CLINICAL SECTION

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Management of the Obstetrical Patient with Hemorrhage due to an Acute or Subacute Defibrination Syndrome

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EDITOR: Not too long ago, the most dreaded perhaps of all hemorrhagic complications in obstetrical practice was that following premature separation of the placenta. When fully under way it is a major emergency. A feeling existed that the hemorrhage involved more than the simple tearing and exposure of open blood vessels. Continuation of the hemorrhage even in the presence of what seemed to be adequate measures for its control, and excessive bleeding from fresh sites during and after operations designed to arrest it, forced the conclusion that the uterine hemorrhage was the expression of a systemic disorder of hemostasis. Development and enlargement of this concept by Schneider, and Duncan Reid and his associates, hastened the early recognition of this clinical syndrome in its various guises, and provided ways for probing its mechanisms and eventually for effective control of the hemorrhage. The remarks that follow are the independent answers to pertinent questions put to a group of workers familiar with these problems. We are indebted to Dr. Duncan Reid for help in framing the questions and selecting the participants. We shall begin by asking: Under what obstetric conditions is a clotting defect responsible for excessive bleeding likely to be encountered? Are there any clotting deficiencies other than that due to defibrination which may develop in complications of pregnancy?

MOLONEY: In my experience, by far the most frequent condition associated with a clotting defect in pregnancy has been fibrinogenopenia in the presence of premature separation of the placenta. The next most common problem has been the fibrinogen deficiency found in prolonged retention of the dead fetus. While clotting defects have been described with amniotic fluid embolism, I have not encountered this complication. Prothrombin and proaccelerin are often decreased along with fibrinogen but deficiencies of these clotting factors
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Do not contribute to the hemorrhagic diathesis, in my opinion. Presence of a circulating anticoagulant has been described in late pregnancy. I have not found such a case, but we have seen two nonpregnant female patients with what seemed to be a circulating antithromboplastic antibody. Presumably this antibody arose by isoimmunization via fetal tissue.

Phillips: In answering this and subsequent questions the term "defibrination" has been interpreted to mean a decrease in fibrinogen level, regardless of the mechanism which may be responsible for this decrease. While clotting defects in obstetrics occur most frequently in cases of abruptio placentae and long-standing intrauterine fetal death, such dyscrasias should be suspected in any case of severe hemorrhage. At Sloane Hospital, Columbia-Presbyterian Medical Center, during the last five years, five cases of defibrination have been encountered in cases of placenta previa, four in normal spontaneous deliveries, three in secondary elective sections, five in cases of retained secundines, and a few in other categories. In addition to hypofibrinogenemia, decreased levels of proaccelerin and plasma thromboplastin component (PTC) and elevated prothrombin times have been encountered. While deficiency of PTC is probably not important except where operative intervention becomes necessary, the low levels of proaccelerin may add to the hemorrhagic difficulty.

Pritchard: Clotting defects thought to be responsible for bleeding have been described in a great variety of obstetrical conditions. A clotting defect which causes excessive bleeding is most likely to be associated with the following conditions, listed in their approximate order of frequency: (1) placental abruption, (2) prolonged intrauterine retention of a dead fetus, (3) amniotic fluid embolism, (4) transfusion of incompatible blood, and (5) infected abortion. Hypofibrinogenemia is the prominent defect in these conditions but is often accompanied by varying degrees of thrombocytopenia, hypoprothrombinemia, reduction in accelerator globulin activity, and a moderate increase in circulating fibrinolytic activity. The deficiency of clinical importance is hypofibrinogenemia, for, in most cases, just the administration of fibrinogen results in prompt control of the hemorrhage, even though the other alterations have not been corrected.

Ratnof: Premature separation of the placenta, the intrauterine retention of the dead fetus, amniotic fluid embolism, and self-induced abortion may be accompanied by a hemorrhagic syndrome in which hypofibrinogenemia or even afibrinogenemia is the most striking feature. Other coagulative abnormalities may be present in some patients with these disorders. These diseases may not encompass all causes of hypofibrinogenemia associated with pregnancy, for some cases cannot be classified adequately. A bleeding tendency may also occur in patients with severe toxemia of pregnancy. Probably the most important abnormality in such patients is thrombocytopenia, which is particularly likely to occur in association with frank hemolytic anemia. A hemophilia-like state may appear in patients within a few months subsequent
to delivery. In such individuals, a circulating anticoagulant directed against antihemophilic factor may be demonstrated in the peripheral blood. Finally, hemorrhagic states unrelated to pregnancy may present specific problems to the obstetrician; idiopathic or drug-induced thrombocytopenic purpura or the rare case of true hemophilia in the female are examples.

**REID:** A clotting defect taking the form of hypofibrinogenemia is occasionally encountered as a complication in severe premature separation of the placenta, long-standing fetal death, and amniotic fluid embolism. Premature separation of the placenta is the most common cause of late pregnancy bleeding. In 90 to 95 per cent of the cases with this condition, placental separation is minimal and the prognosis for mother and baby is good. The remaining 5 to 10 per cent of patients with placental separation, however, are those with the severe form of abruptio, and it is in these cases where a clotting defect is liable to occur. For no understandable reason, an upset in the clotting mechanism in the case of fetal death in utero rarely develops until the fetus has been retained for four to six weeks after the fetal heart tones and motion are lost. Defibrination often occurs prior to the onset of labor, and the appearance of petechiae, ecchymoses, and bleeding from the mucous membranes may be the first signs of a derangement in the clotting ability of the blood. Amniotic fluid embolism, which is fortunately only a rare complication of pregnancy, may be associated with an upset in coagulating ability if the patient withstands the embolic insult. If therapeutic measures designed to combat the initial shock are successful, one must be aware of the possibility of subsequent death from hemorrhage. Defibrination appears to be the main clotting defect which may complicate the course of a parturient patient. An acquired hemorrhagic diathesis has been observed several weeks prior to and after delivery and resembles hemophilia. This difficulty appears to be the result of a circulating anticoagulant which interferes with the precursor of plasma thromboplastin. Recovery depends on multiple transfusions, which may not prove sufficient.

**SCHNEIDER:** Abruptio placentae provides the most frequent coagulation defect, once per 100 to 1000 live births; coagulation of fibrinogen to fibrin is activated, within and of, the circulating blood (over an interval of minutes). This fibrinogenation, naturally, causes a simultaneous “defibrination,” i.e., defibrinogenation. The degree of fibrinopenia provides a convenient index for the degree of an important, underlying, hyperacutely acquired, panhemostatic, depletion—a depletion such that, had it been first studied by a cytohematologist, it might well have been named instead, “acutely acquired thrombocytopenia.” Tissue thromboplastin, autoextracted from the decidua by a kind of feedback of blood, from the expanding arterial retroplacental hematoma, provides release of a more or less activated coagulation mixture into the maternal circulation. By contrast, such autoextraction does not occur during the (venous) hemorrhage from marginal separation of the placenta, i.e., during marginal sinus rupture, or from placenta previa. When the placental separation of abruptio becomes self-limiting, or has become complete, or when
delivery occurs, autoextraction comes to an end and thus the autoextraction may become in a sense, self-limiting. Fibrination may also become self-limiting as the fibrinogen is consumed; some degree of “thrombin inhibitory” action also develops. In experimental fibrination, the deposits of fibrin cause acute cor pulmonale and circulatory failure, to the degree of syncope and/or death. These reactions, though severe, may be transient not only because of humoral, reflex and collateral circulatory mechanisms, but secondarily because there follows a spontaneous early removal of the fibrin occlusions, probably by fibrinolysis. According to current concepts, plasminogen is adsorbed onto fibrin during its formation. If plasmin becomes activated spontaneously in some way as a result of fibrination, then hemorrhage, after an interval, may result secondarily from coincidental thrombolysis of hemostatic thrombi already laid down in relation to traumatic or surgical wounds.

Contrariwise, in amniotic fluid embolism, particulate debris is the primary cause of disseminated pulmonary embolism, hence of acute dilatation of the right heart and of “obstetric shock”; fibrin is not found; little tissue thromboplastin is released into the maternal circulation. In contrast to the fibrinopenia of abruptio, if the shock has been sufficient, there is sometimes a heparin-like total inhibition of coagulation—with continued normal fibrinogen levels. In lesser degrees of amniotic embolism there may be variable degrees of defibrination (due to fibrination or otherwise) and activation of fibrinolysis. Abruptio placentae and amniotic embolism occasionally occur in the same patient.

In the dead fetus syndrome, there is probably release of potent materials from autolysis into the maternal circulation. During labor and delivery of a hydatid mole, during trophoblast embolism, or during decidual embolism fibrinogen-defibrination of variable degree and duration may develop. Likewise, the rare but sometimes massive transplacental autotransfusion of blood from the fetus to its sometimes sensitized mother may conceivably produce microembolism and defibrination just as may any mismatched transfusion. “Blood thromboplastin,” in contrast to “tissue thromboplastin,” providently does not cause fibrination; i.e., in general, platelets do not cause fibrination. Were this not so, there would be a hazard that any thrombus might progress to fibrination. Perhaps, under special conditions, fibrination from blood thromboplastin may develop in transfusion reactions. This or some other mechanism may act even more slowly in the generalized Schwartzman reaction. Since, during pregnancy, the sensitizing dose is not required for this generalized reaction, there is prolonged susceptibility to provocative exposures to bacterial endotoxins. This vulnerability seems to extend into postabortal and postpartum intervals, notably during development of sepsis. In the generalized Schwartzman reaction a peculiarly progressive shock develops with slowly progressive defibrination and deposition of “fibrinoid” (within an interval of hours). Fatal progression of the process has been inhibited in experimental animals and in one woman (Pfau and Mohle) by cautious use of heparin. It is to be emphasized that neither the Schwartzman reaction nor amniotic embolism involves an anaphylactic reaction. Severe hemorrhage, whether alone or superimposed upon any of the above conditions, is sometimes followed by de-
fibrination, perhaps under the initiation of some obscure activation of fibrina-
tion and subsequent fibrinolysis, not necessarily with accumulation of fibrin,
perhaps in a manner comparable to postmortem coagulation and lysis. Thus,
obstetric management of simple maternal or puerperal hemorrhage is still of
prime importance. Prevention of blood loss is to be preferred to blood re-
placement not only quantitatively but qualitatively. Management of abruptio
placentae clinically, to minimize fibrination-defibrination, is to be preferred
to treatment of defibrination.

EDITOR: There is unanimous agreement that coagulation disorders are most
frequently encountered in obstetrical practice in association with premature
separation of the placenta, and that the commonest defect is a fibrinogenopenia.
Other less common causes are a retained dead fetus, amniotic fluid embolism,
placenta previa and infected abortions. Defects in other hemostatic factors may
be observed, though less frequently, namely thrombocytopenia, deficiencies of
prothrombin and accessory coagulants or an excessive amount of anticoagulants.
The hemorrhagic complications of intrauterine fetal death may come about
insidiously or appear suddenly about the time of delivery. This poses several
clinical problems. How may one detect an incipient defibrination in a patient
with intrauterine fetal death? If this develops, what is the earliest time that it
might be expected to appear? Does defibrination constitute a major problem of
management before the twenty-eighth week of pregnancy?

MOLONEY: The best method of detecting deficiency associated with dead
fetus in utero is to carry out serial determinations of fibrinogen concentration
in the maternal plasma. We use the tyrosine method. Usually the fetus must
be dead in utero three to five weeks before a decrease in fibrinogen is demon-
strable. Unless the patient goes into labor or premature separation of the
placenta occurs, the presence of a moderately lowered fibrinogen level d.e.;
not lead to spontaneous bleeding. The problem of management usually con-
cerns the question of risk of bleeding during delivery or cesarian section. Our
practice is to administer 4 Gm. of fibrinogen I.V. before delivery; in severe
cases we give 6 Gm. at one time. The patient is delivered from below or by
section, as indicated. If prolonged labor or rapid defibrination occurs, repeated
doses (4 Gm.) of fibrinogen are given as needed.

PHILLIPS: At the Sloane Hospital it has become routine procedure to obtain
weekly fibrinogen determinations on all patients where fetal demise is sus-
pected. The fibrinogen level may gradually decrease, thus giving warning
that a clotting deficiency may be developing. However, after an initial de-
crase, the level has been known to return to normal or low normal values
spontaneously. Five or six weeks has been the minimum time after fetal death
at which a state of defibrination has been encountered here. However, Ratnoff
reports that it can occur as early as three weeks after the death of the fetus.
Defibrination can constitute a major problem of management during preg-
nancy at any time that an obstetrical complication may occur. It has been
seen in cases of abruptio placentae as early as the sixth month, in cases of
incomplete abortion at 14 weeks, or in cases of fetal death as early as 16 weeks.
PRITCHARD: The best way to detect incipient hypofibrinogenemia in a patient with intrauterine fetal death is to measure the plasma fibrinogen concentration at weekly intervals starting about three weeks after fetal death. More than 100 patients with a fetus dead in utero for varying periods of time have been studied in our laboratory. A plasma fibrinogen level below 150 mg. per 100 ml. has not been detected in less than five weeks after death of the fetus. In 18 out of 50 patients in whom a fetus remained dead in utero for 5 or more weeks it dropped below 150 mg. per 100 ml. The range in these 18 was 46 mg. to 134 mg. per 100 ml. The gestational age of the fetus in these 18 cases at the time of death varied from 16 to 31 weeks and averaged 24 weeks. The period of intrauterine retention ranged from 5 to 12 weeks and averaged 9 weeks. By initiating studies prior to any clinical evidence of abnormal hemostasis, data have been compiled which indicate that in the woman who carries a fetus dead in utero for 5 or more weeks the odds are 1 in 4 that the fibrinogen concentration will drop to a potentially dangerous level.

RATNOFF: When one suspects that intrauterine fetal death has occurred, one should, at intervals of about five days, determine the concentration of fibrinogen in the circulating plasma by a quantitative method. The patient should also be instructed to report any hemorrhagic symptoms, however trifling. If the concentration of fibrinogen falls below 200 mg. per 100 ml. of plasma, steps should be taken to deliver the fetus; if the concentration of fibrinogen is less than 130 to 150 mg. per 100 ml., one may wish to transfuse 3 or 4 grams of human fibrinogen intravenously just prior to delivery. At the time of labor, whether or not the patient has been tested previously, qualitative estimation of the concentration of fibrinogen should be made and therapy directed accordingly. Hypofibrinogenemia may be detected in women in whom fetal death has occurred as early as the sixteenth week after the onset of the last menstrual period, and bleeding may occur within three weeks after fetal death. Thus, hypofibrinogenemia can be a serious problem prior to the twenty-eighth week of pregnancy. A transient hemorrhagic syndrome accompanied by hypofibrinogenemia has been described in association with partial premature separation of the placenta, subsequent to which the fetus has not been delivered. In such cases, the concentration of fibrinogen may return rapidly to normal, even though the fetus is retained in utero.

REID: The patient with intrauterine fetal death should have blood drawn at weekly intervals to perform the “clot observation test.” This merely consists of watching a clot of blood in a clean test tube to see whether it remains stable over a period of 1 to 2 hours, or whether clotting is delayed beyond the conventional 8 to 12 minutes. Defibrination is essentially an intrapartum phenomenon, although, as noted above, it may appear before the onset of labor in patients with long-standing intrauterine fetal death. Thus, this complication rarely poses a serious problem before the twenty-eighth week of pregnancy.

SCHNEIDER: Defibrination in the dead fetus syndrome occurs, (1) by gradual and (2) by acute, onset. Weekly fibrinogen assays, after suspected fetal death, although adequate to detect gradual onset, may be too infrequent to detect
actite onset. Accordingly, acute onset (often associated with onset of labor, occasionally with abruptio) may be first suspected clinically, then be evaluated by fibrinogen assay. Defibrination, first noted to occur in gravidas carrying a fetus dead in utero for eight weeks or longer, has been found at six weeks. When fetal death occurs, the tendency in the human is for early spontaneous delivery. The dead fetus syndrome is most likely to develop when a missed abortion of the second trimester is carried into the third trimester; it rarely occurs before the twenty-eighth week of total gestation, probably never in the first trimester. As long known, to accede to demands of the family to “do something because of the poisons from the dead baby” may be to precipitate disaster by ill-advised efforts to induce labor, perhaps in some instances opening a pathway to autoextraction; the hazard, whether spontaneous or induced, is greatest in association with cervical dystocia due to an “unripe cervix” of premature labor, early in the third trimester.

EDITOR: It seems that the feeling of most members of the group is that weekly determinations of the fibrinogen level in the plasma should be done once the diagnosis of intrauterine fetal death is made. The hemorrhagic manifestations may appear any time from three to six weeks after death of the fetus. Defibrination may occur as early as the sixth month of gestation, but is rarely seen before the twenty-eighth week.

To be in a position to judge incipient defibrination, one must, however, be familiar with fibrinogen levels in pregnant and nonpregnant women. What may be regarded as the range of values of the fibrinogen concentration in the third trimester of normal pregnancy, and how does this compare with the range of values found in nonpregnant females? Below what concentration should one suspect a defibrination process? What test to be done at the bedside do you consider to be most convenient and informative as to the presence and degree of defibrination?

MOLONEY: We accept the range of fibrinogen concentration in the third trimester of pregnancy as 20 to 30 per cent above the usual levels for nonpregnant females, i.e., 300 to 600 mg. If levels are below 200 mg. in the third trimester, fibrinogenopenia should be suspected. The best test for bedside use is still in my opinion the clot observation test (Weiner and Reid).

PHILLIPS: In two series of women studied here during pregnancy, fibrinogen levels at term were found to range from 267 mg. per cent to 512 mg. per cent, with an average of 393 mg. per cent. Normal nonpregnant ranges (by the Ratnoff and Menzie method) are generally considered to be between 200 and 450 mg. per cent, with an average of approximately 300 mg. per cent. Since fibrinogen levels are elevated during pregnancy, any value below 200 mg. per cent should be considered as evidence of a potential clotting deficiency, although not necessarily a dangerous one. Only a combination of decreased fibrinogen levels with clinical manifestations such as hemorrhage, shock, hematuria, et cetera, can indicate the necessity for fibrinogen therapy. Once a value below 200 mg. per cent is reached, however, levels should be followed
at frequent intervals until delivery is accomplished, danger of postpartum hemorrhage is over, and fibrinogen levels have returned to normal. We have found that observation of a tube of whole blood, first for clotting and then for apparent lysis, is the most useful of the bedside tests. Failure to clot, lysis of a formed clot, or strong retraction of the clot to a nubbin of fibrin are all good evidence of potential clotting difficulties. However, if at all possible, quantitative determinations should be made since only in this way can a gradual change be observed. The method of Ratnoff and Menzie has been found to be most convenient both as a qualitative and quantitative determination. The first step of this method consists of dilution of plasma 1 to 20 with saline and subsequent clotting on ground glass by addition of thrombin. To anyone familiar with the method, this step can give an approximate estimate which can be acted upon in an emergency and yet provide for a subsequent quantitative value.

PRITCHARD: The usual range of values for fibrinogen concentration in the third trimester of normal pregnancy found in our laboratory is 300 to 600 mg. per 100 ml. This is about 50 per cent greater than the range found in normal nonpregnant females. If the fibrinogen level approaches 200 mg. per 100 ml. during pregnancy, one should suspect a defibrination process. The test to be performed at the bedside which has proved most convenient and informative is a simple clot observation test. It is performed in the following way: Stoppered ordinary glass test tubes 13 mm. in diameter which contained approximately 0.1 ml. (2 drops) of topical thrombin solution are kept in the freezing compartment of a refrigerator in the area. About 1 ml. of freshly drawn blood is placed in the tube. Normally, a firm clot will appear almost immediately. With hypofibrinogenemia of clinical importance there may be no visible clot or the clot may at first inspection appear normal. In the latter instance, if in a few minutes the tube is tapped against a firm surface, the clot will retract to a small ball from which most of the red cells will be extruded and the liquid phase will exceed the clot in volume.

RATNOFF: The concentration of fibrinogen during the third trimester of normal pregnancy varies from 325 to 550 mg. per 100 ml. of plasma, averaging 450 mg. per 100 ml. at term. In contrast, the concentration of fibrinogen in nonpregnant women averages about 300 mg. per 100 ml., ranging from 170 to 480 mg. One should suspect some abnormality if the pregnant patient’s fibrinogen is less than 300 mg. per 100 ml., but one cannot make a diagnosis of hypofibrinogenemia unless the concentration of fibrinogen falls below 200 mg. per 100 ml. A value such as 250 mg. per 100 ml. may merely mean that the stimulus to hyperfibrinogenemia has been removed. The most informative bedside test in our experience is estimation of the size of the clot obtained when blood is mixed with thrombin. The operating room should be provided with clean Pyrex tubes scored at the 1 ml. mark, each containing 0.1 ml. of topical thrombin solution (1000 National Institutes of Health units per ml.), stored in a deep freeze. When hypofibrinogenemia is suspected, about 10 ml. of venous blood should be drawn, a tube containing thrombin filled to the 1 ml.
mark, and the remaining blood used for quantitative determination of fibrinogen and for cross matching. Failure of blood to clot in the presence of thrombin suggests afibrinogenemia. If hypofibrinogenemia is present, the clot which forms will shrivel to a small size upon gently tapping the tube. Experience judging the size of the clot and the correlation of this size and the quantitative amount of fibrinogen present must of course be gained prior to an emergency. Details of this technic have been published elsewhere (New England J. Med. 253:63, 1955).

REID: The fibrinogen concentration of the plasma of patients in the third trimester of normal pregnancy will vary from 350 to 600 mg./100 ml., while the range of values in the plasma of nonpregnant women is 200 to 350 mg./100 ml. In the pregnant patient, a plasma fibrinogen concentration of 150 mg./100 ml. or less should make one suspect a defibrination process. It is to be emphasized that the presence of a fibrinolyis will influence clot stability regardless of the fibrinogen concentration. As a strictly bedside procedure, the clot observation test has proved of value in estimating the coagulating ability of the patient’s blood. At the time the blood is collected for this test, an aliquot of plasma is taken for a quantitative determination of fibrinogen in the laboratory which can be completed during the period the clot is being observed. The semi-quantitative tests introduced by Schneider and Bonsnes and Sweeney have merit, but these procedures require a certain amount of manipulation with reagents and laboratory equipment. Effective hemostasis, however, is dependent more on clot stability than any arbitrary value of circulating fibrinogen.

SCHNEIDER: Third trimester plasma fibrinogen in normal pregnancy 0.3 to 0.5, in severe toxemia of pregnancy up to 1.0, in men and nonpregnant women 0.2 to 2.4 Gm. per cent. Congenital afibrinogenemia (pregnancy in only one, as yet unreported) or fibrinopenia is so rare as not to cause confusion. Hence, while 150 mg. may be suggestive of early defibrination, yet the critical level for hemorrhagic diathesis from fibrination-defibrination is less than 90 to 100 mg. per cent. Definitive methods for fibrinogen are now so ubiquitous, rapid (a few minutes), accurate and simple, as to render bedside methods unnecessary in hospitals with a spectrophotometer for assay, either by (1) transmittance through diluted plasma clot (Vogt), or more simply (2) by transmittance through fibrinogen salted out with ammonium sulfate. For smaller laboratories, a modified plasma fibrin titer assay (thrombin for coagulation, methylene blue to visualize fibrin) moves this semi-quantitative test from bedside to laboratory. “Clot observation” is simple, dramatizes the severe case. As with whole blood titer, care must be taken that the clot not be lost in the sediment of erythrocytes. Fibrinogen levels, while helpful, do not substitute for obstetric diagnosis and management. The problem, (e.g., in abruptio placentae) is to minimize further fibrination-defibrination.

EDITOR: There is uniform agreement that the fibrinogen levels in the third trimester of pregnancy are higher by 20 to 50 per cent above the level found
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in nonpregnant women. At the third trimester the fibrinogen levels are thought to range between 300 and 500 mg. Most of the participants believe that when the level falls below 200 mg. a defibrination process may be impending, or taking place. Two of the participants feel that such is the case when levels of 150 or less are reached. The clot observation test is felt by the majority to be the most dependable bedside estimate of defibrination.

When the defibrination syndrome is under way, how much fibrinogen may be administered to an obstetric patient with the syndrome? Should this be supplemented with whole blood transfusions, ACD plasma or with commercial serum albumin (containing antifibrinolysin)? What is the danger of viral hepatitis following fibrinogen infusion alone?

MOLONEY: The largest single dose we have given has been 6 grams at once. A total of 14 grams during a prolonged bleeding problem has been the largest total dose in our series. Whole blood is urgently required in adequate amounts to combat shock and blood loss. We have not used concentrated plasma or serum albumin in our obstetrical cases. We have used concentrated plasma with fibrinogen in leukemia and prostatic cancer associated with severe fibrinogenopenia. In our 19 cases of fibrinogenopenia in pregnancy we have had 2 cases in which hepatitis developed following administration of fibrinogen. Since these patients had received whole blood, etc., it is difficult to determine whether a viral agent was transfused with fibrinogen. In my opinion the risk of fatal hemorrhage far outweighs the possible transfer of viral hepatitis. In regard to theories concerning the mechanism of fibrinogen deficiency in pregnancy, the present consensus favors the concept that thromboplastin is infused intravascularly from the placental site and causes defibrinogenation. It is conceded by most investigators that secondary fibrinolysis must ensue to get rid of the deposited fibrin. The chief objection to the theory that fibrinolysis and fibrinogenolysis play the major role in production of the fibrinogenopenic state is the inability to demonstrate lytic activity in vitro. However, it is widely accepted that a potential fibrinolytic enzyme exists in normal plasma and that this lytic enzyme can be activated by various agents, including tissue extracts. In other biologic problems, demonstration of active agglutinins for red cells have evaded investigators for years. Not so many years ago Rh antibodies could not be detected in maternal serum until Coombs and others found methods of demonstrating these agglutinins on the red cell's surface. Like Rh hemolysins which have never been detected in vivo or in vitro, there are fibrinolytic and fibrinogenolytic enzymes, activated by placental or fetal tissues, which present methods fail to detect, but which are the chief causes of fibrinogen deficiency in these obstetrical clotting problems. It is of course possible that intravenous vascular clotting may also precipitate an exaggerated lytic activity or that in some as yet undisclosed fashion antifibrinolytic factors are destroyed or nullified, allowing lysis to occur. In any event, the final solution of the problem will not be reached until more information at the enzyme and protein chemistry level is obtained. There is, however, the practical problem of management of these cases. It is disturbing to note that some authorities are minimizing the importance of fibrinogen therapy. Certainly in
severe deficiencies, especially associated with premature separation of the placenta, adequate replacement of fibrinogen is a life-saving measure. While milder forms of fibrinogenopenia may be treated with whole blood, the ineffectiveness of blood and plasma in afibrinogenemic cases is well documented in the literature. In my own experience with 19 cases of fibrinogenopenia in pregnancy, only one case was terminated fatally. That patient exsanguinated while being given whole blood transfusion and before fibrinogen could be administered. No untoward effects were noted in our series due to administration of fibrinogen. In view of the current concept that the disorder is due to defibrinogenation by a circulating thromboplastin, it seems curious that when 6 grams of fibrinogen are administered by relatively rapid infusion, no massive intravascular coagulation takes place. My own interpretation is that the larger, rapidly administered amounts of fibrinogen cause a rapid rise in concentration of substrate and that this, temporarily at least, inhibits the lytic enzyme activity. Smaller doses (2 grams) and amounts contained in whole blood and plasma do not raise the substrate concentration sufficiently or rapidly enough to “throttle” the enzyme.

I have no experience with the role of ACTH or corticosteroids in the treatment of acute fibrinogenopenia in pregnancy. It would seem hazardous to neglect the use of fibrinogen and employ these agents for theoretical reasons. In practice i.v. fibrinogen has now been used in many cases since we (Moloney, Egan and Gorman) treated the first patient in April 1948. With proper indications and use, i.v. fibrinogen has proven to be a life-saving and relatively safe method of therapy for what was hitherto known as catastrophic hemorrhagic disorder in pregnancy.

PHILLIPS: Seven grams is the maximum quantity of fibrinogen that has been required by any obstetrical patient at this institution. However, 10 grams have frequently been administered by other investigators and there is one report of over 20 grams having been given to one patient. It is desirable, where possible, to give only one “Lot number” to a patient in order to minimize the danger from hepatitis. Fibrinogen is seldom given except in cases of acute hemorrhage. Therefore, whole blood transfusions are usually required to maintain the hematocrit. However, overtransfusion should be avoided since stored bank blood is low in labile clotting factors but provides a fresh source of profibrinolysin which may be activated and so continue the cycle leading to further depletion of fibrinogen. Where possible, fresh blood should be used since it is a better source of proaccelerin and possibly antifibrinolysin. ACD plasma, while useful in maintaining osmotic pressure where whole blood is not available, may be inadvisable as it also adds a potential source of fibrinolysin. Serum albumin is probably more helpful since it will contribute both to the maintenance of osmotic pressure and to control of the fibrinolytic system by addition of antifibrinolysin. It may be particularly efficacious in slowly developing cases of hypofibrinogenemia where hemorrhage has not yet become a problem. Since fibrinogen infusion is almost always accompanied by multiple blood transfusions, no adequate statistics are available on the incidence of hepatitis from it alone. On our obstetrical service, out of ap-
approximately 30 patients to whom fibrinogen and whole blood had been administered, one and possibly two patients have developed hepatitis. This is an incidence of about 4 to 7 per cent, which is low compared to others (45 per cent at one institution).

PRITCHARD: The administration of 4 to 6 Gm. of fibrinogen should promptly raise the plasma fibrinogen concentration by an increment of 100 to 150 mg. per 100 ml. In my experience this dosage along with prompt evacuation of the uterus has resulted in adequate hemostasis. Whole blood should be utilized to combat hypovolemic shock due to hemorrhage. A well contracted myometrium immediately postpartum is the most effective mechanism for achieving hemostasis at the site of placental implantation. In the presence of shock, even though the mechanism for blood coagulation is normal, the uterus typically is hypotonic. Consequently there will be serious hemorrhage from the site of placental implantation. I have had no experience with ACD plasma or commercial serum albumin in these patients but see little need for their use. I prefer to deliver the patient vaginally if it can be accomplished fairly soon and if the degree of hemorrhage is not so great that immediate evacuation of the uterus is mandatory. Whole blood is administered to combat shock, little or no anesthesia is used, and delivery is affected without an extensive episiotomy or lacerations. As soon as the uterus is emptied, constant fundal massage plus a continuous intravenous infusion of oxytocin are started. Usually the uterus contracts well and bleeding is no problem, even though hypofibrinogenemia persists for several hours longer. If excessive bleeding continues, then 4 Gm. of fibrinogen are given. If a laparotomy is to be performed to effect delivery, fibrinogen in a dose of 4 to 6 Gm. is given just before starting the operation. Nine patients have been followed for several months after they received fibrinogen. Two developed clinical homologous serum hepatitis and were quite ill. One of the two received only fibrinogen. A survey of the members of the Central Association of Obstetricians and Gynecologists revealed that, of a total of 727 patients who had been given fibrinogen, one in 20 were known by their obstetricians to have developed homologous serum hepatitis.

RATNOFF: The amount of fibrinogen which should be administered to patients with hypofibrinogenemia varies from case to case. After an initial injection of 4 grams, the concentration of fibrinogen in the patient's plasma should be followed qualitatively and further therapy with fibrinogen administered accordingly. As much as 10 or 15 grams may be needed in some cases, but the usual patient needs only the initial 4 grams. It is important to remember that fibrinogen is not a panacea, and will not correct other coagulative abnormalities or local pathologic changes. Whole blood or plasma should be used for the treatment of shock. As we have gained experience, we have used less and less whole blood, fearing the many acute and chronic complications of transfusion. We have no experience with the use of serum albumin. The view that hypofibrinogenemia results from excessive fibrinolysis is controversial, and considerable experience argues against it. For this reason, we have not directed therapy at the problem of excessive fibrinolysis. The danger of viral hepatitis
following fibrinogen infusion alone is difficult to evaluate, since nearly every patient has also received blood or plasma. However, there is no question that patients receiving fibrinogen have an excessively high incidence of homologous serum jaundice. We do not have exact statistics, but at least five patients in our experience have had hepatitis, an incidence much greater than that of patients who have not been transfused with fibrinogen. It is therefore important to be sure that the indications for the transfusion of fibrinogen are real and that one does not administer this agent through fear and the feeling that “something must be done” for the critically ill patient.

REID: Experience has shown that 4 to 10 grams of fibrinogen will usually be required to restore effective hemostasis in the patient suffering from the defibrination syndrome. This should be supplemented with fresh whole blood transfusions, particularly when bleeding is active. The danger of viral hepatitis resulting from fibrinogen infusion is slight, and it is felt that the advantages accruing to the patient through this type of therapy must far outweigh the risk. A rule of thumb for fibrinogen therapy is to administer 1 Gm. for each 500 ml of blood.

SCHNEIDER: Need for fibrinogen is truly rare; then give enough, 4 to 6 grams. Small amounts are to be deplored, e.g., one gram raises the fibrinogen 20 to 25 per cent. Obstetrical management is directed toward preventing or minimizing further defibrination, not to replace fibrinogen. Mother accomplishes restoration spontaneously with supportive therapy. Overloading of the circulation is a hazard in a patient with recent acute cor pulmonale (from abruptio, or amniotic embolism). Transfusions should not exceed the estimated blood loss. In severe defibrination, ACD plasma restores both fibrinogen and plasma enzymes of coagulation. Unfortunately, hepatitis virus irradiation tends to inactivate fibrinogen and enzymes. Theoretically, antifibrinolysin of serum albumin would be of promise in severe defibrination or when much fibrinolysin is demonstrable. Danger of hepatitis increases with: (1) blood, (2) plasma, (3) fibrinogen, respectively (theoretical 50 per cent risk from a pool of 100 plasmas). Hazard increases if fibrinogen from two lots is used. Some patients are immune. (Experience of one obstetrician: hepatitis in two of four patients). According to Anderson (Michigan State Health Laboratories) there has been, after administration of irradiated fibrinogen, less hepatitis than expected from accompanying blood transfusions—a good product even if allowance is made for undetected hepatitis because of difficulty of obtaining follow-up reports.

EDITOR: It appears that most of the participants regard from 4 to 10 grams of fibrinogen to be the average dose needed for an acute defibrination syndrome. In most instances, 4 to 6 grams have been used. As much as 15 to 20 grams may occasionally be necessary. Whole blood, preferably fresh, should be given principally to combat shock and to replace blood volume. ACD plasma is not advised, and there has not been sufficient experience with serum albumin to
warrant recommending it. There is difficulty of separating the viral hepatitis that may follow whole blood transfusions and that secondary to fibrinogen injection. Most of the participants, however, feel that there may be a slightly higher risk of viral hepatitis from injections of fibrinogen than of whole blood. Considering the benefits of fibrinogen administration, the risk is calculated to be well worth taking.
Clinical Section: Management of the Obstetrical Patient with Hemorrhage due to an Acute or Subacute Defibrination Syndrome