REVIEW ARTICLE

AMNIOTIC FLUID EMBOLISM

SOL M. SHNIDER, M.D., AND FRANK MOYA, M.D.

AMNIOTIC fluid embolism is a dramatic catastrophe which may occur during labor or delivery. It is caused by a sudden infusion of amniotic fluid into the maternal circulation and is clinically reflected by four cardinal signs: respiratory distress, cyanosis, cardiovascular collapse and coma. In addition, if the initial episode is survived, afibrinogenemia, accompanied by profuse uncontrollable bleeding, may occur. This syndrome has been recognized by some as the most common cause of obstetrical death during labor, delivery, and the immediate post-partum period.[1, 2] The anesthesiologist is usually present when this complication occurs, and must, therefore, be alert to the possibility of its occurrence and aware of its management.

It is the purpose of this paper to review the syndrome with particular emphasis on the problems of diagnosis, pathogenesis and management.

HISTORY AND INCIDENCE

Although amniotic fluid embolism was first described by Meyer[3] in 1926, and intravenous injections of amniotic fluid were administered to experimental animals by Warden[4] in 1927, it was not until the publication of Steiner and Lushbaugh[1] in 1941 that widespread interest was aroused. They presented the first 8 documented cases of amniotic fluid embolism. Furthermore, they administered, intravenously, meconium and amniotic fluid to animals, producing "anaphylactoid" shock, pulmonary edema and death. Microscopic examination of the small arteries, arterioles and capillaries of the pulmonary vascular bed revealed the same embolic material as that seen in their 8 patients. Thus the syndrome became a distinct pathologic entity which was to be suspected clinically in every case of sudden severe shock during labor or the immediate puerperium.

Steiner and Lushbaugh[1] suggested that amniotic fluid embolism was probably a more common cause of death than generally recognized, masquerading in nonautopsied fatal cases under such diverse diagnostic guises as thrombotic pulmonary embolism, "obstetric shock" or post-partum hemorrhage. They noted that in their hospital, this syndrome was the most common cause of obstetrical death during labor, delivery, and the immediate post-partum period. A review of the maternal mortality at The Sloane Hospital for Women from 1945 to 1959 (table 1) corroborates this observation. Seven patients died during the intra-partum or immediate post-partum period due to factors directly related to pregnancy and its management. Four of these had pulmonary embolism with amniotic fluid. This represents approximately 20 per cent of all obstetrical deaths occurring during pregnancy and within six months of parturition.

The incidence of this syndrome is low when expressed as cases per thousand deliveries. At Sloane Hospital for Women, it is one case in 14,000 deliveries; The Cincinnati Hospital has reported an incidence of one case in 25,000 deliveries[5]; and the Minnesota Mortality Committee has reported one case for every 37,323 live births.[6] Gross and Benz, however, had the unusual experience of finding fatal amniotic embolism in three consecutive maternal deaths within one year in a general hospital averaging 1,250 deliveries annually. These cases represented all 3 of the maternal deaths in the obstetrical service within that period.[2]

The authors are in the Departments of Anesthesiology and Obstetrics and Gynecology, Columbia University, College of Physicians and Surgeons, and the Anesthesiology Service, The Presbyterian Hospital, and The Sloane Hospital for Women, New York, New York.

TABLE 1

OBSTETRICAL CAUSES OF MATERNAL DEATH IN 55,926 DELIVERIES (1945–1959)*

	Total Cases	Time of Death		
		Ante-partum	Intra-partum and <10 Hours Post-partum	>10 Hours Post-partum
Heart Disease	7	1	3	3
Toxemia of Pregnancy	5	3		2
Amniotic Fluid Embolism	4		4	
Infection	3			3
Hemorrhage	1	1		
Anesthesia	1			1
Total	21	5	7	9

* Death due to factors directly related to the pregnancy and its management.

DIAGNOSIS

Since the Steiner-Lushbaugh publication,[1] over 90 cases confirmed at autopsy have appeared in the literature.[2, 5–16] Other reports of presumptive cases with recovery have been published as well.[47–50] A review of these cases suggests that this syndrome usually occurs in a multipara in her mid-thirties with an uneventful ante-partum course. Characteristically, the labor is tumultuous with excessively strong and frequent contractions. Suddenly, and without warning, the signs of amniotic fluid infusion appear: hyperpnea and/or tachypnea, cyanosis and shock progressing into profound coma. In addition there is often rigor, clonic-tonic convulsions and acute pulmonary edema. If the patient survives this initial phase, incoagulability of the blood develops with excessive bleeding from raw surfaces in the uterus, vagina, and perineum. Usually despite all measures, the woman dies within 2 to 3 hours due to irreversible shock, pulmonary edema, or intractable hemorrhage.

The small arteries, arterioles and capillaries of the pulmonary vascular bed are characteristically dilated and filled with embolic material. This consists of squamous cells, amorphous debris, meconium, and lanugo hair. Varying numbers of polymorphonuclear leucocytes may also be present. These elements can sometimes also be demonstrated in the uterine vessels as well as in the right side of the heart. According to Gross and Benz,[2] a diagnosis of amniotic fluid embolism may sometimes be made by examining the blood aspirated from the right side of the heart. When the blood is centrifuged, the sediment may contain three layers instead of the usual two, the top layer being a broad, flocculent zone, lighter in color, and containing the amniotic fluid sediment. A further finding at autopsy may be the absence of blood clots.[7, 14, 22, 41] However, the presence of liquid blood is not pathognomonic of amniotic fluid embolism, as it may be found after any sudden death.[51]

Case Report. The typical course of a patient from the Sloane Hospital with amniotic fluid embolism will be described since it illustrates many of the diagnostic and therapeutic problems which arise. Other case reports have been presented elsewhere.[52]

A white female, 35 years old, gravida II, para I, in good health, entered the hospital three weeks before her expected date of confinement. Her labor was progressive with very strong and frequent contractions. She was medicated with meperidine, 25 mg. intravenously and 75 mg. intramuscularly, and scopolamine, 0.2 mg. intravenously and 0.2 mg. intramuscularly. Ten minutes later the patient vomited and shortly thereafter was transferred to the delivery room. En route it was noted that the patient was hyperpneic, cyanotic and unresponsive. Moments later the anesthesiologist exposed her larynx; no vomitus was seen in the posterior pharynx or near the glottis. An endotracheal tube was introduced quickly and her rapid respirations assisted with oxygen. Both lungs were clear, the pulse rate was 160/minute, and the systolic blood pressure ranged near 100 mm. of mercury for a short time but then became unobtainable. Oxygen under intermittent positive pressure, intravenous dextran and levarterenol were ineffective, and the heart stopped 40 minutes following the delivery of the infant. Ten minutes of massage to the flabby dilated heart produced no response.

Microscopic examination of the small arteries, arterioles and capillaries of the pulmonary vascular bed revealed embolic material consisting of epithelial cells, amorphous debris, lanugo hair, meconium and many polymorpho-

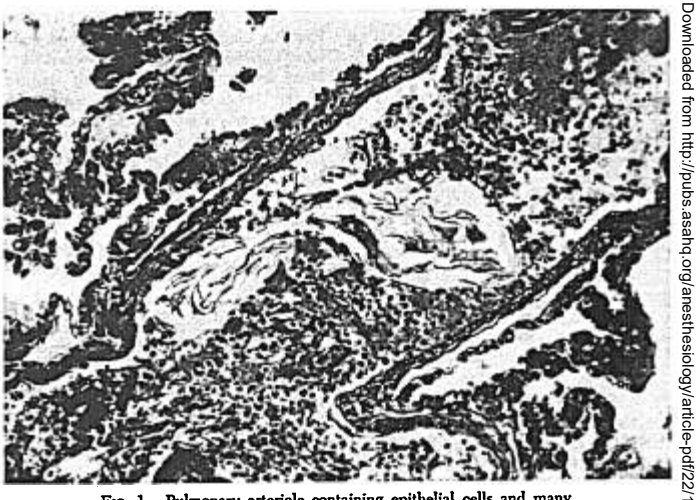

FIG. 1. Pulmonary arteriole containing epithelial cells and many polymorphonuclear leucocytes within the lumen.

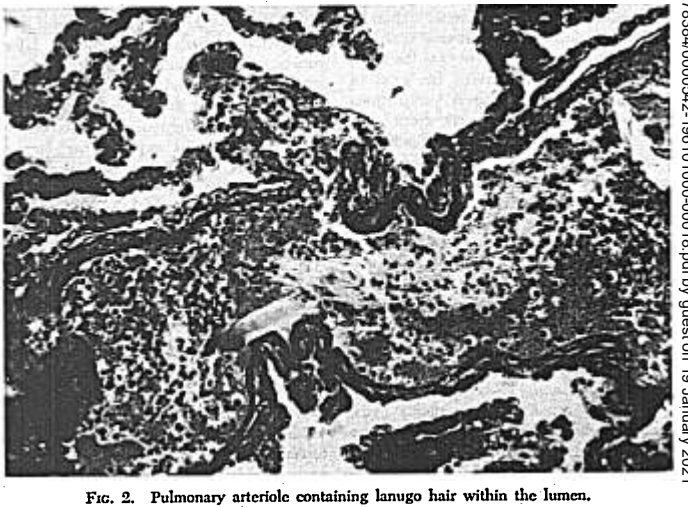

FIG. 2. Pulmonary arteriole containing lanugo hair within the lumen.

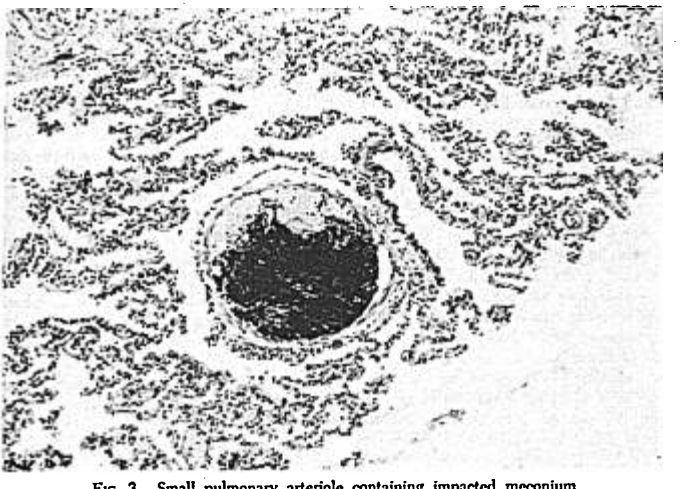

FIG. 3. Small pulmonary arteriole containing impacted meconium and amorphous debris.

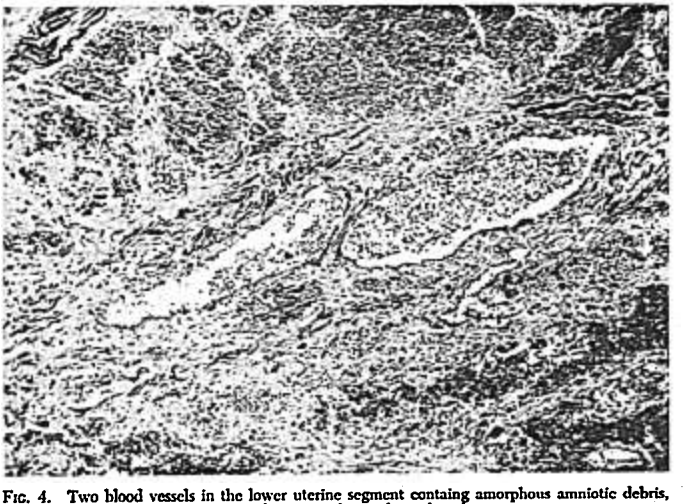

FIG. 4. Two blood vessels in the lower uterine segment containg amorphous amniotic debris, epithelial cells and many polymorphonuclear leucocytes.

nuclear leucocytes (figs. 1, 2 and 3). Similar material was noted in blood vessels of the lower uterine segment near the site of a small cervical laceration (fig. 4).

Differential Diagnosis

The clinical picture must be differentiated from air embolism, toxic reaction to local anesthetic drugs, aspiration of vomitus, eclampsia, hemorrhagic shock, cardiac failure, and cerebral vascular accidents.

Air embolism may occur following the manipulation of a placenta praevia or a ruptured uterus; when air is injected into the uterus criminally to induce abortion or accidentally while douching; or following the administration of blood under pressure. The presence of chest pain which is usually lacking in amniotic fluid embolism and the auscultation of a typical water-wheel murmur over the precordium help differentiate this condition. The other varieties of pulmonary emboli (*e.g.*, fat, venous or cardiac thrombi or placental tissue) are rarely seen complicating a delivery.

Relative or absolute overdosage of local anesthetic drugs may be produced during the administration of regional anesthesia, particularly caudal, lumbar epidural, or pudendal block. The signs and symptoms may be identical with those encountered in amniotic fluid embolism. However, the close temporal relationship of the drug administration to the onset of symptoms usually indicates the real basis of the complication.

Aspiration of vomitus with massive atelectasis usually occurs during induction or emergence from general anesthesia. Although many similarities exist, obstruction of a main bronchus is characterized by retraction of the corresponding chest wall, lack of breath sounds and shift of the mediastinum, signs not found in amniotic fluid embolism.

Eclampsia seen at term may closely resemble the syndrome in several ways but the associated hypertension, albuminuria and edema usually indicate the true nature of the convulsions and coma.

In obstetrics, hemorrhagic shock is most commonly associated with placenta praevia, abruptio placenta, ruptured uterus, retained placenta, inversion of the uterus and uterine atony. These varied conditions producing hemorrhage, hypotension and occasionally afibrinogenemia[53] can usually be differentiated from amniotic fluid embolism by a careful history and physical examination.

Rheumatic heart disease is the most common cardiac condition found in pregnancy. In patients with a limited cardiac reserve pulmonary edema may be precipitated by the emotional stress and physical strain of a tumultuous labor. The history of previous disease associated with characteristic murmurs and electrocardiographic findings aid in the diagnosis.

A cerebrovascular accident (*e.g.*, subarachnoid hemorrhage, cerebral embolism, thrombosis or hemorrhage) may simulate amniotic fluid embolism. However, a careful neurological and cerebrospinal fluid examination, as well as the usual absence of dyspnea, cyanosis and pulmonary edema, serves to distinguish the two conditions.

Pathogenesis

Mode of Infusion of Amniotic Fluid. Amniotic fluid may enter the maternal circulation via either the sinusoids at the uteroplacental site or the endocervical veins. It has been postulated that the great intrauterine pressure associated with tetanic contractions may cause rupture of the fetal membranes in the uteroplacental region.[14] The amniotic fluid dissecting between the membranes and the uterine wall, gains entry into the venous sinusoids and systemic circulation. This is substantiated in part by the identification of "amniotic squamous cells . . . between the amnion and chorion, placental margin, decidual sinusoids and myometrial veins."[49, 50] However, recent work has shown that during uterine contractions, the intramyometrial pressures may exceed 120 mm. of mercury.[8] This pressure would minimize the entry of the amniotic fluid into the vessels of the muscular upper uterine segment. On the other hand, the great intrauterine pressure would more likely drive the liquor amnii toward the cervix and into the circulation via the endocervical veins as was noted in the case report. These vessels are lacerated even in normal labor.

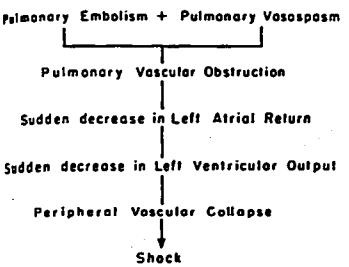

FIG. 5. Etiology of clinical picture: mechanism of shock.

Etiology of the Clinical Picture. The physiological response to the pathologic changes is highly complex and incorporates many systems, reflexes and potential pathways. The sudden onset and usually rapid demise contribute to the sparsity of objective and valid evidence and to our fragmentary understanding of the condition. Therefore, no simplified schema can be all-inclusive or even completely accurate.

The essential pathological finding is pulmonary embolism and mechanical blockade of the vessels distal to the occlusion. Experimental work has demonstrated that particulate matter in the pulmonary vascular tree can produce reflex[56] or "anaphylactoid"[57] vasospasm in unoccluded vessels. The combination of mechanical and spastic components produces 3 main effects: (1) A sudden decrease of blood flow to the left side of the heart with a subsequent fall in left ventricular output. Peripheral vascular collapse rapidly ensues (fig. 5). (2) The sudden development of pulmonary hypertension may precipitate acute cor pulmonale with dilation and failure of the right side of the heart. Increased pressure in the pulmonary vessels may also stimulate pressoreceptors in the walls of the pulmonary blood vessels. This results in reflex tachypnea,[58] peripheral vasodilation and hypotension (fig. 6).[56] (3) An uneven pulmonary capillary blood flow with slightly decreased, normal or increased alveolar ventilation.[59] This deranged ventilation-perfusion ratio (V/Q) of the lung may lead to anoxemia and tissue hypoxia (fig. 7).

The precise mechanism for the production of arterial oxygen desaturation is not well known. It has been postulated that it may be due to venoarterial shunting of blood through precapillary anastomoses, a decrease in the diffusing capacity of the affected alveoli or a reduction in effective alveolar ventilation.[60] Cyanosis, restlessness, convulsions and coma may be explained on an anoxemic basis. The decreased oxygen tension of the arterial blood also produces reflex hyperpnea (carotid and aortic body chemoreceptors). However, hyperventilation may still occur following pulmonary embolism despite normal arterial oxygen saturation, low carbon dioxide tension, alkaline *p*H and section of the vagus and sympathetic trunks.[60] As hypoxia becomes more profound, pulmonary edema develops.

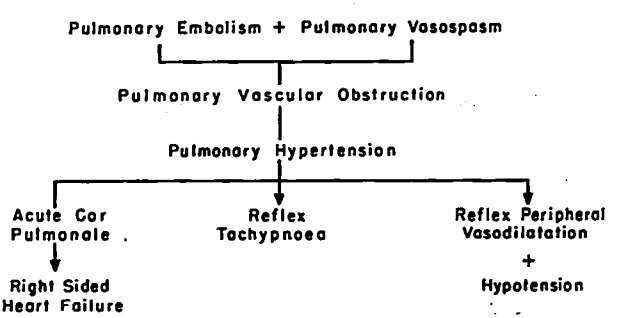

FIG. 6. Etiology of clinical picture: sequelae of pulmonary hypertension.

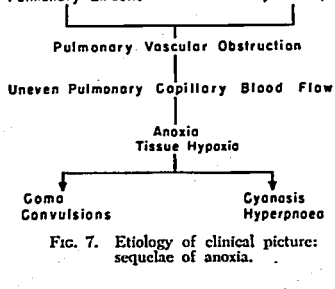

FIG. 7. Etiology of clinical picture: sequelae of anoxia.

In a review of the reported cases of amniotic fluid embolism, dyspnea or respiratory distress is often noted. According to Meakins[61] "dyspnea is the consciousness for increased pulmonary ventilation." Thus dyspnea could not occur in comatose patients. In the shocked, restless, apprehensive patient hyperpnea and tachypnea are often described as "dyspnea." The distinction between hyperpnea and dyspnea is based solely upon the presence or absence of subjective sensations.

Hypersensitivity and anaphylactoid reactions have been presumed to play important roles in the pathophysiology of the syndrome. It is conceivable that during the ante-partum period amniotic fluid may penetrate into the maternal circulation and induce a state of sensitization. Stefanini[62] injected intravenously into a dog 15 ml. of homologous amniotic fluid without effect. Another 15 ml. aliquot was kept in frozen storage and administered to the dog one month later. Hypotension, hypofibrinogenemia and thrombocytopenia resulted. The animal had probably become sensitized to amniotic fluid. Since, according to Stefanini,[62] the fluid is primarily of fetal origin, sensitization may be an important factor.

Pathogenesis of Afibrinogenemia. Perhaps the most interesting feature of the disease is the frequent observation of abnormal blood loss where local factors cannot be held accountable. Hemmings,[9] Dooley and Leary[26] and Eames[28] were the first to observe, that during life, the circulating blood may become incoagulable as a result of amniotic fluid embolism. Other documented cases of hypofibrinogenemia associated with amniotic fluid embolism have been reported.[29, 42, 46] Comprehensive blood studies also revealed an increased plasma fibrinolytic activity,[29, 42, 62] possible hypoprothrombinemia, [29, 46, 62] a fall in circulating platelets,[29, 46, 62] a deficiency in labile factor,[46] and an increase in plasma antithrombin activity.[29, 62]

There are at least three mechanisms by which the incoagulability of the blood may develop: (1) Plasma fibrinogen may be depleted as a consequence of liberation of thromboplastic substances into the circulation (fig. 8).[63] Both placental tissue[64, 65] and amniotic fluid[21, 62] possess thromboplastic activity although the hemostatic effect of the placenta is many times greater than that of amniotic fluid.[66, 67] The fibrin may be deposited as "fibrin emboli" in the greater and lesser circulation. These fibrin deposits have been demonstrated in the blood vessels of patients with documented hypofibrinogenemia and amniotic fluid embolism.[46, 61]

(2) Fibrin and fibrinogen are destroyed by plasma fibrinolysins. Normally the circulating blood contains profibrinolysin (plasminogen, the precursor to fibrinolysin), small amounts of profibrinolysin activator, but little or no free fibrinolysin (plasmin).[68, 69] An activator substance is present in the endo-

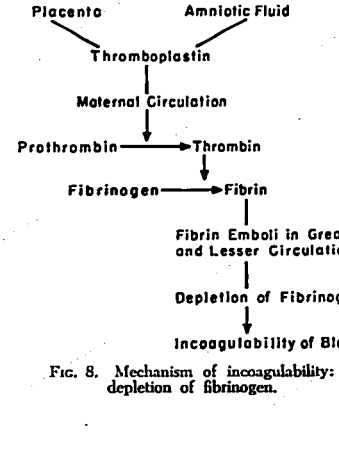

FIG. 8. Mechanism of incoagulability: depletion of fibrinogen.

metrium[70] and amniotic fluid (fig. 9).[62] If large quantities are liberated into the circulation, activated fibrinolysin will hydrolyze fibrinogen, resulting in incoagulability of blood.[71] Furthermore, stress, shock and hypoxia have been shown to increase the fibrinolytic tendency in man.[72] Albrechtsen[43] described the presence of increased activator and free fibrinolysin in the blood of a woman dying from amniotic fluid embolism.

(3) A release of a heparin-like substance which is present in amniotic fluid[62] into the circulation will block the conversion of prothrombin to thrombin as well as inactivate the thrombin[17, 73]; this also can lead to incoagulability of blood (fig. 10).

The clinical diagnosis of hypofibrinogenemia becomes obvious when it is observed that the blood does not clot. If laboratory facilities are available, a plasma fibrinogen determination should be performed. Normal values in pregnancy range from 300 to 550 mg. per cent. The clinical picture of hypofibrinogenemia may develop when the plasma fibrinogen falls below 200 mg. per cent. The clot observation test is a rapid and practical method of diagnosis. A few milliliters of the patient's blood is placed in a clean test tube; normal blood will clot in 8 to 12 minutes and the clot remains intact for at least 24 hours. In afibrinogenemia or hypofibrinogenemia the blood will not clot or if it does so, the clot may undergo partial or complete dissolution within the next five hours.[74]

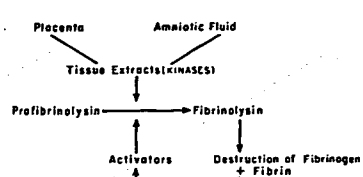

FIG. 9. Mechanism of incoagulability: destruction of fibrinogen.

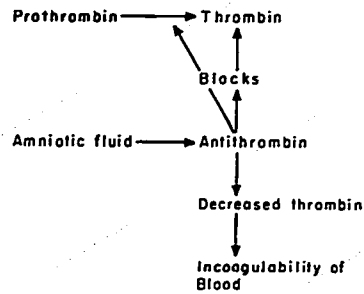

FIG. 10. Mechanism of incoagulability: presence of antithrombin.

MANAGEMENT

The anesthesiologist and the obstetrician must direct their attention to both the prophylactic and active management of the syndrome.

Since tumultuous labor is one of the most frequent predisposing factors, oxytocics must be used with caution. Barno and associates[6] reported that in their series of 15 cases, all but one had exceptionally strong uterine contractions and half of these had received a pituitary extract. They concluded that in these patients, the use of uterine stimulants contributed significantly to the production of amniotic fluid embolism. Once excessively strong uterine contractions begin, they may be controlled by judicious use of medication.[75] It has been shown that meperidine, administered intramuscularly in the active phases of labor, inhibits uterine contractions and slows cervical dilation significantly.[76] On occasion the inadvertent use of large single doses of pitocin during early labor has precipitated a prolonged tetanic contraction.[77] In our experience a tightly contracted uterus can be relaxed only with deep anesthesia. Halothane when administered by means of a precision vaporizer can obtain the desired depth most rapidly and safely, although ether and chloroform are also effective. Cyclopropane on the other hand does not significantly depress uterine activity until plane three is reached and even then it may be insufficient. Nitrous oxide, ethylene, regional anesthesia and

muscle relaxants are of no value in this situation.[78]

Once embolism has occurred rapid action is necessary if there is to be any possibility of saving the patient. Immediate therapy must be directed toward the hypoxia, pulmonary vascular obstruction, shock, and afibrinogenemia.

Anoxemia and hypoxia are best treated by oxygen, administered under positive pressure, using a mask or preferably an endotracheal tube. This therapy also reduces pulmonary edema by several means. It combats the progressive effects of anoxia in causing undue capillary leakage, and modifies the intrapulmonary pressure so as to resist the tendency of the normal negative pressure in the chest to increase the flow of fluid out of the alveolar capillaries.[79] The increased oxygen tensions in the pulmonary circuit may also produce a local vasodilation[80, 81] tending to overcome the reflex vasospasm that is present.

In the past, general anesthesia,[82] papaverine,[82] nitroglycerine[83] and aminophylline[84] have been suggested to relieve the pulmonary vasospasm. All these produce vasodilation of the peripheral blood vessels as well, tending to aggravate the pre-existing hypotension. On the other hand, levarterenol infusions have also been used in the treatment of pulmonary embolism[85, 86]; although the systemic shock may be reversed, the existing pulmonary hypertension may be exaggerated which may in turn precipitate failure of the right ventricle. Methoxamine, mephentermine, methamphetamine and ephedrine do not constrict pulmonary vessels of dogs but unfortunately their pulmonary vascular effects have not been confirmed in man.[87] Even so these sympathomimetic drugs are recommended in therapy of the hypotension.

Blood replacement should be adequate but care must be exercised not to overload the circulation because of the concurrent pulmonary hypertension. Plasma, dextran or other plasma expanders may be used if blood is not immediately available. The patient should be placed in slight Trendelenburg position to aid, by gravity, the venous return to the heart.

The following drugs have been used as adjuvants in the over-all resuscitation of the patient. Hydrocortisone (100–200 mg. intravenously) may aid in combating any histaminic reaction that may be present and the overwhelming stress situation. Digitalis (*e.g.* Lanatoside "C" 1.6 mg. intravenously in divided doses) and atropine (1 mg. intravenously) may be of help in restoring normal function of the cardiovascular system. Morphine has in the past been erroneously used to combat the "dyspnea and apprehension." Since, as explained above, the dyspnea is actually anoxic and the hyperpnea reflex in origin, the use of morphine is physiologically unsound and should be condemned.

Afibrinogenemia frequently responds to the administration of fibrinogen. A minimum of 4 Gm. is usually necessary but possibly three times that amount may be required before normal clotting and hemostasis are restored. Reid and associates[19] have reported four presumptive cases of amniotic fluid embolism successfully treated with fibrinogen and blood transfusions.

Summary

Amniotic fluid embolism should be suspected in every case of severe shock during labor or the immediate puerperium.

At The Sloane Hospital for Women, this complication represents the commonest cause of obstetric death during labor, delivery or the immediate post-partum period.

The syndrome is clinically manifested by four cardinal signs: respiratory distress, cyanosis, peripheral vascular collapse, and coma. In addition, hypofibrinogenemia with excessive bleeding often develops.

The possible mechanisms of infusion of amniotic fluid into the circulation and the development of the clinical picture are reviewed.

Urgent treatment includes artificial ventilation with oxygen, vasopressors, blood replacement and fibrinogen.

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DENTAL ANESTHESIA Most cardiac patients can have dental extractions with safety with local anesthesia provided by 1.5 to 8 ml. of 2 per cent lidocaine with 1/80,000 epinephrine. General anesthesia should be used only if necessary, *i.e.*, in the very young, in the uncooperative adult or in the presence of acute infection. The choice of agent and the method of administration should be left entirely to the anesthesiologist. (*McIntyre, H.: Dental Extractions in Patients with Heart Disease, Brit. Med. J. 1: 1778 (June 11) 1960.*)

FETAL OXYGEN GRADIENT Observations of blood oxygen tensions in 4 patients delivered by cesarean section have been made. Samples were obtained from the umbilical artery, umbilical vein, and the intervillous space. In the 3 patients considered to have normal pregnancies and deliveries, the average oxygen pressure difference between fetal and maternal human blood averaged 24.0 mm. Hg. In the one patient whose delivery was complicated by severe spinal hypotension, the pressure difference was only 10 mm. Hg. (*Prystowsky, H., Hellegers, A., and Bruns, P.: Fetal Blood Studies: Supplementary Observations on Oxygen Pressure Gradient Between Maternal and Fetal Bloods of Humans, Surg. Gynec. & Obstet. 110: 495 (Apr.) 1960.*)