1969

# Fetal damage during anticoagulant therapy for antepartum thromboembolic disease

Kanchan L. Lodhia
*University of Nebraska Medical Center*

# FETAL DAMAGE DURING ANTICOAGULANT THERAPY FOR ANTEPARTUM THROMBOEMBOLIC DISEASE

by

Kanchan L. Lodhia

A THESIS

Presented to the Faculty of

The College of Medicine in the University of Nebraska

In Partial Fulfillment of Requirements

For the Degree of Doctor of Medicine

Under the Supervision of Robert H. Messer, M.D.

Omaha, Nebraska

February 3, 1969

TABLE OF CONTENTS

# FETAL DAMAGE DURING ANTICOAGULANT THERAPY FOR ANTEPARTUM THROMBOEMBOLIC DISEASE

## Introduction

Although thromboembolic phenomenon occurs relatively rarely in pregnancy, possible adverse effect on the fetus during therapy makes it a subject of significant concern in antenatal care. In this paper the recent literature is reviewed for the prevalence of the disease, its pathophysiology, therapy, and the risk to the fetus. Four new cases are presented, and the dangers of anticoagulant therapy are discussed.

## Extent and Incidence

Thromboembolic disease may manifest as phlebothrombosis without primary associated inflammation of the vessel wall. More commonly there is mural pathology associated with the attached thrombus wherefore the term thrombophlebitis is appropriately descriptive. The involvement of a more vital organ, the lungs, when a dislodged thrombus is carried away by the blood stream causes a high incidence of sudden deaths and makes pulmonary embolism a dreaded third member of the triad in thromboembolic disease.

Aaro, Johnson, and Juergens[1] found the most common type of venous thrombosis associated with pregnancy to be thrombophlebitis of superficial, usually varicose,

veins of the lower extremity. Deep venous thromboses were found in the veins of the lower extremity as well as in the pelvis. However, pelvic thrombophlebitis is stated to be seen most frequently with postpartum infection and sepsis. The authors found pulmonary embolism in two out of nine cases of antepartum deep thrombophlebitis. Husni, Pena, and Lenhart[5] reported four cases of pulmonary embolism among 20 cases of superficial and deep thrombophlebitis during pregnancy. They found that phlebitis occurred predominantly in the last trimester, and very rarely during the first trimester of pregnancy. For some unexplained reason Aaro et al[1] found antepartum thrombophlebitis to have a marked predilection for the left lower extremity as compared to an even distribution between the left and the right legs after pregnancy is terminated.

Ullery[6] reported an incidence of antepartum thrombophlebitis to be 0.018 percent in his series in 1954. Aaro et al[1] found 87 cases of thrombophlebitis during 25,082 pregnancies, an incidence of 0.15 percent. Villasanta[8] reported an incidence of 0.027 percent in 43,790 pregnant women. Husni et al[5] reported an incidence of 0.085 percent in 23,485 pregnancies.

Pathophysiology

Since Virchow's triad of conditions predisposing

to thrombosis were proposed over a century ago, viz. (1) blood stasis, (2) vessel injury, and (3) hypercoagulability of the blood, very little has been added to further illuminate the mechanism and biochemistry of thrombus formation.[7] The precise interrelation of the various factors involved in the in vivo clotting of blood have not been fully worked up. Villasanta[8] states that the proposed theories fail to explain the relatively low overall incidence of thromboembolic disease in pregnancy in spite of the conditions in gestation that enhance intravascular clotting of the blood: varicose veins, increased intra-abdominal pressure on the iliac veins with resultant venous stasis in the lower extremities; arteriovenous shunt in the placenta with consequent increased venous incompetency in the lower extremities; anemia; obesity; and increased blood fibrinogen level. Furthermore, Beller[2] observes that in the postpartum period the concentration of blood coagulation factors declines from the markedly high levels during pregnancy to almost normal values by the third postpartum day in most instances, yet statistically the incidence of pulmonary embolism is highest at this time. In spite of our lack of thorough knowledge in this field, significant progress has been made in therapy and prophylaxis during the past few decades.

Therapy and Risks

Avoidance of prolonged bed rest, elevation of the lower extremities, proper hydration, and use of elastic stockings or elastic wraps on the legs promote good venous return and comprise accepted practice in prophylaxis for thrombophlebitis during pregnancy in the more susceptible patient. Surgical therapy, exemplified by venous ligation, vein stripping, and embolectomy is uncommon during pregnancy. Anticoagulant treatment is today the mainstay in thromboembolic disease during gestation.

Before anticoagulants came into use, the disease often progressed to pulmonary embolism and death. Villasanta's[9] review of the literature up till 1964 revealed a mortality of 12.8 percent among 163 pregnant females with thrombophlebitis who received no anticoagulants. Among 134 antepartum patients treated with anticoagulants, the mortality was 0.7 percent. Heparin, bishydroxycoumarin (Dicumarol), or a combination of the two were used. More recently dextran has been found promising.[3,5,8] Heparin prolongs the clotting time by acting as an antithrombin and antithromboplastin. The coumarin derivatives, known also as the oral anticoagulants, act indirectly by depressing formation of blood clotting factors II, VII, IX, and X. Dextran prevents the agglutination of red cells, decreases the whole blood viscosity, and produces a molecular coating over the intima of the blood vessel.

Anticoagulant therapy entails definite risks both to the mother as well as the fetus. Among contraindications to anticoagulant use are thrombocytopenic purpura, open wounds or ulcerations, impaired hepatic or renal function, hypertension, subacute bacterial endocarditis, peptic ulcers, colitis, and esophageal varices. Hemorrhage is the major complication of anticoagulant therapy. Villasanta[9] nevertheless found in the literature very few cases of complications to the mother following anticoagulant treatment.

Possible danger to the human fetus during antepartum anticoagulant therapy could have been predicted even before the coumarin derivatives were isolated. It was after the incrimination of sweet clover eaten by the pregnant cow as the cause of hemorrhagic disease in newborn calves that investigations by Link and his associates (as narrated by Vigran[7]) led to the discovery of the coumarin compounds. Indeed nature had provided the first animal experiment for safety of the oral anticoagulants in pregnancy. Reports of successful use of coumarin drugs as well as adverse effects to the fetus without harm to the mother began to appear after the first use of the coumarin drugs in antepartum thrombophlebitis in 1945. Cases of fetal death with maceration of the fetus[4] were described in association with anticoagulant treatment. Nevertheless, Ullery[6], in 1954, concluded that the risk

to the mother as well as the fetus was minimal when prothrombin time was maintained between 18 and 23 seconds (20 to 30 percent of normal). Villasanta[8] found 17 reported cases of thrombophlebitis treated with heparin as the sole anticoagulant with no ill effect on the fetus. In contrast, in 89 published cases treated with coumarin derivatives, he found 14 cases of fetal death in utero and four additional cases of fatal hemorrhagic lesions in the newborn, giving a mortality of 20 percent. In another report Villasanta[9] found in the literature two cases of surviving children with congenital anomalies related to coagulation defect. The fatal cases included a stillborn infant with hemorrhage of the thymus as well as other organs; a neonatal death with tentorial tears; another stillborn with multiple hemorrhages; a few cases of intrauterine death with severe maceration masking possible evidence of hemorrhage; and a case of abortion.

Villasanta found no particular coumarin derivative to be incriminated more than any other. Similarly, the total doses given, as well as the duration of treatment were found to be insignificant. Extreme prolongation of the prothrombin time is thought not to be responsible for the fetal hemorrhages since one mother with prolongation of the prothrombin time to 97 seconds delivered a normal baby whereas death from hemorrhages were reported in cases with maintenance of prothrombin time at recommended

values.

Four cases of adverse effect to the fetus during anticoagulant therapy, including two from the University of Nebraska Hospital, are now presented.

## Case Reports

### Case No. 1

The patient was a 35 year old para 3-0-1-3 whose last menstrual period was on December 15, 1956, and whose expected date of confinement was September 22, 1957. This patient had severe rheumatic heart disease and had been on anticoagulants for some years, primarily on bishydroxycoumarin (Dicumarol). Because of fibrillation, she was also on digitalis. The general trend had been to maintain a prothrombin time around 30 to 40 percent of normal, seldom ranging below 25 percent. The obstetrician's office records contain the following laboratory values:

| Date | Prothrombin time |
|---|---|
| March 11, 1967 | 37 percent |
| March 26, 1967 | 40 percent |
| April 23, 1967 | 21 percent |
| June 25, 1967 | 15 percent |

Between the office visit on June 25 and the next one a week later, fetal heart tones and fetal movements had disappeared. The patient delivered spontaneously by breech presentation five weeks prematurely. The fetus was

estimated to have been dead in utero for three weeks. Unfortunately, a postmortem examination was not performed. Records do not show evidence of gross hemorrhagic lesions.

Case No. 2

This 21 year old Negro female para 2-1-0-2 with a history of the last menstrual period on September 8, 1963, and an expected term date of June 15, 1964 was admitted to the hospital on October 14, 1963, for thrombophlebitis of the right lower extremity. She had a past history of recurrent thromboplhebitis and grand mal epilepsy. She was said to have had either plication or ligation of the inferior vena cava early in 1963. Records show the following drug doses and laboratory values:

| Date | Sodium Warfarin (Coumadin) Dose | Prothrombin Time | Control |
|---|---|---|---|
| October 15 | 40 mgm | 18 sec | 13 sec |
| October 16 | 20 mgm | 22 sec | 12 sec |
| October 17 | 10 mgm | 29 sec | 12 sec |
| October 19 | 5 mgm | | |
| October 20 | 5 mgm | 38 sec | 12 sec |
| October 21 | 5 mgm | | |
| October 22 | 5 mgm | 35 sec | 14 sec |

Additionally, 100 mgm of heparin TID was given on October 15, 16, and 17. She also received phenylbutazone during hospitalization. Diphenylhydantoin (Dilantin) and primidone (Mysoline) prescribed during her hospital stay were continued upon discharge in October following satisfactory recovery. Anticoagulants were discontinued after October 22.

The patient was readmitted on November 24 with recurrence of the thrombophlebitis in the right lower extremity. She was given phenylbutazone, and anticoagulants were given according to the following schedule with the laboratory values as shown:

| Date | Sodium Warfarin (Coumadin) Dose | Prothrombin Time | Control |
|---|---|---|---|
| November 4 | 40 mgm | | |
| November 5 | 10 mgm | 14 sec | 12 sec |
| November 6 | 5 mgm | 22 sec | 12 sec |
| November 7 | 5 mgm | 27 sec | 12 sec |
| November 8 | 5 mgm | 28 sec | 13 sec |
| November 9 | | 26 sec | 12 sec |
| November 10 | 7.5 mgm | | |
| November 11 | 7.5 mgm | 22 sec | 12 sec |
| November 12 | 10 mgm | 22 sec | 12 sec |
| November 13 | 15 mgm | 15 sec | 13 sec |
| November 14 | | 14 sec | 12 sec |
| November 15 | 30 mgm | | |

| Date | Sodium Warfarin (Coumadin) Dose | Prothrombin Time | Control |
|---|---|---|---|
| November 16 | 5 mgm | 30 sec | 13 sec |
| November 17 | 5 mgm | 30 sec | 13 sec |
| November 18 | 5 mgm | 29 sec | 14 |
| November 19 | 17.5 mgm | 25 sec | 13 sec |
| November 20 | | 24 sec | 13 sec |
| November 21 | 5 mgm | 31 sec | 13 sec |
| November 22 | | 34 sec | 13 sec |
| November 23 | | 22 sec | 13 sec |
| November 24 | 7.5 mgm | 18 sec | 13 sec |
| November 25 | | | |
| November 26 | 15 mgm | | |
| November 27 | 15 mgm | 17 sec | 13 sec |
| November 28 | 15 mgm | 21 sec | 12 sec |
| November 29 | 10 mgm | 31 sec | 14 sec |
| November 30 | 7.5 mgm | 44 sec | 14 sec |
| December 1 | 7.5 mgm | 33 sec | 13 sec |
| December 2 | 7.5 mgm | 37 sec | 13 sec |
| December 3 | 10 mgm | | |

The patient was dismissed from the hospital on December 3 and arrangements were made for a visiting nurse to supervise an alternating warfarin dose of 7.5 mgm and 10 mgm per day. Blood was obtained on an outpatient basis for the following prothrombin time values:

| Date | Prothrombin Time | Control |
|---|---|---|
| December 3 | 29 sec | 13 sec |
| December 9 | 35 sec | 14 sec |
| December 16 | 19 sec | 13 sec |
| December 23 | 46 sec | 14 sec |
| December 30 | 53 sec | 14 sec |

On December 23 the drug dose was increased to 10 mgm daily following the preceding week's low prothrombin time. On December 30 warfarin was stopped when the prothrombin time for the previous week was seen to be 46 seconds. She received 5 mgm of the drug on January 1, and 7.5 mgm on January 2.

On the morning of January 3 she was admitted in active labor with vaginal bleeding. Fifteen mgm of phytonadione (Aquamephyton) was administered after the prothrombin time was found to be 24 seconds. A 5 lb. 1 oz. stillborn female was delivered. No record of an autopsy or description of any obvious hemorrhage are found.

Case No. 3

This 38 year old white female para 3-0-1-3 with a history of the last menstrual period on June 20, 1965, and estimated date of term of March 27, 1966 was hospitalized at another hospital from October 13 until October 19 for right axillary vein thrombophlebitis. She had a long term

history of bleeding tendencies. Records show the following:

| Date | Sodium Warfarin (Coumadin) Dose | Prothrombin Time | Control |
|---|---|---|---|
| October 13 | | 12.5 sec | 12 sec |
| October 14 | 50 mgm | | |
| October 15 | 15 mgm | 22 sec | 11 sec |
| October 16 | 7.5 mgm | 25 sec | 12 sec |
| October 17 | 10 mgm | | |
| October 18 | 10 mgm | 30 sec | 12 sec |
| October 19 | 7.5 mgm | | |

A total of 350 mgm of heparin was given on the 13th and a clotting time of 40 minutes is recorded. From the 14th until the 17th of October, she received 200 mgm of heparin daily. Clotting time was 27 minutes on October 14. She also received phenylbutazone (Butazolidin) while in the hospital. She was dismissed on October 19 on 7.5 mgm of warfarin daily. During an office visit on October 25 her prothrombin time was 31 seconds with a control of 14 seconds.

On November 10 the patient was admitted again, for acute and chronic abdominal pain. Prothrombin time was found to be 18 seconds with a control of 11 seconds. Microhematuria was seen, and a possibility of internal hemorrhage prompted cessation of anticoagulant administration at this

time. She was dismissed after a few days with no further anticoagulant therapy.

The patient was seen for the first time at the University Hospital for a prenatal checkup on December 10. During subsequent visits she gave a history of spotting on December 14, and bleeding hemorrhoids on December 20.

She was admitted to the University Hospital on March 14, 1966, for chronic back pain, obesity, mild hypertension, fatigue from overwork, and for observation for possible future recurrence of axillary vein thrombosis during the remainder of her pregnancy. Following a relatively uneventful course she delivered an 8 lb. 14 oz. female infant with hydrocephalus after oxytocin induction. At approximately one month of age, the child underwent a craniotomy at which time an old hematoma, estimated to be formed prenatally, was found. The child is institutionalized at the present time.

Case No. 4

This 22 year old white female nullipara was admitted to the hospital on February 20, 1967, with a diagnosis of a missed abortion. Her estimated date of confinement was July 1, 1967. She had a past history of pulmonary embolism treated with vena cava plication and ligation of the ovarian veins. On a previous admission, she was started on sodium warfarin (Coumadin) prophylaxis when it was learned that

she was pregnant. The following drug doses and laboratory values are available:

| Date | Sodium Warfarin (Coumadin) Dose | Prothrombin Time | Control |
|---|---|---|---|
| December 8 | | 13 sec | 13 sec |
| December 9 | 40 mgm | | |
| December 10 | 7.5 mgm | 16 sec | 14 sec |
| December 11 | 10 mgm | 14 sec | 13 sec |
| December 13 | 10 mgm | 32 sec | 13 sec |
| December 14 | 10 mgm | | |
| December 15 | 15 mgm | 18 sec | 13 sec |
| December 16 | 10 mgm | 18 sec | 13 sec |

From December 16 until December 21 the patient received 10 mgm of the drug daily. From December 22 until January 25 she took 7.5 mgm daily. From January 26 until delivery after hospitalization on February 20, 5 mgm and 7.5 mgm were prescribed on alternate days. Prothrombin time after December 16 are shown below:

| Date | Prothrombin Time | Control |
|---|---|---|
| December 22 | 37 sec | 13 sec |
| December 29 | 32 sec | 13 sec |
| January 5 | 24 sec | 13 sec |
| January 26 | 32 sec | 13 sec |
| February 9 | 22 sec | 13 sec |
| February 23 | 19 sec | 13 sec |

A few days after admission she went spontaneously into labor and delivered a dead male fetus. Other data are not available on the fetus.

## Comments

The four cases presented add to the mounting evidence against the use of the coumarin drugs during pregnancy. However, controlled studies are lacking on the subject apparently due to the relative rarity of the disease during pregnancy. In the cases found in the literature as well as those presented here, unequivocal evidence of hemorrhage is lacking in a large percentage of the fetuses lost. It is therefore not surprising that proponents of continued utilization of oral anticoagulants in pregnancy as well as those convinced otherwise are both found at present.

There is little doubt that heparin is safe for the fetus when given to the mother with careful maintenance of clotting time within a recommended range. Its safety lies in its high molecular weight of around 20,000 that probably prohibits passage through the placenta. On the other hand a molecular weight of approximately 1,000 apparently allows the coumarin drugs to pass through the placental barrier and into the fetus. The fortuitous phenomenon that results are not disastrous to a larger percentage of fetuses is explained by Beller[2] to be due to a

compensation mechanism for the inadequate production of coagulation factors in the fetal liver. Despite the deficiency of blood coagulation factors, the bleeding and clotting time in the newborn as well as the fetus are found to be shorter than in the adult. Hemorrhagic complications in the fetus are thought to arise when these unknown compensatory mechanisms are functioning improperly.

Studies on the treatment of acute thrombophlebitis with dextran have aroused enthusiasm among investigators. Cox, Flotte, and Buxton[3] reported in 1965 on the treatment of thrombophlebitis with dextran of average molecular weight of 75,000 as well as with dextran 40,000. They found that as the time interval between onset of symptoms and the initiation of therapy passes 48 hours the chances of objective improvement are much reduced. When used within 48 hours of onset of symptoms it was found to be an effective treatment. Husni et al[5] reported in 1967 on 20 cases of antepartum deep thrombophlebitis treated either conservatively, with anticoagulants, or with dextran. They found a remarkably good response to dextran with no untoward results to the fetus.

Unfortunately, dextran cannot completely replace the coumarin drugs in pregnancy in spite of its apparent advantages of relative ease of administration and the lack of a need for specific laboratory control. Nevertheless, an

attempt to use dextran instead of the coumarin compounds in acute antepartum thrombophlebitis merits serious consideration.

The low cost of the oral anticoagulants plus the ease of administration which make them suitable for outpatient therapy undoubtedly are the major factors that account for their popularity both in antepartum and in general use. Clearly, research is indicated to discover new anticoagulants which would combine the above advantages with characteristics that guarantee safety to the fetus. In the meantime perhaps an extra effort should be made by the clinician to replace the coumarins with the other available therapeutic agents, heparin and dextran, where feasible.

## Summary

Thromboembolic phenomenon characterized by thrombophlebitis, phlebothrombosis, and pulmonary embolism is rare during pregnancy. Pathophysiology of the disease is poorly understood.

Anticoagulant therapy markedly reduces the associated high mortality. The coumarin drugs are incriminated in adverse effect on the fetus during antepartum thrombophlebitis in the four cases presented, adding mounting evidence against their use in pregnancy. Until new and safer drugs are available, heparin and dextran should be utilized where possible.

## REFERENCES


1. Aaro, A.L., Johnson, T.R., and Juergens, J.L., Acute Deep Venous Thrombosis Associated with Pregnancy, Obstet Gynec 28:553-558, (Oct) 1966.

2. Beller, F.K., Thromboembolic Disease in Pregnancy, Clin Obstet Gynec, 11:290-311 (Mar) 1968.

3. Cox, E.F., Flotte, C.T., Buxton, R.W., Dextran in the Treatment of Thrombophlebitis, Surgery 57:225-229 (Feb) 1965.

4. Epstein, W.A., Antepartum Fetal Death During Anticoagulant Therapy for Thromboembolism: Report of three cases, New York Mount Sinai Hospital Journal 26:562-565 (Nov-Dec) 1959.

5. Husni, E.A., Pena, L.I., and Lenhart, A.E., Thrombophlebitis in Pregnancy, Amer J. Obstet Gynec, 97:901-905 (Apr) 1967.

6. Ullery, J.C., Thromboembolic Disease Complicating Pregnancy and the Puerperium, Amer J Obstet Gynec, 68:1243-1260 (Nov) 1954.

7. Vigran, I.M., Clinical Anticoagulant Therapy, Philadelphia Lea and Febiger, 1965, pp. 27-273.

8. Villasanta, U., Therapy in Antepartum Thrombophlebitis, Obstet Gynec 26:534-541 (Oct) 1965.

9. Villasanta, U., Thromboembolic Disease in Pregnancy, Amer J Obstet Gynec, 93:142-160 (Sept) 1965.