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Maternal afibrinogenemia

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MATERNAL AFIBRINOGENEMIA

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PREFACE

Maternal and/or fetal death during pregnancy or labor is an entity which has shown a marked reduction in incidence due to improvements in medicine in general and especially in better obstetrical methods and expanded knowledge of the process of reproduction.

The problem has not been eliminated as yet, however, indicating the need for additional study of the reproductive process and dissemination of the results of such study to all members of the profession, present and future. The death of a mother, an infant, or both is indeed a tragedy of major dimension which can never be glossed over in a statistical analysis, no matter how minute the incidence may be.

It is my intent in writing this paper to review what has been reported concerning a cause of maternal and fetal death which is infrequently anticipated and yet which should deserve as much respect as any other toxemia.

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AFIBRINOGENEMIA ASSOCIATED WITH PREMATURE SEPARATION OF THE PLACENTA

(a) De Lee (1), in 1901, first noted indications that a state of incoagulable blood might exist as an unrecognized cause of maternal mortality. In a review of three cases, occurring in three years, which "have forced on the writer the belief that there are alterations of the blood or blood vessels, of a temporary nature, which prevent the clotting and thus, during labor or operations, cause death." These were cases of premature separation of the placenta. One of these patients died. All exhibited lack of blood coagulation. He recommended treatment with gelatin gauze packs and calcium chloride if the cause could not be determined.

In 1915, Williams (2) reported a case in which placental separation was followed by a fatal hemorrhage due to a failure in the clotting mechanism. He thought that the blood was like that of persons who were victims of certain types of snake bites.

Wilson (3), in 1922, in a review and report of his own experience, presented a paper on abruptio placenta and described fourteen deaths from continued hemorrhage from a series of sixty-nine cases. He

proposed the hypothesis that the placenta was the source of some toxic material which he called a "hemorrhagin" and which gained entry into the maternal circulation to produce the clotting defect.

An autopsy report made by Kellogg (4) in 1928 reveals the extensive hemorrhage into all organs as well as the inability of the blood to clot in a patient who died following the occurrence of a severe abruptio placenta.

In 1936, Dieckmann (5), in a study of the blood chemistry and renal function in premature separation of the placenta, observed that a certain number of patients had a prolonged bleeding time, and, in some instances, there was a marked decrease in blood fibrinogen.

Maloney and his associates (6) report upon a patient with acquired afibrinogenemia in pregnancy with a diagnosis of premature separation of the placenta. Maloney and his colleagues were the first to include fibrinogen as an adjunct to blood transfusion in the treatment of this condition. Their case had none of the usual manifestations of toxemia of pregnancy but had a bleeding disorder characterized by spontaneous bleeding from the gingiva and into the subcutaneous tissues with incoagulability of the

blood. Further studies revealed a total lack of fibrinogen as the cause of the hemorrhagic diathesis. The patient recovered under treatment with Cohn's fraction I.

These authors favored the concept that the hemorrhage was related to vessel damage due to toxin arising within the decidua or from a proteolytic enzyme effect.

Obata (7), in his placental investigations in 1919, was impressed by the fact that following the "injection of placental extract in mice, hemorrhages and thromboses in the animals were in agreement with the anatomical features of eclampsia, but the decreased coagulability of the blood appeared to be a discordant finding." Two rabbits and two mice were killed with an overdose of Obata's saline extract of placenta and were found to have a decrease in the coagulability of the blood, hemorrhages in the lungs and liver and pulmonary and hepatic thromboses.

In a comparison of the sera of normal and eclamptic individuals with respect to their capacity to neutralize the toxic property of his saline placenta extract, Obata found that normal human serum, either from men or women, pregnant or not, possessed a uniform power of neutralizing the placental factor, while

the serum of eclamptic women had considerable less neutralizing power, but the neutralizing power was restored soon after the attack.

Eley (8), in 1936, demonstrated an anti-hemophiliac activity in saline extracts of placenta and subsequently produced intravascular coagulation in the blood of guinea-pigs and monkeys by lethal amounts of the material. Despite repeated slight trauma incident to active childhood, two hemophiliac children were able to lead normal active lives for periods of several months by the continued administration of Eley's placental extract at carefully regulated intervals.

Further studies were carried on and, in Russia in 1937, Yudin (9) and his associates carried out extensive investigations on fibrinolysis during the development of the technique of preparing cadaver blood for transfusion. These workers found, after a study of over five hundred bodies, that if the blood were obtained from the body of a person who had died of a severe disease such as cancer, tuberculosis, sepsis or trauma with prolonged shock, that it slowly formed a coagulum that remained firm until putrefaction. On the other hand, the blood of corpses in cases of sudden death, whether due to acute severe trauma, angina pectoris or apoplexy, when taken into the test tube,

quickly coagulates into an ordinary clot, but very soon, after one-quarter to one and one-half hours, this clot dissolves of its own accord and the blood again liquefies. Chemical analyses revealed the dissolution of the fibrinogen to be the cause of this reliquefaction of the original clot.

A description of the sequence of effects on the circulation of dogs when thromboplastin was injected, was reported in 1941 by Howell (10). With excessive amounts, death was due to extreme intravascular coagulation. Defibrination and incoagulable blood resulted when sublethal doses were administered. A negative phase was described during which further injection of thromboplastin produced no systemic effect.

Chargoff (11), in 1945, identified the coagulant factor contained in saline extracts of placenta as thromboplastin protein. He also obtained similar extracts of thromboplastic material from lung tissues of cattle. Both substances were found to be lipoproteins of high molecular weight.

In a reinvestigation of Obata's experiments (7) in mice and his own on rabbits, Schneider (12,13) in 1947, concluded that the agent which accounts for the toxic effects and fibrin deposition which leads to the massive intravascular coagulation is thromboplastin.

He further observed (12) that following sublethal doses of placental extracts, mice were able to withstand many times the lethal dose. The period of desensitization continued for some eight to twelve hours. This refractory phase was interpreted as due to inactivation of the placental toxin (thromboplastin) by a serum factor, an anti-thromboplastin. He concluded that pregnancy increases the sensitivity of rabbits at least twofold to intravascular injections of thromboplastin extracts.

Fulton and Page (14) in 1948, in similar experiments, confirmed the presence of a refractory phase in mice following the injection of a crude thromboplastin extract prepared from the placenta. These observers noted that during the time the animals were able to survive lethal doses of the preparation, the blood was incoagulable. Upon the intravenous administration of fibrinogen, the mice again became sensitive. These investigators attributed the refractory phase to a defibrinated circulation.

Thus, it is seen that the cause of afibrinogenemia in severe premature separation of the placenta remained for many years, a matter of speculation. It has been attributed to the entrance into the maternal circulation of a substance or substances from the uterus

which, in turn, defibrinates the blood. Those materials suggested include thrombin from the retroplacental clot (15), a proteolytic enzyme from the decidua (15,16) and thromboplastin derived presumably from the damaged decidua and placenta (15,16,17,18,19).

Most of these investigations provide some basis for the assumption that thromboplastin is the most probable agent responsible for the incoagulable state of the blood seen in severe premature separation of the placenta, and, as will be discussed later, in long-standing intrauterine fetal death and in amniotic fluid embolism.

(b) Premature separation of the normally implanted placenta, when it occurs in the severe form, has the dubious distinction of being the obstetrical complication with the greatest maternal risk (20). While the factors which contribute to the condition and the pathological changes both in the uterus and the body generally are well recognized, the precipitating cause of premature separation of the placenta remains to be elucidated. Death may occur subsequent to renal and pituitary damage, but the vast majority of patients who succumb from premature separation do so directly from shock associated with uterine hemorrhage.

An investigation (20) regarding the coagulation

mechanism in patients with obstetrical hemorrhage was begun in 1948 and involved several hundred patients with early and late pregnancy bleeding as well as those with postpartum hemorrhage. Included were patients with abortion, hydatidiform male, placenta praevia, and the mild, moderate, and severe forms of premature separation of the placenta.

The following tests were performed on blood samples from these patients: clotting test of Lee and White (21), prothrombin time by the one-stage method of Quick (22), fibrinogen determinations (23,24), platelet count (25), tests for anticoagulant (26) and fibrinolytic activity (27,28,29). These observations revealed alterations in blood clotting in severe cases of premature separation of the placenta. It was also demonstrated that the blood clotting was normal in patients with mild and moderate degrees of premature separation.

The nature of the blood changes consisted of a reduction or complete disappearance of circulating fibrinogen, some slight decrease in prothrombin concentration, and, occasionally, especially after delivery, the appearance of a circulating fibrinolysin.

In these studies, the fibrinogen concentration of the blood was normal prior to and shortly following severe abruptio placentae. While the majority of

these patients had some decrease in prothrombin concentration, the reduction never approached a hemorrhagic level. It appeared that the incoagulable state of the blood in premature separation of the placenta was not the result of hypoprothrombinemia. The adequacy of the prothrombin time indicated that components of the prothrombin complex which include the various accelerators do not play a decisive role in the production of incoagulable blood in severe premature separation. Accordingly, the incoagulability of the blood was attributed to a deficiency in the fibrinogen concentration.

This syndrome was reproduced in eighteen dogs by the intravenous infusion of human placental thromboplastin. This resulted in fibrinogen depletion, a variable reduction in prothrombin and accelerator globulin concentrations, an inability of the blood to clot, focal lesions in the liver and kidneys, and oliguria. All these findings are sometimes encountered in severe cases of abruptio placentae.

Since thromboplastin seems to have been indicted as the inciting agent of this chain of events, the question naturally arose concerning the method of infusion into the maternal circulation of the placental thromboplastin.

The method of infusion has raised the following idea (20) based upon the fact that intrauterine pressure is quite great as is evidenced by the gush of blood and amniotic fluid seen at Caesarian section when the uterus is opened in such cases. It is postulated that when the intrauterine pressure exceeds the pressure within the venous sinusoids at the site of placental detachment, the coagulant-containing materials are forced into the latter blood channels as a result of the pressure difference. As long as the membranes remain intact, the intrauterine pressure remains high and probably increases with further retroplacental bleeding.

Such a concept is compatible with the observation that clotting difficulties have never been seen when a small area of the placenta is involved but only when retroplacental bleeding and the degree of concealed hemorrhage has been marked.

The arrest of defibrination which has been noted to follow artificial rupture of the membranes is submitted as further evidence that increased intrauterine pressure is responsible for the escape of coagulant material from the uterus. The possibility of a fibrinolytic activity in these patients has been challenged by the failure to demonstrate a fibrinolysin in

animal experiments (19). However, clot dissolution has been seen in severe cases of premature separation following restoration of fibrinogen levels and so indicating the presence of a fibrinolysin. With normal fibrinogen levels and after rupture of the membranes, clot fragmentation disappeared. This change in clot stability indicates that a fibrinolysin was presumably present. Moreover, in a patient who recovered from amniotic fluid embolism with afibrinogenemia, clot fragmentation was observed after normal fibrinogen levels were reached (30).

The recent demonstration of fibrinolytic activity in a fatal case of amniotic fluid embolism with defibrination adds to the evidence that a fibrinolysin appears when thromboplastin-containing material enters the circulation (31).

Thus, one may hypothesize a certain chain of events in severe premature placental separation. Amniotic fluid rich in thromboplastin is forced pathologically into the maternal circulation by a difference in pressure gradients and causes massive intravascular coagulation which is followed by the appearance of a circulating fibrinolysin, fibrinolysis, and resultant massive hemorrhage.

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THE FIBRINOLYTIC SYSTEM

At this point, it would seem judicious to present a brief and simplified concept of what the fibrinolytic system is and how it operates, especially in the problems presented in this paper.

The reason for the existence of a fibrinolytic enzyme system in the blood is obscure, but the most reasonable explanation would be that it becomes activated after the occurrence of injury in order to remove any deposited fibrin slowly and repair the damage which was initiated by the action of thromboplastic proteins (19). This hypothesis is in keeping with clinical observations and places the fibrinolytic enzyme system in the class of an adaptive mechanism responding to an injury.

Fibrinolysin, while capable of dissolving a fibrin clot (32,33) according to some authorities also digests fibrinogen and prothrombin (34). The continual utilization and conversion of fibrinogen into fibrin as a function of the normal reparative processes of the body (35) suggests that minute amounts of fibrinolysin are required to prevent excessive fibrin deposition on the endothelium of the capillary bed. The presence of a fibrinolytic inhibitor in the blood is believed to

furnish a physiologic antagonist which impedes excessive fibrinolytic activity (33,36).

As to the source of fibrinolysin, it has been shown (37) that it is present in the areas of the vascular system where the blood is in a fluid state at postmortem. From such findings, it has been concluded (37) that fibrinolysin is probably derived from the endothelial cells of the blood channels and body cavities.

Stefanini (34) sums up the more technical aspects of this interesting enzyme system when he states that "an inert proenzyme is found in Cohn's plasma fraction III-3 and in serum (profibrinolysin). It is water soluble and precipitated by 33 per cent saturation ammonium sulfate or acidification to pH 5.5. Profibrinolysin is converted to fibrinolysin by the activity of fibrinolysokinases. These are produced by bacteria (streptokinase) and in mammals are found in very small amounts in the serum and in various tissues. The activator is a relatively heat labile substance, very complex in chemical structure and definitely different from thromboplastin. The activity of fibrinolysokinase is countered by an inhibitor (antifibrinolysokinase) which accompanies the activator in tissues and can also be found in the serum. Active fibrinolysin is inhibited by antifibrinolysin, which combines with fibrinolysin

according to definite stoichiometric proportions. Fibrinolysin is not trypsin. Activation of fibrinolysin and of the fibrinolysin/antifibrinolysin equilibrium is under the control of the basic mechanisms in the economy of the body. Activation of fibrinolysin may be induced by "stress" and is one of the facets of the so-called "alarm reaction". The pituitary-adrenocortical-splenic axis controls the activity of antifibrinolysin."

According to Ungar and Damgaard (38), the inactivation of fibrinolysin by antifibrinolysin is regulated by ACTH and cortisone and by at least two splenic factors of opposing activity (splenin A and splenin B). The equilibrium of the fibrinolytic system is very well regulated, and tissue destruction of important degree or other comparable stimulus is necessary to induce activation of fibrinolysin.

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MANAGEMENT OF PREMATURE SEPARATION OF THE PLACENTA

Before proceeding with a discussion of the other obstetrical entities which may give rise to the phenomenon of afibrinogenemia, the management of premature separation of the placenta during labor and delivery in an effort to anticipate, combat and cope with the problem of afibrinogenemia will be discussed.

The prevention of death and complications arising from hemorrhage in premature separation of the placenta has been approached mainly from the standpoint of the method of delivery.

Until 1933, the preferred method of treatment of premature separation of the placenta at the Boston Lying-in Hospital was Caesarian section. At that time, a review of forty-two consecutive patients with extensive placental detachment treated by this method showed a maternal mortality of twenty-one per cent (39). A number of the patients died at or soon following delivery from hemorrhage and shock. When death did occur from uremia, characteristically in the second week following delivery, autopsy revealed nephrosis (40). In a later series from the same hospital, the results were not appreciably different when Caesarian section continued as the method of delivery.

In view of the fact that the highest mortality rate occurred in those cases treated by Caesarian hysterectomy, a more conservative method of treatment was deemed worthy of trial, and the usual normal delivery method was employed. With the use of conservative treatment, the maternal mortality rate at the Boston Lying-in Hospital became very low (41). In a report of 353 cases of premature separation of the placenta at that hospital between 1916 and 1937, the following data are presented. Of these cases, 234 had external and 119 had internal hemorrhage. In 170 cases with external hemorrhage delivered via the pelvic route there were no deaths. In 30 cases with external hemorrhage treated by Caesarian section, the mortality was 3.3 per cent. In 69 cases with internal hemorrhage delivered by Caesarian section mortality was 14.5 per cent. In 34 cases of internal hemorrhage treated conservatively, the mortality rate was 2.9 per cent. The conservative method consisted of induction of labor by artificial rupture of the membranes with or without cervical packing and eventual delivery via the pelvic route.

Weiner, Reid, and Roby (20) state that an evaluation of the degree and severity of the placental separation is a prerequisite to treatment. Placental

separation occurring in the mild or moderate form is generally not accompanied by shock. The uterus is soft and relaxed and the fetal heartbeat is usually of good quality. If uterine tenderness is present, it is restricted to a small area. While the serosal covering of the uterus may show localized areas of discoloration when seen at Caesarian section, the myometrium is devoid of changes. The clinical course of the patient is in general benign and, while blood replacement is often needed, therapeutic response is entirely satisfactory.

Patients with severe premature separation of the placenta some time in their course reveal shock which becomes extreme if not treated. In these cases, the fetal heartbeat is usually absent. The uterus by palpation is boardlike and tender. Morphologic alterations in the uterus responsible for these signs and symptoms have been described by Couvelaire who proposed the term utero-placental apoplexy to identify these changes. Accumulation of blood beneath the peritoneal surface gives the uterus a mottled, discolored appearance typical of the disease. Both grossly and microscopically, the myometrial fibers are widely separated by the infiltration and extravasation of the retroplacental blood. In addition to the concealed uterine hemorrhage, extravasation of blood into the broad

ligaments and retroperitoneally through the lower abdomen may reach sizable proportions at Caesarian section or determined by vaginal examination in the early puerperium.

The group at Boston Lying-in Hospital outline the preferred method of management as follows. Pelvic examination with artificial rupture of the membranes is done in the operating room with preparation for laparotomy if a placenta praevia is encountered in addition to the findings previously described as indicative of premature separation. In addition to initiating labor, the rupture of membranes seems to deter the further placental separation and control the bleeding. It is believed that amniotomy immobilizes the portion of the placenta which is separated which promotes local thrombosis and prevents further hemorrhage and separation. Should labor fail to occur in two to four hours, a small amount of a pituitary preparation is given. Caesarian section in the group with milder separation is used when effective labor fails to transpire in six to twelve hours.

The treatment of the severe form of placental detachment is directed mainly to save the mother, since infant mortality is so high in this group. The first step is the detection of the presence of any existing

afibrinogenemia. This is done by the clot observation test which will be discussed later. If an afibrinogenemia is found to exist, the situation demands immediate fibrinogen replacement--whole blood is not enough according to this group. Multiple transfusions are begun to combat shock. On the average, two to four transfusions are given in the first hour. Concurrently, an equal number of grams of fibrinogen (Cohn's fraction I) dissolved in dextrose and water and given intravenously. Morphine and atropine are given to quiet the patient. Early in the second hour, a pelvic examination is performed in the operating room to determine the condition of the cervix and rupture the membranes which seems to decrease the process of defibrination and fibrinolytic enzyme activity.

Additional blood and fibrinogen are given on indication. If after the clotting mechanism has returned to normal and the patient does not deliver via the pelvic route in nine to twelve hours, Caesarian section is done. A prolonged and drawn out labor seems to cause a return of the incoagulable state of the blood. General anesthetic is used during all operative procedures.

These authors (20) feel that hysterectomy for post-partum hemorrhage associated with premature

separation is unwise therapy since this procedure transfers the bleeding tendency to areas outside the uterine corpus such as the ovarian pedicle, cervical stump and incised peritoneum. They feel that optimum treatment must take into consideration the fact that the patient's blood is or is about to become incoagulable and that definitive therapy must include the use of fibrinogen per se rather than merely whole blood transfusions which are relatively ineffective.

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AFIBRINOGENEMIA ASSOCIATED WITH AMNIOTIC FLUID EMBOLISM

In 1941, Steiner and Lushbaugh (42) described the syndrome of amniotic fluid embolism which they considered to be the major cause of maternal death during labor. Dyspnea and sudden shock were the chief clinical signs, and death was ascribed to embolic effects of amniotic fluid and an associated anaphylactoid reaction. Widespread embolization of the pulmonary arterioles and capillaries by particulate matter contained in amniotic fluid were believed to be responsible for the pathology. The predisposing factors in this syndrome seemed to be tetanic uterine contractions, multiparity and exceedingly large infants.

In a report of eleven cases, Shotton and Taylor (43) concluded that violent uterine contractions were undoubtedly the force which drove the amniotic fluid into the maternal circulation. If the membranes were intact over the cervix, great intrauterine pressure might cause an abnormal rupture of the membranes in the region of the placenta with entry of the amniotic fluid into the maternal veins at this point. If the membranes are already ruptured, intrauterine pressure would drive the fluid toward the cervix and into the circulation via

the cervical veins. The time of rupture of the membranes was recorded in each of these cases and it was found that the rupture took place at least forty minutes or more before the onset of the shock-like picture. They contend that this supports the argument that the most likely portal of entry is in the region of the cervix.

After reporting a fatal case of amniotic fluid embolism at Nebraska Methodist Hospital, Schenken (44) and his associates concluded that the basic factors in the pathogenesis of this syndrome are entrapped amniotic fluid containing considerable debris; a rent in the fetal membranes, preferably in the placenta where the venous sinuses are most numerous and widely patent; and uterine contractions forceful enough to overcome the pressure in the open venous sinusoids.

Ratnoff and Vosburgh (31) report a case of a woman in profound shock thirty minutes post-partum who died eleven hours later. At autopsy, emboli of amniotic material were demonstrated in the pulmonary vessels. Approximately three and one-half hours later, it was noted that the patient was bleeding from the sites of venipunctures. Shortly thereafter, her blood failed to clot in vitro and blood studies revealed multiple clotting defects including a hypofibrinogenemia.

Two unexplained observations appear in an analysis of these cases (45). One is that the amount of mechanical blockage by the amniotic debris in the pulmonary vessels is hardly sufficient to be the cause of death. Two, the clotting of the blood was rarely seen.

A review of cases of fatal amniotic fluid embolism at Boston Lying-in Hospital (45) suggested that this unexplained hemorrhage might be due to an alteration in the coagulation mechanism due to the presence of the amniotic fluid. A large number of samples of amniotic fluid were studied to detect any substance which might be to blame. It was demonstrated that uncontaminated amniotic fluid collected during labor contained a thromboplastin-like substance. Amniotic fluid was shown not to contain fibrinogen, thrombin, prothrombin accelerators, heparin or fibrinolytic activity (46).

When amniotic fluid was injected into rabbits, as in the original experiments of Steiner and Lushbaugh (42), thrombosis rather than mechanical embolism from amniotic debris was observed (47). It was suggested (48) that death might result from either extensive intravascular clotting or post-partum hemorrhage. Death from hemorrhage was regarded as due to an afibrinogenemia, the end result of intravascular clotting and the fluidity of the blood are believed due to

a fibrinolytic enzyme which can be demonstrated in the blood after sudden death. It was predicted (48) that the detection of afibrinogenemia by the "clot observation test" and fibrinogen replacement by Fraction I would prevent maternal death.

In spite of the evidence presented here negating the role of mechanical blockage of pulmonary vessels as the cause of death in amniotic fluid embolism, I feel it would be purely speculative to completely cast such an idea aside without further study. However, the important idea to be derived from the foregoing study of amniotic fluid embolism is the recognition of the fact that a failure in the clotting mechanism does occur and can be traced to a deficiency of fibrinogen.

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AFIBRINOGENEMIA ASSOCIATED WITH LONG-STANDING INTRAUTERINE DEATH AND Rh ISOSENSITIZATION

Another instance in which afibrinogenemia has been reported is in those cases of long standing intrauterine fetal death and Rh isosensitization as evidenced by a positive indirect Coomb's test.

Weiner, Reid, Roby and Diamond (49) report three cases each of which delivered dead babies and bled a great deal at delivery. In each instance, the fetus had been dead for several weeks. The patients were all Rh negative, and fetal death was attributed to blood incompatibility. A study of the blood of these patients revealed a marked depletion of fibrinogen. On the basis of normal liver function studies in one patient, it was concluded that the depletion of fibrinogen was not due to any hepatic disease. The suggestion was made that thromboplastic material from the uterine contents gained entrance into the maternal circulation and caused massive intravascular coagulation with consumption of fibrinogen.

Afibrinogenemia was not detected if fetal death had been of short duration, suggesting that a marked degree of autolysis of decidual and placental tissue was necessary to permit the situation to occur. An

outstanding clinical difference between these patients and those with premature separation of the placenta was that in these patients, the hemorrhagic tendency may become first manifest by ecchymoses, and mucous membrane bleeding of the respiratory and gastrointestinal tracts.

Ratnoff and associates (50) describe a patient who was Rh negative, had Rh antibodies in the circulating blood and a dead fetus in utero. The patient exhibited hypofibrinogenemia for four and one-half weeks. The hemorrhagic state was corrected by a subtotal hysterectomy which was performed while the plasma level of fibrinogen was sustained by intravenous infusion.

Three other such cases were recently reported by Hodgkinson, Margulis, and Luzadre (51). One case had a retained dead fetus for over two months. Following induced labor and delivery, the patient bled profusely and was given four thousand cubic centimeters of whole blood but died, with complete failure of blood coagulation. A second case, Rh negative, had a dead fetus of two months duration and a history of gingival bleeding for that time. Profuse bleeding occurred at the time of delivery from the vagina and gingiva. The blood fibrinogen level was demonstrated to be zero. After being given calcium gluconate, protamine sulfate,

corticotropin and blood, her clotting was restored after the fibrinogen level reached 110 mg. per cent. Previous to this, any clot which formed lysed soon thereafter in vitro. A third case was studied thoroughly after the diagnosis of intrauterine fetal death and fibrinogen levels remained normal. An uneventful delivery and post-partum period ensued.

Fibrinogen depletion is assumed (52) to be the result of intravascular coagulation caused by the escape of a coagulant, thromboplastin, from the uterus into the maternal circulation. The defibrinating material is presumably derived from autolysis of decidua or placental tissue.

Placental autolysis following fetal death in utero varies greatly. Morphologic changes vary from practically no change to almost complete liquefaction. The latter is probably necessary for defibrination to occur. Acquired afibrinogenemia is a potential hazard for any patient with long-standing death of the fetus in utero.

These authors (52) conclude that normal labor and pelvic delivery would appear to be safer and the preferred method of treatment for such cases. Severe hemorrhage may, of course, necessitate termination of the pregnancy. If intrauterine infection is present,

abdominal hysterectomy is the preferred elective. Fibrinogen levels must be restored immediately prior to delivery since administration of fibrinogen prior to this time is of little avail since this substance continues to disappear from the blood until after delivery and does not recur after delivery.

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THE CLOT OBSERVATION TEST

Reference has been made in this paper to the so-called "clot-observation test" in detection of hypofibrinogenemia in association with the previously discussed syndromes.

Where fibrinogen concentration is decreased to a critical level, initial clotting appears, followed within an hour by fragmentation and dissolution of the clot. A simple clinical test is used to detect the defect in blood clotting in these cases. Failure of freshly drawn venous blood to clot or to form a normal-sized stable clot is believed sufficient evidence to conclude that the circulating blood fibrinogen had become reduced to a critical level. Subsequent fibrinogen determinations have substantiated this conclusion. Hemostasis was considered inadequate if the clot, when incubated at 37 degrees centigrade, dissolved within an hour. It is now known that an unstable clot may form when fibrinogen levels are in the range of the minimal values for hemostasis (100-150 mg. per cent), or in the presence of a fibrinolysin, or as a combined effect of both of these factors. These findings were first reported in 1949 (17) and since then, the experience with a limited number of patients has been

reported (15,16,6,18,19,49,53).

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SUMMARY

This paper presents an account of past and more recent work in the study of the state of hypofibrinogenemia or afibrinogenemia associated with severe premature separation of the placenta, amniotic fluid embolism, and long-standing intrauterine fetal death with concomitant Rh isosensitization.

Observers have noted for many years that patients who experienced severe premature separation of the placenta hemorrhaged uncontrollably and at autopsy, the blood failed to clot. The reason for this was a matter of speculation and lead to studies which revealed a relative or complete lack of circulating fibrinogen as a consistent finding.

Experimental work with placental extracts showed them to be rich in thromboplastin or a thromboplastin-like substance. Animal experiments with such extracts showed that when such extracts were infused intravenously rapidly in dogs and cats, death soon followed, simulating the chain of events in cases of severe premature separation of the placenta. If given slowly, the animals survived but exhibited defibrination of the blood (24,25,26). Pregnant animals seemed more sensitive to such extracts then other animals.

Amniotic fluid was demonstrated to be rich in thromboplastin. The thromboplastin content of the amniotic fluid is dependent on the amount of tissue derived from fetal exfoliation and decidua when the fluid gains access between the chorion and myometrium (27) following placental separation.

The fact that the syndrome occurs usually near the end of the first stage of labor suggests that a certain set of circumstances is needed for its development. These include both an available portal of escape and the forceful expulsion of amniotic fluid from the uterus.

There are two avenues of entrance of amniotic fluid into the maternal circulation. The commonly accepted manner involves a rupture of the membranes in the upper uterine segment with escape of fluid through the utero-placental site by a difference in the pressure gradient set up by violent and tetanic uterine contractions.

One manner by which amniotic fluid may escape into the maternal circulation has been well demonstrated (28,29). Amniotic squamous cells have been identified between the amnion and chorion, in the placental margin, the decidual sinusoids, and myometrial veins. Following rupture of the fetal

membranes, the amniotic fluid may dissect between them and the uterine wall and, in rare instances, reach the placental margin to enter the venous sinusoids and the systemic circulation. The escape of fluid is enhanced by forceful contractions and those conditions in which the uterine vessels are opened abnormally as in rupture of the uterus, Caesarian section, marginal separation of the placenta, and normal separation of a partial placenta accreta (29).

The second and more frequent outlet is through the endocervical veins. These vessels become lacerated during labor and account for the "bloody show". The upper portion of the cervix is thought to be incorporated in the lower uterine segment during labor. Some of the endocervical veins are thus included in the lower uterine segment and would not be covered by fetal membranes unless they remained intact until the presenting part had traversed the dilated cervix (20).

Should the membranes rupture prior to labor, the distal portion of the lower uterine segment might become devoid of fetal membranes and allow the amniotic fluid to come in contact with myometrium. If the fetal vertex were to tamponade the cervix, intrauterine pressure might increase sufficiently as the result of labor to allow the trapped fluid to enter the uncovered endo-

cervical veins. If the fluid is infused slowly, defibrination will result, the decidual vessels will fail to thrombose and hemorrhage will result.

Further work demonstrated the presence of a circulating fibrinolysin in such patients including a patient who survived amniotic fluid embolism after treatment with fibrinogen (17). The presence of this enzyme is interpreted as the response of the body to the abnormal extreme fibrin deposition which occurs when all the available fibrinogen is utilized in the massive clotting. The fibrinolysin lyses the clots and uncontrollable hemorrhage ensues. The presence of this fibrinolysin is easily demonstrated by the "clot-observation test".

In cases of amniotic fluid embolism, the same set of circumstances prevail. Tetanic contractions initiate the chain of events which results in inability of the blood to clot.

A similar set of circumstances may occur in instances of long-standing intrauterine fetal death, usually two months or more, associated with Rh isosensitization. Following the death of the fetus, autolysis increases the thromboplastin content of the amniotic fluid and, if violent uterine contractions with intact fetal membranes are allowed to occur, the fatal chain

of events may supervene.

The routine use of oxytocic drugs is condemned (20) since it is felt that superimposing the contractile effect of the drug on the uterus about to enter labor, or in active labor may increase the frequency of amniotic fluid infusion by producing tetanic uterine contractions. It is felt that amniotomy is well indicated in violent labor to decrease intrauterine pressure.

Fibrinogen is the only definitive treatment of afibrinogenemia and the amount given should be equal to the amount in the blood (8-12 grams) to allow for the possibility of complete defibrination. Four grams has been shown to be the smallest effective amount which can be given.

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CONCLUSION

1. Maternal afibrinogenemia is a syndrome produced by the infusion of thromboplastin rich amniotic fluid into the maternal systemic circulation, resulting in massive intravascular thrombosis, utilization of all available fibrinogen, and a fibrinolytic response lysing the thrombi and producing uncontrollable hemorrhage.

2. This syndrome has been described in cases of severe premature separation of the placenta, amniotic fluid embolism, and long-standing intrauterine fetal death with concomitant Rh isosensitization.

3. Tetanic uterine contractions are necessary to force the amniotic fluid into the maternal circulation by causing greatly increased intrauterine hydraulic pressure.

4. A deficiency of circulating fibrinogen and/or the presence of a circulating fibrinolysin may be detected by the "clot-observation test".

5. Delivery via the pelvic route with amniotomy to reduce intrauterine pressure is the preferred method of management. More radical procedures merely place the patient in more danger.

6. Fibrinogen in amounts adequate to replace the

entire amount normally present in the body is the only definitive treatment for afibrinogenemia and should be available for immediate use should the need arise.

7. Anticipation, recognition, and proper treatment of this syndrome will decrease the incidence of tragic maternal and/or fetal death.

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APPENDIX

CASE HISTORY

The following is a case history of a 27 year-old white female, gravida 3, para 2, who entered the obstetrical ward at Nebraska Methodist Hospital at the time during which the author of this paper was a senior clerk on the obstetrical service. This case provided the stimulus for my investigation into the problem of afibrinogenemia as a cause of maternal death.

"This gravida 3, para 2, white female entered Nebraska Methodist Hospital at 8:00 p.m. on October 13, 1953 for routine induction. The patient was given quinine grains 5, strychnine grains 1/30th at 9:00 and again at 9:30 and again at 10:00. Castor oil, ounces 1, was administered at 11:00 and a soapsuds enema was given at 1:00 a.m. on October 14, 1953. Pitocin, minims 1, was administered at 5:00 a.m. on October 14. Prior to this time, the patient had had no labor contractions. It was noted at 5:30 that the patient had a watery show and, at 6:00, a slight bloody show, at which time, the fetal heart beat was 136. The cervix was dilated 3 cm. and the presenting part was at station zero, the position not given. At 6:25, it was noted that labor contractions were occurring one

to one and one-half minutes, and lasting for 60 to 70 seconds. The patient was having a watery show, was restless, and apparently, blood pressure was not obtained, and her respirations were noted as being slow. At 7:00 a.m., oxygen was begun because of marked cyanosis; at 7:05, the patient precipitated. The baby, however, was stillborn. Vaginal hemorrhage apparently was more than normally expected. Blood was crossmatched and the uterus was packed. The bleeding apparently was under control between 7:30 and 8:45 at which time it was noted that the uterus was firm at intervals, but bleeding had started again and the pack was saturated. The patient continued to receive blood, a total of four pints being administered. By 9:15, the patient's respirations were shallow, pallor was marked, and oxygen was again started. A venous cutdown in the left ankle and in the right antecubital fossa were done at this time. At 9:30, the patient was given coramine ½ cc. and pitocin, one-half ampule. This again was administered at 9:50; however, the patient failed to respond to the medication and respirations ceased at approximately 9:55. The patient was pronounced dead at 10:15 a.m."(54).

The significant gross findings at post mortem examination included the following:

1. Most of blood from the veins of the broad ligament was fluid when the veins were cut open.

2. Numerous petechial hemorrhages on the visceral pericardum.

3. Subendocardial hemorrhages in the ventricles, the largest being 3½ cm. in greatest diameter.

4. Massive submucosal hemorrhages present in both renal pelves and extending into the ureters for a short distance.

5. Normal appearing placental site.

6. No blood clots in the uterus.

7. Large amounts of packing removed from the uterus contained no clotted blood, but were well soaked in liquid blood.

8. No hemorrhage in the wall of the uterus.

9. A few petechial present in the gastric mucosa.

The post-mortem report continues, "This is a case of massive post-partum hemorrhage with death resulting from shock and loss of blood. It is of marked interest to note that there is no evidence of any clotted blood present in the uterus, or about the packing which was placed in the uterus, even four hours after this procedure was performed. It is also of note that there is no clotting of the blood which was taken for cross-matching, approximately four hours prior to death.

Of added interest and importance are the hemorrhages in the subendocardial area, also in the renal pelves and gastric mucosa. This would tend to place this as a case of afibrinogenemia which is known to occur after premature separation of the placenta. This was an apparent case of premature separation of the placenta, and the gross findings help to substantiate that this represented a case of afibrinogenemia. Although adequate antemortem laboratory studies are not available to prove absolutely that the etiology of this case is afibrinogenemia, both the clinical course and autopsy findings are highly suggestive."

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BIBLIOGRAPHY

1. De Lee, Joseph B.: A Case of Fatal Hemorrhagic Diathesis, With Premature Detachment of the Placenta. Am. J. Obst. 44:785, 1901.

2. Williams, J. W.: Premature Separation of the Normally Implanted Placenta, Am. J. Obstet. and Gynec. 15:357, 1928

3. Willson, Prentiss: Uteroplacental Apoplexy (Haemorrhagic Infarction of the Uterus) In Accidental Hemorrhage Surg., Gynec. and Obstet. 34:57, 1922.

4. Kellogg, F. S.: Premature Separation of the Normally Implanted Placenta With Special Reference to the Kidney in These Cases. Am. J. Obstet. and Gynec. 15:357, 1928.

5. Dieckmann, W. J.: Blood Chemistry and Renal Function in Abruptio Placentae. Am. J. Obstet. and Gynec. 31:734, 1936.

6. Maloney, W. C.: Egan, W. J.: Gorman, A. J.: Acquired Afibrinogenemia In Pregnancy New Eng. J. Med. 240:596, 1949.

7. Obata, Isei: On The Nature of Eclampsia J. Immunol, 4:111, 1919.

8. Eley, R. Cannon: Green, Arda Alden: McKham, Charles F.: The Use of a Blood Coagulant Extract From the Human Placenta in the Treatment of Hemophilia. J. Pediat 8:135, 1936.

9. Yudin, S. S.: Transfusion of Stored Cadaver Blood. Lancet 2:360, 1937.

10. Howell, William H.: The Effects on the Circulation in Dogs Following Injection of Thromboplastin. J.A.M.A. 117:1058, 1941.

11. Chargoff, E.: The Isolation of Preparations of Thromboplastic Protein from Human Organs J. Biol. Chem. 161:389, 1945.

12. Schneider, Charles L.: The Active Principle of Placental Toxin; Thromboplastin; Its Inactivator in Blood; Antithromboplastin. Am. J. Physiol. 149:123, 1947.

13. Schneider, C. L.: Complications of Late Pregnancy in Rabbits Induced by Experimental Placental Trauma. Surg. Gynec. and Obst. 90:613, 1950.

14. Fulton, Lee D.: Page, Ernest W.: Nature of the Refractory State Following Sublethal Dose of Human Placental Thromboplastin. Proc. Soc. Exper. Biol. and Med. 68:594, 1948.

15. Weiner, Albert E.: Reid, Duncan E.: Roby, Charles, C.: Coagulation Defects Associated with Premature Separation of the Normally Implanted Placenta. Am. J. Obst. and Gynec. 60:379, 1950.

16. Reid, Duncan E.: Quoted by Weiner, A.E.: Reid, D. E.: Roby, C. C.: Incoagulable Blood in Severe Premature Separation of the Placenta: A Method of Management. Am. J. Obst. and Gynec. 66:475, 1953.

17. Weiner, Albert E.: Reid, D.E.: Roby, C. C.: Hemorrhagic Aspects in Toxic Separation of the Placenta. Read at a meeting of the Boston Obstetrical Society, Nov. 15, 1949.

18. Seegers, Walter H.: Schneider, C. L.: Quoted by Weiner, A. E.: Reid, D. E.: Roby, C. C.(16)

19. Page, Ernest W. : Fulton, Lee D.: Glendenning, Mary Beth: The Cause of the Blood Coagulation Defect Following Abruptio Placentae. Am.J.Obst. and Gynec. 61:1116, 1951.

20. Weiner, A. E.: Reid, D. E.: Roby, C. C.: Incoagulable Blood in Severe Premature Separation of the Placenta: A Method of Management. Am. J. Obstet. and Gynec. 66:475, 1953.

21. Lee, R. I. and White, P. D.: A Clinical Study of the Coagulation Time of Blood. Am. J. M. Sci. 145:494, 1913.

22. Quick, Armand J.: The Physiology and Pathology of Hemostasis. Philadelphia, Lea and Febiger, 1951. p.p. 125-134.

23. Peters, J. and Van Slyke, D. D.: Quantitative Clinical Chemistry. Baltimore, Williams and Wilkins Co., 1932. p.p. 696-698.

24. Ratnoff, O. and Menzie, C.: A New Method for the Determination of Fibrinogen in Small Samples of Plasma. J. Lab. and Clin. Med. 37:316, 1951.

25. Wintrobe, M. M.: Clinical Hematology, 2nd Ed. Philadelphia, Lea and Febiger, 1947, p.209.

26. Allen J. G. et al: A Protamine Titration As An Indication of a Clotting Defect in Certain Hemorrhagic States. J. Lab. and Clin. Med. 34:473, 1949.

27. MacFarlane, R. G. and Pilling, J.: Observations on Fibrinolysis. Lancet 2:562, 1946.

28. Smith, G. V. and Smith, O. W.: Evidence That Menstrual "Toxin" and Canine "Necrosin" are Identical. Proc. Soc. Exper. Biol. and Med. 59:116, 1945.

29. Frommeyer, W. B. and Epstein, R. D.: Hemorrhagic Diseases. New Eng. J. Med. 241:743, 1949.

30. Reid, D. E.: Weiner, Albert E.: and Roby, C. C.: Presumptive Amniotic Fluid Infusion with Resultant Postpartum Hemorrhage Due to Afibrinogenemia. J.A.M.A. 152:227, 1953.

31. Ratnoff, Oscar D. and Vosburgh, G. J.: Observations On The Clotting Defect in Amniotic Fluid Embolism. New Eng. J. Med. 247:970, 1952.

32. Tagnon, H. J.: Levenson, S. M.: Davidson, C. A.: and Taylor, F. H. L. : The Occurrence of Fibrinolysis in Shock, with Observations of the Prothrombin Time and the Plasma Fibrinogen During Hemorrhagic Shock. Am. J. M. Sc. 211:88, 1946.

33. MacFarlane, R. G. and Biggs, Rosemary: Fibrinolysis: Its Mechanism and Significance Blood 3:1167, 1948.

34. Stefanini, Maria: Mechanism of Blood Coagulation in Normal and Pathologic Conditions Am. J. Med. 14:64, 1953.

35. Foster, D. P. and Whipple, G. H.: Blood Fibrin Studies III Fibrin Values Influenced by Transfusion, Hemorrhage, Plasma Depletion and Blood Pressure Changes. Am. J. Physiol. 58:393, 1921.

36. Guest, M. Mason: Daly, Byrne, M.: Ware, Arnold G: and Seegers, Walter, H.: A Study of the Antifibrinolysin Activity in Human Plasmas During Pathological States. J. Clin. Investigation 27:793, 1948.

37. Mole, R. H.: Fibrinolysin and the Fluidity of the Blood Post Mortem. J. Path. and Bact. 60:413, 1948.

38. Ungar, G. and Damgaard, E.: Studies on the Fibrinolysin/Antifibrinolysin System in Serum. I Action of the Anterior Pituitary Adrenal Cortex and Spleen, J. Exper. Med. 93:89, 1951.

39. Smith, Judson A.: Caesarian Section at the Boston Lying-In Hospital. Surg. Gynec. and Obstet. 57:821, 1933.

40. Oliver, Jean: MacDowell, Muriel: and Tracy, Ann: The Pathogenesis of Acute Renal Failure Associated with Traumatic and Toxic Injury Renal Ischemia, Nephrotoxic Damage and the Ischemuric Episode. J. Clin. Investigation 30:1307, 1951.

41. Irving, Frederick, C.: The Conservative Treatment of Premature Separation of the Normally Implanted Placenta. Am. J. Obstet. and Gynec. 34:881, 1937.

42. Steiner, P. E. and Lushbaugh, C. C.: Maternal Pulmonary Embolism by Amniotic Fluid, J.A.M.A. 117:1245 and 1340, 1941.

43. Shotton, D. M. and Taylor, C. W.: Pulmonary Embolism by Amniotic Fluid. J. Obstet. and Gynec. Brit. Emp. 56:46, 1949.

44. Schenken, J. R.: Slaughter, G. P.: and De May, G. H.: Maternal Pulmonary Embolism of Amniotic Fluid. Am. J. Clin. Path. 20:147, 1950.

45. Reid, D. E.: Weiner, A. E.: and Roby, C. C.: Intravascular Clotting and Afibrinogenemia, The Presumptive Lethal Factors in the Syndrome of Amniotic Fluid Embolism. Am. J. Obstet. and Gynec. 66:465, 1953.

46. Weiner, A. E.: Reid, D. E.: and Roby, C. C.: The Hemostatic Activity of Amniotic Fluid Science 110:190, 1949.

47. Weiner, A. E.: Reid, D. E. and Roby, C. C.: Unpublished Experiments, 1949. Quoted in Weiner, Reid, and Roby (45).

48. Weiner, A. E. and Reid, D. E.: The Pathogenesis of Amniotic Fluid Embolism III. Coagulant Activity of Amniotic Fluid. New Eng. J. Med. 243:597, 1950.

49. Diamond, Louis K.: Weiner, A. E.: Reid, D. E.: and Roby, C. C.: Coagulation Defects with Intrauterine Death from Rh Isosensitization. Am. J. Obstet. and Gynec. 60:1015, 1950.

50. Ratnoff, Oscar D.: Lanster, Carl F.: Scholl, John G.: and Schilling, Myron O.: A Hemorrhagic State During Pregnancy With the Presence of Maternal Rh Antibodies, Death of the Fetus and Hypofibrinogenemia. Am. J. Med. 13:111, 1952.

51. Hodgkinson, C. P.: Margulis, R. R.: and Luzadre, J. H.: Etiology and Management of Hypofibrinogenemia of Pregnancy, J.A.M.A. 154:557, 1954.

52. Reid, D. E.: Weiner, A.E.: Roby, C. C.: and Diamond, L. K.: Maternal Afibrinogenemia Associated with Long-Standing Intrauterine Fetal Death. Am. J. Obstet. and Gynec. 66:500, 1953.

53. Schneider, C. L.: "Fibrin Embolism" (Disseminated Intravascular Coagulation) With Defibrination As One of the End Results During Placenta Abruptio. Surg. Gynec. and Obstet. 92:27, 1951.

54. Nebraska Methodist Hospital Post Mortem Reports, 1953: A-53-127. Courtesy of John R. Schenken M.D., Director of Laboratories.

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