: less than 50 mg./100 c.c. 2 g. of fibrinogen and 1,000 c.c. of bank blood were given and vaginal bleeding ceased.

Tests. 8 days after admission: Hb. 12·5 g.%. Blood urea: 49 mg./100 c.c. Uric acid: 5·5 mg./100 c.c. F: 455 mg./100 c.c.

Patient was transferred to a medical ward.

Case 9

An unbooked 28-year-old Para 3, 28 weeks pregnant, was admitted having suffered from abdominal pain and vaginal bleeding for 5 hours. She was very pale and shocked. BP 90/60 mm. Hg. All the signs of concealed accidental haemorrhage were present and she was bleeding profusely per vaginam.

Blood Tests. Hb. 11·2 g.%. CT: 8 min., completely dissolved. PI: failed to clot in 2 mins. F: test done—result mislaid. After 1,000 c.c. of blood had been given after a further 4¾ hours, the CT was 4½ min., stable clot.

Repeat Tests. Hb. 11·2 g.%. CT: 7 min., stable. PI: 74%. F: 180 mg./100 c.c.

The forewaters were ruptured under anaesthetic and 31¾ hours later a 1 lb. 11 oz. macerated foetus was delivered. The placenta was accompanied by 30 oz. of clot and 6 oz. of fresh blood. During the induction delivery interval repeated clot observation tests were done and at no time were they abnormal.

Repeat Tests at Delivery. Hb. 9·9 g.%. CT: 4 min., stable. PI: 100%. F: 227 mg./100 c.c. Progress was uneventful.

Case 10

A 25-year-old unbooked Para 1 in her 34th week of pregnancy was admitted to hospital complaining of abdominal pain following a fall on the abdomen. For 3 hours she had been bleeding profusely per vaginam. She was pale and shocked. BP 104/40 mm. Hg and showed all the signs of a severe concealed accidental haemorrhage. Vaginal bleeding was brisk, fluid blood being seen.

Blood Tests. Hb. 6·7 g.%. CT: 11 min., unstable clot formed. PI: 70%. F: 115 mg./100 c.c.

Patient received 2,000 c.c. of bank blood and then CT 4½ min., stable clot. The membranes were only ruptured 26 hours after admission and she was delivered of a 5 lb. 14 oz. infant 3 hours later. There was a 34 oz. retroplacental clot and no fresh bleeding with the birth of the placenta. Urinary output, which had been 8 oz. from admission to time of induction, was now increased and 16 oz. were obtained at delivery.

Tests at Delivery. Hb. 14·6 g.%. CT: 3½ min., stable clot. PI: 91%. F: 139 mg./100 c.c.

The blood electrolyte levels were normal and urinary output increased after delivery and she made an uneventful recovery.

Case 11

An unbooked 28-year-old Para 5 was admitted in her 38th week of pregnancy. She was extremely collapsed, cold, clammy and pulseless. BP 40/0. Saline and 1,000 c.c. of blood were infused rapidly and this improved her condition sufficiently to allow blood to be taken for investigation.

Blood Tests. CT: 15 min., clot dissolved almost immediately. PI: 58%. F: 106 mg./100 c.c.

A further 500 c.c. of blood and 2 g. of fibrinogen were infused and then the forewaters ruptured.

Tests. CT: 4½ min., stable. PI: 67%. F: 140 mg./100 c.c.

Five hours later a 6 lb. 4 oz. stillborn infant was delivered. The placenta and a 34 oz. retroplacental clot followed and no fresh bleeding.

Tests Repeated at Delivery. Hb. 10·4 g.%. CT: 3½ min., stable clot. PI: 60%. F: 166 mg./100 c.c.

Tests repeated after 24 hours. Hb. 8·7 g.%. CT: 2½ min., stable. F: 297 mg./100 c.c.

Recovery was uneventful.

Case 12

This unbooked 38-year-old Para 9 was admitted in her 34th week of pregnancy. She stated labour had started with more bleeding than usual. She was not distressed and BP was 100/60 mm. Hg. The foetus could be felt, L.O.A. position, and the foetal heart was 138 per min. Vaginal bleeding was excessive.

Blood Tests. Hb. 7·2 g.%. CT: failed to clot. F: less than 50 mg./100 c.c.

She received 1,500 c.c. of blood and 2 g. of fibrinogen. During the resuscitation period the uterus became woody and the foetal heart was no longer heard.

Tests Repeated. CT: 4 min., stable. PI: 100%. F: 201 mg./100 c.c.

Vaginal examination done now showed that the membranes were intact, and a non-pulsating cord was found in the sac. The membranes were ruptured; 3 hours later patient was delivered of a 5 lb. 10 oz. stillborn infant and a 30 oz. retroplacental clot and 10 oz. of fresh blood accompanied the placenta. There was no further bleeding and so tests were not repeated. Recovery was uneventful.

Case 13

A 38-year-old unbooked Para 1 was admitted in her 28th week of pregnancy. She had had severe abdominal pain and bled profusely per vaginam since the previous day. She was pale and oedematous. BP 100/70 mm. Hg, and the uterus showed all the signs of a concealed accidental haemorrhage.

Blood Tests. Hb. 8 g.%. CT: no clot. PI: failed to clot 2 min. F: 97 mg./100 c.c.

She was delivered in 5½ hours of an early macerated 6 lb. 8 oz. infant. Despite the 2,000 c.c. of blood she received during this period she had a 50 oz. postpartum haemorrhage as well as a large (4×3 inch) retroplacental clot. The uterus continued to ooze despite being well contracted. A further 1,000 c.c. of blood and 2 g. of fibrinogen were infused immediately and this caused the bleeding to cease. F now 193 mg./100 c.c. Recovery was uneventful.

Case 14

This unbooked 26-year-old Para 4 was admitted in her 36th week of gestation. Lower abdominal pain and vaginal bleeding had been present for 9 hours. She was pale, shocked and oedematous. BP 110/20 mm. Hg. All the signs of severe concealed accidental haemorrhage were present.

Blood Tests. Hb. 8 g.%. CT: 4 min., unstable clot. PI: failed to clot 2 min. F: less than 50 mg./100 c.c.

Transfusion of 1,000 c.c. of blood was started. During resuscitation the patient developed chest pain and coughed up a small quantity of blood-stained sputum. No abnormality could be found in the chest on clinical examination.

Progress tests were not done on this patient and membranes were ruptured without knowing the coagulability of the blood. After 9 hours of ruptured membranes she was delivered of a 5 lb. 8 oz. stillborn infant. There was a 24 oz. retroplacental clot present and no fresh bleeding. No further treatment was given and no further tests done, and the patient recovered uneventfully.

Case 15

This booked 20-year-old Para 2 was first admitted in her 26th week, having an episode of painless vaginal bleeding. Bleeding settled on bed rest and a placentogram showed a posterior placenta praevia 'dipping into lower uterine segment'. There was no further bleeding until the 36th week when, over a period of 24 hours, she oozed blood and clot per vaginam, estimated at 15 oz.

Blood transfusion was started and an examination under anaesthetic was planned. On arrival in the operating theatre the patient was extremely collapsed out of proportion to the amount of blood lost. Blood was forced in and at examination 10-15 oz. of blood clot were found in the vagina. The cervix was 3-fingers dilated and a Type-III post-placenta praevia was diagnosed.

Immediate Caesarean section resulted in the delivery of a still-

born infant. Except for the uterus tending to relax despite 2 intravenous injections of Ergotrate, the bleeding did not appear to be excessive. After operation, BP 84/0 mm. Hg, vaginal oozing persisted. The uterus was explored but no placental remains were found. Hydrocortisone, 100 mg. in normal saline, was now started and the blood taken for further compatibility tests remained fluid. The buccal mucous membrane and gums started to bleed. The spleen was palpable below the costal margin and hypofibrinogenaemia or thrombocytopenic purpura were thought of as the platelets were scanty. An intramuscular injection of 10 units of Pitocin failed to stop the vaginal ooze.

After a further 1½ hours and there being no fibrinogen available, a hysterectomy was done. Ecchymoses were seen in the bowel wall, and as the bare area of the pelvis tended to ooze excessively, it was packed.

3 g. of fibrinogen, which was now available, was given as well as the 6th pint of blood and the patient appeared to improve; 6 hours after the operation the patient, whose systolic blood pressure had remained at 84 mm. Hg, suddenly collapsed. Despite further blood transfusion and noradrenaline (Levophed) infusion she remained comatose and died 3 hours later.

Blood Tests at time of Collapse. Hb. 11 g.%. White-cell count: 16,800 per c.mm. Pl: scanty. F: 88 mg./100 c.c.

Necropsy. Blood in all cavities, including 1½ pints in peritoneum. Numerous subserous and submucous ecchymoses, including large subcapsular haematoma in the liver. Pituitary and adrenals appeared normal.

CT=coagulation time. TT=topical thrombin test. PT= prothrombin time. PI=prothrombin index. Pl=platelets. F=fibrinogen test.

CONCLUSIONS

1. Preventable maternal deaths from shock and uncontrollable haemorrhage due to the clotting defect of hypofibrinogenaemia are still occurring today, 20 years after the cause was first described.

2. Any obstetrical case in which thromboplastins can be absorbed into the maternal circulation from the uterus and its contents may cause the drop in plasma fibrinogen, but certain conditions, the chief being the more severe forms of accidental haemorrhage, are more commonly associated with hypofibrinogenaemia.

3. Its incidence is higher than is generally expected, especially in the Bantu. Though other factors may be concerned in this increase, specifically testing for hypofibrinogenaemia will enable more subclinical forms to be diagnosed.

4. Signs and symptoms vary according to the acuteness of onset of the associated obstetrical abnormality such as the amount of blood loss and shock, but any blood issuing from an obstetric patient that fails to clot is pathognomonic of the condition.

5. Diagnosis is easily confirmed by the clotting time, a clot observation test, the topical thrombin test and a prothrombin time which, if greater than 2 minutes, indicates a plasma fibrinogen level below the critical level.

6. Early detection and prompt correction of the lowered plasma fibrinogen is the first aim in treatment; for as long as blood clotting is defective, the patient's life is in danger.

7. Liberal amounts of blood, preferably fresh, must be used to combat haemorrhage and shock.

8. Plasma may be used when blood and/or fibrinogen are not available, as it combats shock and restores fibrinogen levels, particularly if used in concentrated form.

9. Human fibrinogen, though costly, restores safe plasma-fibrinogen levels rapidly. Massive doses are occasionally needed but usually smaller doses will suffice to restore a normal clotting mechanism.

10. Artificial rupture of the membranes as soon as possible will prevent further defibrination taking place and will induce labour in most cases.

11. Caesarean section is seldom if ever indicated and should only be carried out after rupture of the membranes. Hysterectomy is only a last resort when all other haemostatic measures have failed. The clotting mechanism must be restored before surgery is undertaken.

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