Thromboembolic Disease in Obstetrics and Gynecology

John A. Jenning
THROMBOEMBOLIC DISEASE IN OBSTETRICS AND GYNECOLOGY

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INTRODUCTION

THE TERM “thromboembolic disease” is used in this discussion to include thrombophlebitis, phlebothrombosis, and embolic phenomena secondary to either or both of these disease processes. The purpose of this discussion will be an attempt to consolidate some of the information available in the literature on the etiologic factors and pathogenesis, incidence, prevention, and treatment of thromboembolic disease, particularly as it applies to the obstetric and/or gynecologic patient. One of the striking findings in studying the literature available on this disease or group of diseases is the lack of uniformity of opinions expressed by investigators concerning the prevention and treatment of thromboembolic disease.

HISTORY

Puzos, in 1759, was the first to describe a condition which he called “milk leg”.

This condition was actually thromboembolic disease of the lower extremities. The case which he described was that of a postpartum patient; thereby, perhaps, giving obstetricians and gynecologists the right to claim this as originally an obstetrical disease. However, it was not until 64 years later, in 1823, that the actual pathological changes of venous thrombosis were observed and described.

ETIOLOGY AND PATHOGENESIS

Initial thrombus formation is not a function of blood clotting unless there is an occlusion of the vessel or a significant slowing of the blood flow within the vessel and a secondary clot forms. Thrombosis occurs only in the moving stream of blood and ceases as soon as occlusion occurs.

The initial thrombus or “platelet cement” attempts to smooth out and streamline the lumen of the vessel. The thrombus is formed from the platelets of the blood stream that agglutinate and are precipitated as hyaline masses whenever there is appropriate slowing of the stream. As the process progresses the “coralline” thrombus is formed. The platelets are formed in ridges between which the fibrin is laid down.

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Under the microscope these ridges and valleys are seen as the "lines of Zahn". The thrombus at this time resembles a coral formation.

As more platelets are layered on the surface of the thrombus, a significant degree of obstruction develops, as more and more obstruction develops the thrombus formation gradually decreases and finally stops with the achievement of complete obstruction. At this time true clotting begins and forms the propagated clot. The propagated clot then extends along the course of the affected blood vessel until it reaches the junction with another vessel which has a moving stream of blood flowing through it. In this situation the clot is attached only at the small area of its origin, and the remainder of the clot is like a long tail waving in the stream of blood. Obviously, it does not take much agitation to break this clot loose and carry it as an embolus to some distant site.

The condition described thus far is a true phlebothrombosis inasmuch as there is no reaction in the walls of the blood vessel or adventitial tissues to the presence of the clot. However, within a relatively short time a reaction does occur resulting in local pain, erythema, edema, and infiltration with phagocytic cells. As the reaction develops, the process then properly becomes known as thrombophlebitis. Many times this process is reversed when, in response to a local injury to a blood vessel or even its surrounding tissues, the tissue reaction is instituted as an attempt to repair the injury. Either as a result of the narrowing of the blood vessel and slowing of the flow of blood or of actual intimal injury, the coralline thrombus is laid down and the process progresses from there. If the process and the reaction to it becomes massive enough, adjacent vessels may become involved, resulting in obstruction of both arterial and venous supply of an extremity. The ultimate in involvement is represented by a condition known as phlegmasia cerulea dolens. This rare condition is a massive thrombosis of the venous tree of the extremity, characterized by dramatic onset, the blue-black discoloration of the foot, the florid, dark calf and thigh areas, and the acute pain, edema, and associated shock.

A number of factors have been implicated in the etiology of thromboembolic disease. As mentioned above, trauma is a big factor, either trauma to the blood vessel itself or to the surrounding tissues. One of the most common causes of injury is the mishandling of blood vessels during surgical procedures.

Venous stasis is a very important factor in thromboembolism. Prolonged bed rest, particularly with improper positioning in bed causing pressure on certain points most likely to put undue pressure on underlying veins, leads to venous stasis and can cause thromboembolism. Elderly patients, with poor circulation strictly on the basis of age or as the result of cardiac difficulties, diabetes, arthritis, gout, debilitation, or other medical problems, are particularly prone to venous stasis and thromboembolism. Marked venous varicosities, particularly in the lower extremities, but also those involving the vulva or within the pelvis itself lead to areas of venous stasis. This is particularly true in the obstetrical patient, both antepartum and postpartum, but is pertinent in any patient.
Previous thromboembolic disease, which has left a residual of venous insufficiency, venous valvular incompetence, and partial venous obstruction increases the chances of future episodes of thromboembolism.

Another contributory cause resulting from our modern way of life is a condition known as “Thruway Disease”. As the name implies, this results from the extended periods of sitting in a car, particularly as the driver, and traveling on the almost endless and uninterrupted stretches of expressways and turnpikes. This is particularly dangerous when one of the above mentioned factors is already present.

Certain biochemical alterations of blood components have been described and may play a role in the etiology of thromboembolism. It has been shown that platelets exhibit an enhanced stickiness following trauma and surgical procedures. The uterus is known to contain a tissue activator for the fibrinolytic system, and it is postulated that there may also be an inhibitor for this system.

Sharnoff, et al, showed two definite periods of hypercoagulability of the blood in surgical patients. During these periods the Lee-White clotting times fell below four minutes. At the same times, or slightly preceding them, there was shown to be a definite and statistically significant rise in the platelet count of the peripheral blood. The explanation offered by Sharnoff and his associates for this phenomena is based on the megakaryocytes constantly being produced by the bone marrow and entering the peripheral blood stream. The pulmonary capillaries are too small in caliber to allow these large cells to pass through intact. As they are forced through the capillaries they are broken up into platelets. With periods of relative inactivity, as in the preoperative, the rate of pulmonary blood flow is decreased and many of the megakaryocytes tends to pile up behind these closed channels. During surgery and with the first postoperative ambulation, the heart rate and pulmonary blood flow increase and many of the megakaryocytes are forced through, resulting in a sudden increase in circulating platelets.

According to Pritchard there are a number of changes in the blood coagulation system during normal pregnancy. The concentration of fibrinogen rises from the normal of 300 mg. per cent to 450 mg. per cent at or near term. In the presence of severe pre-eclampsia, eclampsia, extensive trauma, infection, or any marked stress, the concentration rises still further. The concentration of prothrombin increases about 20 per cent. There are also significant increases in proconvertin (Factor VI, pro-SPCA) and plasma thromboplastin component (PTC, Christmas factor). The platelet count usually does not undergo any significant change with normal pregnancy. In some of the complications of pregnancy such as eclampsia, severe pre-eclampsia, or severe hypofibrinogenemia the platelet count may fall to very low values.

The exact significance of the above mentioned changes in the clotting factors in normal pregnancy are not well understood, since the standard laboratory tests for hemostatic function, i.e., whole blood clotting times, bleeding times, clot retraction,
and thromboplastin generation, do not change significantly from the values found in normal non-pregnant women.

**DEVELOPMENT OF THROMBOEMBOLISM**

Fundamental to the prophylaxis and treatment of thromboembolic disease, to be discussed later, is the knowledge of when thromboembolism is most likely to occur.

Burns\(^2\) reported a series of 101 cases of thromboembolic disease in obstetric and gynecologic patients at Temple University Hospital over a three year period. In this series the time of onset was variable with the average being 5.5 days following operation or delivery. Pulmonary embolism occurred in seven patients, one in an obstetric patient and six in gynecologic patients. These occurred on the second and third day postoperatively and the fifth day postpartum. One pulmonary embolus occurred on the tenth postoperative day while the patient was on dicumarol treatment for thrombophlebitis, with the prothrombin time at 38 per cent of normal.

In a study of 678 cases treated in the Women's Clinic of the University of Helsinki from 1953 to 1957, Hiilesmaa\(^3\) points out that in endeavoring to determine the time of onset of thrombosis or embolism following surgery or delivery, one must rely upon the time when the diagnosis is made, since it is usually impossible to determine the exact time the process began. This factor, therefore, would make the time of onset seem later than it actually is.

The group of 678 patients included 512 parturients and 166 gynecologic patients. Of these, he excluded 56 obstetric patients and 37 gynecologic patients who developed the disease prior to delivery or surgery. Another 37 patients were excluded because they developed their thrombosis prior to admission to the hospital, and 35 patients were excluded because the date of diagnosis could not be determined from the chart. This left 404 parturients and 109 gynecologic patients in which the time of diagnosis could be determined.

In the parturient group, 333 cases, 82.4 per cent, had the diagnosis made during the first week postpartum, the peak occurring on the third day. Sixty cases, 14.8 per cent, were diagnosed during the second week. In cases of operative delivery, the largest accumulation of diagnoses occurred slightly later, on the sixth postoperative day.

In the gynecologic group, 46.7 per cent were diagnosed during the first postoperative week and 40.3 per cent during the second week. There was no clear peak incidence; but there was a slight accumulation on the ninth postoperative day in those cases in which a laparotomy had been performed. Pulmonary embolism occurred as early as the second postoperative day and as late as the forty-third postoperative day with the average occurring on the twelfth day.
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A few cases in both groups occurred very early in the postpartum or postoperative periods, indicating the necessity of being on guard for this complication constantly.

Walker and Parry found that of 102 fatal cases of postoperative or post-traumatic pulmonary embolism, 40.2 per cent occurred in the first week, 29.4 per cent in the second week, 16.6 per cent in the third week, and only 13.8 per cent still later.

In Hiilesmaa's study a group of 52 pregnant patients were admitted to the hospital because of thromboembolism. A study of the distribution of the cases according to the month of gestation during which the disease developed showed only about one-fifth of the cases developed before the sixth month and none prior to the third month. After the sixth month the distribution was fairly even.

INCIDENCE

The incidence of thromboembolic disease among pregnant women varies slightly from one author to the next. The incidence is generally considered to be much lower in this group than in parturients or postoperative patients. Ullery arrived at an incidence of 0.018 per cent. According to Quenneville et al the general incidence of antepartum thromboembolism was 0.132 per cent. Hiilesmaa presented a series of 3,162 gravidas admitted to the hospital for various reasons, such as hyperemesis, threatened abortion, toxemia, false labor, and hemorrhage. In this group, which was obviously not a group of normal gravidas, there were 56 cases of thromboembolism or an incidence of 1.7 per cent. In this group the thrombosis was deep in 39 cases and superficial in only 17 cases. Hiilesmaa felt this was not a true distribution of cases since only the more severe cases were hospitalized for treatment.

Barry and Olson reported nine cases in 50,000 obstetric patients at Philadelphia Lying-In Hospital for an incidence of 0.018 per cent. Burns reported 10 cases of antepartum thromboembolism in 6,552 obstetric patients at Temple University Hospital over a three year period for an incidence of 0.15 per cent.

A number of very large series of parturients have been reported with a rather wide range of incidence of thromboembolism. One of the lowest incidences was reported by Ullery in a group of 50,332 parturients in Pennsylvania from 1933 to 1953 with only 172 cases of thrombosis (9.34 per cent) and seven fatalities due to pulmonary embolism (0.013 per cent). Burns in his series from Temple University Hospital from 1949 to 1951, reported 51 cases of thrombosis in 8,012 parturients for an incidence of 0.64 per cent with only one case of pulmonary embolism, which was not fatal. Hiilesmaa noted a study made by Maurizio and Malagamba (1954) from Genoa, Italy in which they reported an incidence of 0.48 per cent and several studies from Germany and Switzerland in which the incidence varied from 0.6 to 1.6 per cent. In Hiilesmaa's own study of 39,493 parturients, there was thrombosis without embolism in 432 patients, thrombosis and pulmonary embolism in 16 patients,
and pulmonary embolism without diagnosed thrombosis in the lower extremities or pelvis in 8 patients. The total number of cases of thromboembolism was 456 or 1.15 per cent and the number of cases of pulmonary embolism was 24 or 0.06 per cent. Three fatal cases gave an incidence of 0.007 per cent. He then divided this group into normal and operative deliveries. In 3,241 operative deliveries there were 68 cases of thrombosis (2.09 per cent), 10 cases of pulmonary embolism (0.30 per cent), and one fatality (0.030 per cent). In 36,252 “normal” deliveries there were 388 thromboses (1.07 per cent), 14 pulmonary emboli (0.04 per cent), and 2 fatalities (0.005 per cent).

In Burns’ series mentioned above he also reported an incidence of thromboembolic disease following operative delivery of 1.81 per cent, exactly the same incidence that he found following major gynecologic surgery.

When Hiilesmaa separated the patients with toxemia and the patients with placenta praevia from the series total, he found in the group that remained an incidence of thromboembolism of 1.12 per cent. In patients with toxemia the incidence was 2.5 per cent; and the same incidence was found in patients with placenta praevia. Deep vein thrombosis was predominant in these two groups; whereas, superficial vein thrombosis was more common in the patients with neither toxemia nor placenta praevia. Also, the incidence of pulmonary embolism and of fatalities was several times higher in these two groups. The cases with toxemia, of which there were 2,022 cases, were then divided into an operative group and a non-operative group. The non-operative group, 1,734 cases, included 34 cases of thromboembolism for an incidence of 1.9 per cent. The operative group, 288 patients, had 17 cases of thromboembolism, an incidence of 5.9 per cent. On the basis of this information it may justifiably be concluded that the danger of thromboembolic complications is particularly high when the treatment of toxemia includes an operative procedure. Whether this increased danger is due to the operative procedure or to the severity of the toxemia necessitating the operation was not shown by this study.

Hiilesmaa also evaluated a group of 30,945 gynecologic patients to determine the incidence of thromboembolism. He divided this group into three categories: operated, non-operated, and radium-treated patients. In 17,740 operated patients there were 129 thromboses (0.72 per cent), 19 pulmonary emboli (0.11 per cent), and 6 fatalities (0.033 per cent); 13,345 non-operated patients had 28 thromboses (0.22 per cent), two pulmonary emboli (0.02 per cent), and one fatality (0.008 per cent); 860 radium-treated patients had 9 thromboses (1.04 per cent), two pulmonary emboli (0.232 per cent), and two fatalities (0.232 per cent). He also observed that both the operated and non-operated patients developed deep thrombosis about twice as frequently as superficial thrombosis.

Hiilesmaa quotes a number of studies in which the incidence of thrombosis varied from 0.53 per cent to 7.96 per cent and fatal pulmonary embolism varied from 0.029 per cent to 0.7 per cent.
Hiilesmaa then divided his operative group into two subgroups: laparotomy cases and vaginal cases. The laparotomy group showed an incidence of thrombosis of 1.06 per cent and fatal pulmonary emboli of 0.06 per cent; the vaginal operation group 0.45 per cent thromboses and 0.01 per cent fatal pulmonary emboli. A statistically significant increased incidence was noted in those patients having total or subtotal abdominal hysterectomies.

In Lubow’s series of 1956, as quoted by Hiilesmaa, the patients were not allowed to ambulate before the fourth day after D & C, the sixth day after evacuation, the tenth day after plastic repair of the cervix, the twelfth day after laparotomy, and as late as the 21st day after vaginal plastic repair. In this series the incidence of thromboembolism was 10 per cent after cesarean section, 7.5 per cent after subtotal hysterectomy, and 6 per cent after total hysterectomy. Postoperative pulmonary embolism occurred in 2 per cent of the cases and was fatal in 0.1 per cent.

**Prophylaxis**

In reviewing the etiologic factors enumerated previously several prophylactic measures are suggested. General measures such as adequate hydration and nutrition; correction of medical problems, e.g., congestive heart failure, uncontrolled diabetes, etc.; support of existing venous varicosities by leotards or similar devices; and correct positioning where prolonged bed rest is required, are all useful in reducing the incidence of thromboembolism. Chappie and others suggest that elective surgery be delayed for a time after long air or auto travel to allow time for adequate circulation to be reestablished. Because patients tend to be more inactive in a hospital environment it has been advised that the preoperative hospitalization be shortened as much as possible and all possible preoperative studies or tests be done prior to admission to the hospital.

During surgery care should always be taken to avoid as much as possible excessive trauma to blood vessels. Position on the operating table is important and devices such as leg straps and shoulder braces should be avoided. Undue pressure on veins from retractors or assistants for prolonged periods during operative procedures may cause stasis of blood or actual injury to vessels.

Early ambulation following delivery or surgery has been shown time and again to reduce the incidence of thromboembolic disease. Hiilesmaa refers to a study reported in 1954 by Borgstrom in which there was an incidence of postoperative thromboembolism in 7.9 per cent of the cases. With early ambulation alone the incidence dropped to 3.7 per cent. With the use of prophylactic anticoagulation with Dicumarol without early ambulation the incidence was 4.2 per cent. When early ambulation and prophylactic anticoagulation were combined the incidence fell to 1.8 per cent. Lehman in 1954 reported a similar study with equally convincing results. These figures are not quoted to advocate routine prophylactic anticoagulation; but merely to point out that prophylactic anticoagulation may be very helpful in certain selected cases where it is felt that the risk of thromboembolism is very high. Greenhill expresses the opinion that patients who have had a previous thromboembolic phenomenon and are therefore likely to develop a second episode should be prophylactically anticoagulated.
Sharnoff et al.,31 after reporting their study referred to earlier32 showing two periods of hypercoagulability, the first during surgery and the second at the time of ambulation, conducted a study on a series of 52 patients in which they administered prophylactic heparin prior to these events. The usual method of administration was to give 100 mg of heparin subcutaneously late in the evening prior to or on the day of operation regardless of pre-existing blood values. Lee-White clotting times were carried out throughout the operation, and the clotting time was maintained above five minutes by the administration of additional heparin as indicated. Just prior to resuming ambulation an additional 50 mg of heparin was given subcutaneously. They report no serious bleeding occurred as a result of the anticoagulation. In sixteen instances the coagulation time fell four minutes during surgery and required additional intravenous heparin. When the surgeons did not know the heparin had been given, they reported no increase in bleeding but when they knew, they expressed the feeling that there was excessive bleeding. No actual measurement of blood loss was performed. In no instance was it necessary to give Protamine.

Two cases of excessive bleeding occurred after discontinuing heparin — one transurethral prostatectomy and one vaginal hysterectomy. In this series no death occurred as a result of thromboembolic disease. One case of pulmonary infarction did occur ten days after an intestinal resection for carcinoma. The Lee-White clotting time was less than two minutes. Two deaths occurred several days after discontinuing heparin.

Vein ligation was introduced by Hunter in 1784 for suppurative thrombophlebitis, and its acceptance by the medical profession has wavered pro and con since that time. Chappie4 feels that vena cava ligation should be considered in cases of septic thrombophlebitis, recurrent pulmonary embolism, or where anticoagulation is definitely contraindicated. However, because of recurrence of emboli from sources proximal to the ligation and the often resulting edema of the lower extremities its routine use is not recommended. When femoral vein ligation is performed the ligation should be flush with the profunda vein to prevent any cul-de-sac in the superficial vein where more thrombi could form.

Diagnosis

Up to the present time the diagnosis of thromboembolic disease depends upon clinical signs and symptoms since there are no specific laboratory tests available to indicate an existing thrombotic state. Chappie4 feels that venography is a useful scientific tool; but it can be irritating and traumatic to an already damaged intima. Intraosseous venography may be very useful in locating a silent, deep thrombosis which is giving rise to recurrent embolic phenomena.

Chappie4 notes that Bache and his associates demonstrated a selective absorption of fibrinolysin (plasmin) to a fibrin clot. With the use of radioactive tagged plasmin it may some day be possible to localize an area of thrombus formation.

Clinically, superficial thrombophlebitis often presents as a reddened, warm, slightly indurated, tender, cord-like area following the course of a superficial vein.
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Low grade temperature elevation generally occurs with an elevated pulse rate disproportionate to the degree of fever.

Deep vein involvement, of course, does not show the visible signs mentioned above; but is usually evidenced by increase in the size of the affected extremity over the uninvolved member. Pressure exerted in an anterior direction which produces pain is known as a “positive Bancroft’s sign” and is indicative of deep vein involvement. The well known “Homan’s sign” is elicited by dorsiflexion of the ankle with the knee in the extended position. Similar to Bancroft’s sign, pressure on the muscles overlying the deep veins of the thigh will produce pain if they are involved. Applying a blood pressure cuff over a suspected area and elevating the pressure will also produce pain if involvement is present. Comparing the pressure necessary to produce pain between an involved extremity and the uninvolved extremity will show a lower threshold in the involved side. The temperature and pulse elevations mentioned above are also present in deep vein thrombosis and assume even greater importance in diagnosis other clinical signs may not be obvious. The fever and tachycardia show no response to antibiotics but respond rapidly to anticoagulant therapy.

A silent deep thrombophlebitis or phlebothrombosis may reveal itself only by recurrent small pulmonary emboli. The more common locations for the thrombus are in the iliofemoral, pelvic, and abdominal veins although it may occur anywhere in the venous tree. According to Chappel4 “intraosseous venography at the malleoli or tibial tuberosity will demonstrate the deep circulation of the extremity, while injection through the trochanter or iliac crest will show the pelvic and abdominal veins.”

The diagnosis of massive pulmonary embolus rapidly becomes apparent with signs of cyanosis, acute pain, hemoptysis, cough, syncope, sweating, tachycardia, and if massive enough, rapid demise. More difficult may be the diagnosis of the small or recurrent embolization with rather transient symptoms. The pain may be pleuritic, abdominal, cardiac or respiratory in character and may be relieved somewhat by change in position or splinting.

A cough of varying severity, bronchiectatic in type, may be present; but may be suppressed by splinting. Pleural friction rubs may or may not be present. Pleural effusion may appear. Chest x-ray may be normal at the onset, but changes generally develop within a relatively short time and present as a hazy infiltrate, which later acquires more sharply defined borders and a reaction in the overlying pleura.10

Pulmonary embolus may produce acute heart failure, which recurrent emboli may be associated with chronic failure. ECG changes should be observed sequentially and important findings are incomplete acute cor pulmonale and transient T-wave inversion. The changes may be differentiated from myocardial infarction by the lack of rise in the serum transaminase levels.

Ten per cent of pulmonary emboli come from thrombi in the head, neck, and upper extremities; and if a location of the thrombus cannot be found elsewhere these areas must be investigated carefully.
A high index of suspicion, careful, repeated examinations of the patient, and scrutiny of the temperature and pulse record will be very rewarding by enabling the physician to diagnose the early developing thromboembolism and begin treatment early when the best results can be obtained.

**Anticoagulant Drugs**

Heparin is a highly polymerized polysaccharide with a molecular weight estimated to be about 20,000. Preparations of heparin are more or less inhomogeneous inasmuch as the basic tetrasaccharide unit is esterified in varying degrees with sulfuric acid. Heparin is the strongest organic acid found in the body, the high electronegative charge probably being on the basis of the sulfamido groups formed by the esterification. This highly electronegative charge is most likely the basis of heparin's anticoagulant power. If the electronegative charge is neutralized by a highly electropositive compound, such as protamine or the highly basic dye, toluidine blue, heparin is precipitated; and its activity is inhibited.¹

The pharmacological actions of purified heparin preparations are limited almost entirely to the blood. According to Goodman and Gilman even large doses given intravenously have no effect on blood pressure, peripheral or coronary circulation, respiration, body temperature, renal and hepatic functions, blood chemistry, formed elements of the blood, or vital processes other than blood coagulation and lipid metabolism.

Heparin exerts at least four somewhat interrelated effects on blood clotting. First, it acts to prevent the conversion of prothrombin to thrombin. Unlike Dicumarol, which inhibits the production of prothrombin by the liver, heparin inhibits the utilization of prothrombin. Part of this apparent inhibition depends upon heparin's second function, that is, antagonism of thromboplastin, which is essential for the conversion of prothrombin to thrombin. The exact mechanism for this action is not known. Third, heparin prevents thrombin from reacting with fibrinogen to form fibrin. Fourth, heparin prevents the agglutination of platelets.

Heparin can be administered intravenously, intramuscularly, or subcutaneously. A single dose of 60 mg. intravenously prolongs the coagulation time approximately fivefold after a latent period of ten minutes, and the effect disappears within one to three hours. If used intravenously frequent repeated doses or a continuous drip of 300-500 mg. in 1000 cc of diluent should be used. Lee-White clotting times should be done prior to the initial dose and at suitable intervals thereafter. The clotting time should be maintained between 15-20 minutes for adequate anticoagulation.

Aqueous heparin can also be administered by deep intramuscular or deep subcutaneous injection. By the intramuscular route the usual dosage is 12,000 units (120 mg.) every eight hours or 20,000 units (200 mg.) every twelve hours. Subcutaneous injection of 20,000 units will maintain adequate anticoagulation for 12-16 hours.
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Many newer heparin preparations have been produced. One of these is Depo-heparin, a repository form in a gelatin-dextrose medium. With deep subcutaneous injection of 20,000 to 30,000 units the effect starts in two to four hours and may maintain adequate anticoagulation for a day or more.

Heparin is contraindicated in patients with a pre-existing tendency to bleed (hemophilia, purpura, jaundice, etc.), threatened abortion, subacute bacterial endocarditis, suspected intracranial hemorrhage, ulcer of the gastrointestinal tract, and shock.

Bishydroxycoumarin or dicumarol is a compound which was originally obtained from spoiled sweet clover and is now produced synthetically. The drug has no important pharmacological action other than the effect upon blood coagulation. Dicumarol affects blood coagulation by causing hypoprothrombinemia by depressing the hepatic production of prothrombin. It acts only in vivo and only after a latent period of 24 to 48 hours. It is postulated that both vitamin K and bishydroxycoumarin have an affinity for the apoenzyme essential for prothrombin synthesis. The drug seems to act as an antivitamin and vitamin K serves as a prosthetic group which combines with an apoenzyme to form the active enzyme responsible for the manufacture of prothrombin.

The initial oral dosage of dicumarol is recommended to be 200 to 300 mg. and requires 48 to 96 hours to produce the maximum change in the prothrombin time. Following this the prothrombin time should be maintained between 15-25 per cent (25-35 seconds) with additional daily doses of 50-200 mg. From two to seven days are required following discontinuation of the drug for the prothrombin activity to return to normal. Prothrombin times must be determined very frequently during anticoagulation with dicumarol because of the variability in response to the drug; and also, fixed dosage schedules are unsafe on the same basis.

A number of derivatives of bishydroxycoumarin have been produced which have certain advantages and/or disadvantages over the original preparation. Very slight changes in the molecule generally decrease its anticoagulant power; but often give a compound with a more predictable action, thus permitting a more fixed dosage schedule and fewer prothrombin time determinations. It is not within the scope of this paper to list all the available preparations.

Dicumarol and its derivatives are contraindicated as in heparin in patients with hemorrhagic tendencies, blood dyscrasias, ulcerative lesions of the gastrointestinal tract, diverticulitis, colitis, subacute bacterial endocarditis, threatened abortion, recent operations on the brain or spinal cord, and regional anesthetic or lumbar block. In addition dicumarol is contraindicated in patients with vitamin K deficiency and liver disease, and when proper facilities are not available for prothrombin determinations. It must be remembered that dicumarol is a very potent drug and its use must be carefully supervised.
Early diagnosis and adequate treatment of thromboembolic disease should be aimed at accomplishing several objectives.  

1) Reduction in the incidence of pulmonary emboli.  
2) Prevention of chronic venous insufficiency and its sequelae.  
3) Reduction in the length of and thereby the cost of hospitalization.  

Many different regimes of therapy have been suggested and each has its proponents and opponents.

Burns, in reporting a series of 101 cases of thromboembolic disease in obstetric and gynecologic patients at Temple University Hospital, presented his plan of therapy as follows:

A) The Lee-White clotting time should be maintained between 15 and 30 minutes and the prothrombin time between 15 and 30 per cent of normal.

B) Trendelenburg position should be used to increase the circulation to the extremities.

C) Antibiotic therapy should be used routinely as a prophylactic measure to prevent secondary infection. Zollinger et al* in their series of patients used antibiotics only when they felt there was a specific indication for them. Greehill recommends the routine use of penicillin to prevent secondary infection. Douglas recommends also the use of penicillin and states that he reserves anticoagulants for cases in which embolization occurs. Chapple states that "antibiotics have no routine place in the treatment of thrombophlebitis and should be reserved for infective complications." It would seem more logical to withhold antibiotics until such time as infection does occur, since, generally speaking, thrombophlebitis does not involve bacterial infection.

D) Paravertebral block is recommended to relieve pain and other local blocks to relieve arterial spasm; however, these blocks should not be used after anticoagulant therapy has been started because of the danger of bleeding and resultant permanent nerve danger. Burns reports one of the deaths in his series was due to subarachnoid hemorrhage following a spinal anesthetic for the relief of pain after dicumarol therapy had been started. Burns also suggests the use of intravenous procaine for the relief of pain.

E) The patient should begin active leg exercises in bed when symptoms begin to subside but should not be allowed out of bed until all signs and symptoms are absent, the temperature is normal for 24 hours, and the anticoagulant level is adequate.
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F) If heparin is the anticoagulant used it should be continued in full therapeutic doses for 24 hours after ambulation and then in decreasing doses for five to seven days after ambulation and then in decreasing doses for three to four weeks. The literature contains many references to the fact that recurrences of thrombophlebitis and emboli are more likely to develop if the anticoagulants are stopped abruptly, even after what is apparently an adequate course of therapy.

In his series of 101 patients Burns found that pulmonary embolus occurred in seven patients, one in an obstetric patient and six in gynecologic patients. These emboli occurred on the second and third postoperative days and on the fifth postpartum day. One pulmonary embolus occurred on the tenth postoperative day while the patient was on dicumarol treatment for thrombophlebitis, but the prothrombin time was 38 per cent of normal. The fact that the prothrombin time was not within the therapeutic range in this case would seem to be important in view of a number of reports in the literature stating that the danger of embolization is greater with insufficient anticoagulation than with no anticoagulation at all. Lam and Hooker reported no fatal pulmonary emboli in 5147 operations at this hospital prior to 1930, while eight instances were noted in 6157 operations performed after anticoagulants and vein ligation were introduced in 1943. Zollinger et al. after studying 1917 cases of thrombophlebitis treated at Ohio State University Hospital during a ten year period, felt that, on the basis of recorded prothrombin times and/or clotting times, anticoagulant therapy in the group in general had been very inadequate and erratic. Pulmonary embolus occurred in 126 of 572 patients (22 per cent) with deep vein thrombosis. Of these 126 patients, 34 died, representing 27 per cent of those patients with emboli and 6 per cent of all patients with deep thrombophlebitis.

Hiilesmaa explains that if the anticoagulant level is not adequate the “thrombus-free level” is not reached, prophylactic anticoagulant is incapable of preventing clot formation, and therapeutic anticoagulant cannot prevent the propagation of the clot. The clot, which subsequently forms or increases in size, is a much more delicate structure and less adherent to the vein wall. This type of clot is much more likely to break loose and form an embolus. Hiilesmaa lists a number of authors who have reported adverse effects from anticoagulant underdosage and a number of deaths ascribed to this cause. Quenneville et al. reported a high incidence of thromboembolic complications under conservative treatment and also under anticoagulants before effective prothrombin levels were obtained.

At the other end of the anticoagulant range, i.e., excessive anticoagulation, there is, of course, the danger of hemorrhage. As was noted previously, excessively prolonged bleeding time and hemorrhage due to heparin therapy can be controlled by the slow intravenous infusion of a diluted solution of protamine sulfate in a dose equivalent, milligram for milligram, to the previously administered heparin. Not more than 50 mg. of protamine should be administered at any one time. The other antiheparin drug which may be given is Toluidine blue in a dose of 4 to 6 mg. per kilogram of body weight.
Prolonged prothrombin time due to coumarin derivatives can be counteracted by the administration of vitamin K or vitamin K oxide intravenously in doses of 50 to 150 mg. for rapid antagonism. Menadione is much less effective and slower acting. With vitamin K or K oxide the prothrombin time begins to drop within two to four hours and the effect lasts one to two days.

The use of the anticoagulants in antenatal patients has been a very controversial matter in the past because of the danger of maternal hemorrhage and also the danger of the transmission of the anticoagulant across the placental barrier, possibly resulting in a deleterious effect upon the fetus. Quick reported a series of dogs fed therapeutic doses of dicumarol in the last week of pregnancy in which none of the puppies survived without vitamin K administration. Sacks and Labate administered 3750 mg. of dicumarol to an antepartum patient in the last trimester. The fetus died in utero after 53 days of therapy and autopsy showed hemorrhages into the lungs, thorax, and pericardium. Kraus et al felt on the basis of animal experiments that dicumarol was contraindicated in the pregnant patient. Barry and Olson reported a case of thrombophlebitis in the 37th week of pregnancy which was treated with heparin intravenously. After 2 days of anticoagulation, labor started and the anticoagulant was stopped. The following day the patient delivered a normal, living child after a normal labor. No abnormal bleeding occurred during labor, delivery or in the postpartum period. Davis reported a case in which 800 mg. of dicumarol had been administered during the 28th week of pregnancy. The patient did well and delivered a normal child at term. Quenneville also reported fetal complications following the use of coumarin derivatives during pregnancy.

Barry surveyed the literature in 1956 and found 135 reported cases of thromboembolic disease in antenatal patients. Of the 135 patients, 38 were given anticoagulants. Seven of these 38 developed pulmonary emboli, all nonfatal. Of the remaining 97 who did not receive anticoagulants, 18 had pulmonary emboli and 15 died, resulting in a maternal mortality rate of 15 per cent. Mansell reported a series of 80 cases of antenatal thromboembolism untreated with anticoagulants with a mortality rate again of 15 per cent. Studies such as these indicate the definite need for anticoagulant treatment of antenatal patients with thromboembolic disease.

Eastman pointed out that drugs with a molecular weight of less than 1,000 pass the placental barrier easily, depending upon certain other factors; but above that weight a certain selectivity occurs. As was pointed out previously, heparin has a molecular weight of about 20,000 and the coumarin derivatives have a relatively small molecular size. It has been shown that little if any heparin administered to the mother crosses the placental barrier and enters the fetal circulation. Dicumarol crosses the placental barrier more easily; and, added to the hypoprothrombin effect of the drug is the physiologically low content of prothrombin in the plasma of the newborn.

The consensus in recent years seems to be that heparin is the drug of choice during pregnancy and the coumarin derivatives should be used only if the patient
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does not tolerate heparin or in severe cases requiring prolonged anticoagulant therapy. Quenneville recommends heparin alone but feels that dicumarol can be used if the prothrombin time does not exceed 15 per cent of normal.

The management of the anticoagulants at the time of delivery presents other problems from two aspects, i.e., the inherent complications of labor and delivery (abruptio placenta, postpartum hemorrhage, etc.) and the clotting ability of the baby’s blood (hemorrhagic disease, traumatic delivery, etc.). Quenneville suggests three solutions to this problem:

1) Stopping treatment one or two weeks prior to delivery. This has the disadvantage that the thrombotic disease may recur during this interval.

2) Carrying the patient at subtherapeutic prothrombin levels (20-25 seconds) in the last days prior to delivery and through labor. Another possibility would be to carry the patient at full therapeutic doses until labor starts and then give vitamin K. to the mother and to the baby after delivery. The disadvantage of this plan is that it takes 8 to 12 hours for the prothrombin time to reach safe levels. By that time most primiparas and practically all multiparas would be delivered.

3) Stopping coumarin before the expected time for labor to start and then carrying the patient on heparin until labor starts. With the initiation of labor, protamine sulfate could be given and normal clotting time restored almost immediately. With the use of induction of labor this plan should work very well, although Quenneville admits that he has not given this plan adequate trial for valid evaluation.

Burns started patients on heparin and dicumarol in the immediate postoperative and postpartum periods with no untoward effects. He did defer treatment for 24 to 48 hours in patients who had had extensive pelvic procedures resulting in large, open, raw surfaces. He found that dicumarol in the postpartum period had little apparent effect on the nursing infant; however, if given early or for a prolonged period, he recommended that the infant should probably be protected with vitamin K. Hiilesmaa quotes a number of authors who recommend a much longer interval between surgery and anticoagulation.

In his series referred to earlier, Burns found that the incidence of sequelae was definitely decreased by adequate anticoagulant therapy. He also felt that his plan of therapy was effective in reducing the length of hospital stay, depending upon the interval between the time of diagnosis of thromboembolic disease and the beginning of treatment. He divided his patients, who were treated with anticoagulants, into three groups and compared each group with a group of patients with similar illnesses or surgical procedures as to the length of stay in the hospital. In the first group anticoagulant therapy was started as soon as the diagnosis was made. The hospital stay averaged 2.6 days longer than in the control group. In the second
group, anticoagulant therapy was begun within 48 hours of the diagnosis and the increased hospital stay was 7.0 days. The anticoagulant was started after 48 hours in the third group and the increased hospital stay was 10.4 days.

Zollinger divided his cases into three groups according to the form of treatment used; i.e., bed rest with elevation of the extremities with or without antibiotics, heparin alone, and heparin for the first 24 to 72 hours in conjunction with one of the prothrombin depressants. He found little difference in results of treatment among the groups; however, he stated that the anticoagulant therapy was very inadequate.

Hodgson, Coon, and Mackenzie studied, for evidence of postphlebitic sequelae, a group of 511 patients treated at the University of Michigan Medical Center from 1946 to 1955. These patients were treated initially for either venous thrombosis or pulmonary embolism and anticoagulants. Twenty-five per cent of these patients had succumbed to their primary disease. Forty-one per cent were available for follow-up. Hodgson, et al compared this group with a group of 206 patients treated by Gjores in Sweden without anticoagulants (Table I).

Table I

<table>
<thead>
<tr>
<th>POSTPHLEBITIC SEQUELAE</th>
<th>Gjore’s Group</th>
<th>Hodgson’s Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal Legs</td>
<td>2.4%</td>
<td>26%</td>
</tr>
<tr>
<td>Some Subjective Complaints</td>
<td>86.4%</td>
<td>74%</td>
</tr>
<tr>
<td>Pain</td>
<td>68%</td>
<td>59%</td>
</tr>
<tr>
<td>Swelling</td>
<td>96.1%</td>
<td>54.5%</td>
</tr>
<tr>
<td>Ulceration</td>
<td>39.3%</td>
<td>6.8%</td>
</tr>
</tbody>
</table>

Another approach to the treatment of this disease is by the lysis of the already formed clot by proteolytic enzymes. Chappie refers to a number of articles published by other authors which have described the successful use of intravenous streptokinase to lyse preformed intravenous thrombi. The mechanism of this action apparently depends upon the combination of the streptokinase with plasminogen from the plasma and clot to form plasmin, which is the active enzyme which lyses the fibrin clot. Administered intramuscularly or buccally, streptokinase may act as an anti-inflammatory agent; but it is not active lytically. Actase fibrinolysin (human), produced by Ortho Pharmaceuticals, is a commercially available streptokinase activated human plasminogen. Thrombolysin fibrinolysin (human) produced by Merk, Sharp, and Dohme is a similar product which has been produced more recently. According to Chappie early preparations of Actase frequently produced a rather marked temperature rise, but later preparations have been much improved in this respect. No significant changes in the coagulation components of the blood have been noted and Chappie recommends concomitant anticoagulation. The enzyme lyases the clot, but does not protect the irritated vein intima from forming another clot as soon as
the enzyme is dissipated. Fragmentation of the clot is a potential complication of this form of treatment and Chappie points out that if this occurs it is important to continue the fibrinolysin in order to finish the dissolution of the fragments.

The recommended regime of therapy with actase fibrinolysin is to dilute one vial of actase, after reconstitution with 10 cc of sterile water, in 250 cc of 5 per cent dextrose in water and infuse intravenously over a one hour interval. The infusion should be completed within two hours after reconstitution. In thrombophlebitis and phlebothrombosis from one to three infusions may be given over a one to five days period, depending upon the clinical response. In pulmonary embolism two vials of actase should be added to 250 cc 5 per cent dextrose in water and infused intravenously over one hour. Additional infusions may be given over a one to three days period, depending upon clinical response.

The most frequently used dosage of thrombolysin fibrinolysin has been four vials per day by intravenous infusion, administering one vial every hour for four consecutive hours. The dosage range is one to two vials an hour, by intravenous drip, for one to six consecutive hours.

Deaton et al in a comparative study of heparin, Varizyme, a combination of heparin and Varizyme, and Plasmin in various dosage schedules in intimectomized dogs found that the most effective treatment for the prevention of clots and for clot lysis was a continuous intravenous drip of plasmin over a six hour period with one third of the total dose given intravenously prior to the six hour infusion. The same procedure was repeated 24 hours later. Using this technique on 96 vessels in 24 dogs, there were 85 to 100 per cent of the vessels open in six hours and 25 to 85 per cent open at thirty hours, depending on the dosage of plasmin used. They used this same regime on 37 patients. Twenty-three of them were objectively studied after treatment and fifteen had "good results." They reported no adverse effects in the human patients.

SUMMARY

The history, etiology, pathogenesis, and incidence of thromboembolic disease are reviewed. A study of the time of onset of the disease in pregnancy indicates that it is rarely if ever seen in the first trimester of pregnancy and about 80 per cent of the cases develop in the last trimester. Thromboembolism occurs in the first week postpartum or postoperatively in about 80 per cent of parturients and 45 per cent of the postoperative gynecologic patients. After normal delivery the highest incidence occurs on the third postpartum day and after operative delivery on the sixth postpartum day. After gynecological laparotomies the highest incidence occurs about the ninth postoperative day. Toxemia and placenta praevia seem to have a marked thrombogenetic effect. In operative gynecologic cases the highest incidence of thromboembolism occurs following total and subtotal abdominal hysterectomy.

* Streptokinase-plasminogen preparation, Varizyme, Lederle Laboratories.
A number of factors are discussed concerning prophylaxis of thromboembolism and the question of prophylactic anticoagulation and/or vein ligation.

The literature is resplendent with differing opinions as to the treatment of thrombophlebitis in both the pregnant and the nonpregnant patient. An attempt is made to present a sampling of these opinions. Several general conclusions can be gleaned from the material presented; namely, anticoagulation reduces the length of hospital stay and the development of postphlebitic sequelae; inadequate or erratic anticoagulation is dangerous; anticoagulants reduce the incidence of fatal and nonfatal pulmonary emboli if controlled properly; if anticoagulation is required during pregnancy it is probably better to anticoagulate with heparin rather than one of the coumarin derivatives, unless a sensitivity is shown to heparin or long term anticoagulation is anticipated; if a coumarin derivative is used during the antenatal period the prothrombin time should not be allowed to fall below 15 per cent of normal at any time, and anticoagulation may safely be started in the immediate postpartum or postoperative period unless a large, raw surface has been left.

The basic anticoagulant drugs are discussed and the use of their antagonists is described. Several methods of handling the antenatal patient on long-term anticoagulant therapy at the time of parturition are described. The most logical and seemingly safest method would be to change the patient from the coumarin derivatives to heparin near term and then neutralize the heparin with protamine sulfate during labor and delivery.

Two of the newer thrombolytic enzymes are briefly described and these would seem to hold some promise for improving the treatment of thromboembolism. More investigation and larger clinical trial will be needed before these preparations will be able to be completely evaluated.

REFERENCES

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