Antepartum pulmonary embolism

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Antepartal thromboembolic disease appears to be increasing during the prenatal period and decreasing in the puerperium. Antepartal pulmonary thromboembolism, although rare, may be commoner than expected and in our series of 20 cases half of them appear in the first trimester. Once a firm diagnosis is made, which is usually possible, the patient is treated with anticoagulants. Intravenous heparin is used for the first 7 to 10 days followed by sodium warfarin until term, at which time it is stopped and heparin is again started and maintained through delivery and the early puerperium. Maternal complications of anticoagulant therapy have not been a problem. One fetus died in utero and was macerated at delivery without evidence of hemorrhage. Others have described this phenomenon. Four patients had adjunctive operations—femoral thrombectomy, vena caval ligation, and pulmonary thrombectomy when anticoagulants failed to control the disease. There were 2 maternal deaths. One death followed complete anticoagulation therapy and pulmonary arterial thrombectomy, the other patient died before treatment could be instituted.

PULMONARY embolism is an infrequent complication of pregnancy. Nonetheless, it is a serious complication, one so serious that it ranks as a major cause of maternal mortality. The maternal mortality figures in England and Wales[1, 2] show pulmonary embolism to be second only to abortion as the greatest cause of maternal death.

Method

The statistics presented here are based on a retrospective study of the hospital records of all women, ages 9 to 50, discharged from the Strong Memorial Hospital of the University of Rochester Medical Center with a diagnosis of deep venous thrombosis and/or pulmonary embolism. The study covers a 12 year period from Jan. 1, 1959, to Dec. 30, 1970. As this is a retrospective study, it has the disadvantages of all such studies because it includes only those patients diagnosed as having clinical evidence of thromboembolic disease and the diagnosis is subject to clinical opinion. Only those cases with sound clinical and laboratory data were accepted for this study.

The definition of deep vein thrombosis in this study is the presence of a blood clot in the deep veins of the lower extremities or pelvis. Cases of phlebitis, thrombophlebitis of superficial veins, and septic thrombophlebitis were excluded. Pulmonary thromboembolism refers to the blocking of a pulmonary artery by a thrombus. Pulmonary emboli of all other sources, such as fat or amniotic fluid, were excluded. Thromboembolic disease is used to denote the two entities of deep venous thrombosis and pulmonary thromboembolism and their close association.

Prothrombin time was expressed as a percentage of the control and whole blood clotting times were done by the Lee and White method.

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Table I. Frequency and number of deaths of thromboembolic disease in hospitalized females 9 to 50 years of age, 1959-1970

	Pulmonary thromboembolism		*Deep vein thrombosis*		
Service	*Total*	*Deaths*	*Total*	*Deaths*	*Total*
Obstetric	40	4	32	0	72
Medical	55	12	45	1	100
Surgical	16	1	22	0	38
Total	111		99		210

Table II. Occurrence, incidence, and number of deaths of thromboembolic disease in pregnancy

	Pulmonary thromboembolism			*Deep vein thrombosis*		
Time of occurrence	*Total*	*Maternal death*	*Fetal death*	*Total*	*Maternal death*	*Fetal death*
Antepartum	20	2	2	14	0	1
Postpartum	16	1	0	16	0	0
Postabortion	4	1	—	2	0	—

Incidence

During the 12 year period of this study there were 29,770 deliveries at the Strong Memorial Hospital. During the same period of time there were 210 female admissions, ages 9 to 50, with the diagnosis of thromboembolic disease (Table I). Seventy-two of these patients were pregnant, which makes the recorded incidence of thromboembolic disease 0.242 per 100 deliveries.

The frequency of thromboembolic disease during pregnancy was almost equally divided between the antepartal and the postpartal period shown in Table II. The 20 patients who had pulmonary embolization antepartally will be the subject of this report.

Patient sample and disease onset

The patients represent a heterogeneous group of Caucasians and Negroes of all socioeconomic levels. The age, parity, and time at onset of the disease are listed in Table III. Eleven of the patients were over 30 years of age and 4 were under 20. Parity was well distributed from 0 to 9, but a clustering is noted with high parity—4 of 20 (20 per cent) were para 7 or greater.

One can see from Table III that half of the pulmonary embolization took place in the first trimester. Only one occurred in the middle trimester and 9 took place in the last trimester.

Deep vein thrombosis was demonstrated clinically or by x-ray in 12 of 20 patients at the time of pulmonary embolization. The presence of antepartum deep vein thrombosis in the extremities or antepartum pulmonary embolism does not appear to have any relation to age or duration of pregnancy, but there were observable predisposing factors in these patients as shown in Table IV. A high percentage of the patients had some type of vascular disease and 3 had thromboembolic disease previously.

Diagnosis

Each of these patients had clinical and laboratory evidence of pulmonary thromboembolism. The symptoms and physical findings have not changed during the 12 years of this study, but the laboratory tests have improved and new ones have been added, hence not all of our patients had every diagnostic test now in use. The commonest complaints were chest pain and dyspnea. These and the commonest physical findings are listed in Table V. The laboratory findings are shown in Table VI. Fifteen patients had positive x-rays and 5 were negative or equivocal. Two of these 5 had massive bilateral pulmonary

Table III. Age, parity, and time at onset of pulmonary thromboembolism

Case No.	*Age*	*Parity*	*Duration of pregnancy (wk.)*	*Pulmonary embolism*	*Deep vein thrombosis*
1	17	0	12	+	+
2	35	1	8	+	0
3	32	8	10	+	0
4	32	4	9	+	+
5	19	1	10	+	+
6	33	8	12	+	0
7	36	9	7	+	0
8	32	3	8	+	+
9	39	3	8	+	+
10	20	1	12	+	+
11	30	4	24	+	+
12	30	0	27	+	0
13	39	1	31	+	0
14	20	2	31	+	+
15	27	2	32	+	+
16	25	2	34	+	+
17	35	7	35	+	+
18	18	0	37	+	+
19	19	5	39	+	0
20	23	2	38	+	0

Table IV. Predisposing factors in pulmonary embolism

Vascular disease		9
Varicose veins	6	
Previous thromboembolic disease	3	
Obesity		4
Hypertensive disease		2
Pancreatitis		1
Thrombocytopenic purpura		1
Sickle cell disease		1
Placenta previa		1
Steroid contraceptive (failed)		1

Table V. Incidence of positive diagnostic findings in 20 patients

	No positive	
Symptoms		
Chest pain		20
Pleuritic	19	
Nonpleuritic	1	
Dyspnea		10
Hemoptysis		4
Physical findings		
Râles		9
Friction rub		7
Tachycardia over 120		15
Calf tenderness		8
Positive Homan's sign		6

embolization at autopsy. The electrocardiogram was not particularly helpful. Phlebograms showed clot in the lower extremities about half of the time. Pulmonary arteriography and pulmonary lung scan have been used more recently. In one case where the x-ray was equivocal, pulmonary arteriography was positive.

Treatment

The initial treatment in 17 patients was heparin which in the last 15 cases was administered every 6 hours so as to provide a clotting time between 2 and 2.5 times the pretreatment control. The duration of the heparin therapy was usually one to 2 weeks. Sodium warfarin was used for longer term control. It was started 36 hours before discontinuing the heparin and was given in a loading dose of 20 to 40 mg. Subsequent dosage ranged from 2 to 10 mg. daily as needed to maintain the prothrombin time between 18 and 30 per cent of normal. Once the disease was under control and the warfarin therapy stabilized, the patients returned to their homes and were followed weekly as ambulatory patients. At term, patients were admitted to the hospital for conversion from

warfarin to heparin therapy, and labor was induced. Heparin therapy was continued through delivery and the first postoperative day, after which warfarin was substituted and continued for 4 to 8 weeks post partum. Not all patients received the standard therapy for a number of reasons, such as abortion, premature labor, and placenta previa. The type and duration of therapy and the maternal and fetal complications are summarized in Table VII.

Four patients had operative treatment as well as anticoagulation. There were 2 iliofemoral thrombectomies for extensive disease and one ligation of the vena cava following repeat pulmonary embolization, all of which were successful. One patient had a femoral vein ligation which was followed by a second pulmonary embolus and pulmonary artery thrombectomy but died shortly after the operation.

Outcome

There were 2 maternal deaths, 2 fetal deaths, and 4 abortions, as shown in Table VIII. There were no neonatal deaths. One maternal death was associated with a second fatal pulmonary embolism, despite heparin therapy, operative ligation of the femoral vein, and pulmonary artery thrombectomy. Her 10 week fetus died with her. The second maternal death occurred in the emergency room at 27 weeks of gestation following a grand mal seizure and before therapy could be instituted. Autopsy revealed massive bilateral pulmonary artery embolization. Her 27 week, 1,500 gram fetus died in utero. One abortion was induced with intra-amniotic hypertonic saline because of massive doses of maternal diagnostic radiation during early pregnancy. There were 2 spontaneous abortions and one immature (600 gram) fetal death. One spontaneous abortion occurred in a patient with sickle cell disease who had threatened abortion before the pulmonary embolus and anticoagulant therapy (heparin for 10 days and warfarin for 2 weeks). The second abortion was a missed abortion which terminated spontaneously. A macerated fetus without evidence of hemorrhage was described by the pathologist. The immature fetal death followed some maternal bleeding at midpregnancy and a macerated, 600 gram fetus was delivered. The pathologist observed nothing more than maceration of the fetus, but the placenta was infarcted over a third of its area. This patient had threatened abortion prior to the embolus and the use of anticoagulants.

Table VI. Incidence of positive radiologic findings in 20 patients

Radiologic test	*No. positive*	*No. tested*
Chest x-ray	15	20
Electrocardiogram	4	16
Lung scan	2	3
Pulmonary arteriography	2	2
Phlebograms (leg veins)	6	11

Of the 17 patients who received anticoagulants, 8 had some type of complication related to the anticoagulant therapy. Four patients had pulmonary embolization while receiving therapeutic doses of anticogulants. Of these, 3 were re-embolization and one was initial. The remainder of the complications were related to bleeding and are listed in Table IX. The bleeding was small in amount in 15 of the 17 patients but in 2 patients transfusions were necessary. One of these patients had a delayed postpartum hemorrhage on the third day. The other had complete placenta previa, was heparinized, had a wound hematoma after cesarean section, and the heparin was stopped. Pulmonary reembolization occurred following which heparin was again administered.

The fetal and neonatal complications possibly associated with the anticoagulant therapy are listed in Table X. There was no complication associated with administration of heparin to the mother. Of the 13 patients who received warfarin, there were 5 possible complications, but only one (neonatal bleeding) was directly related to the therapy and was not serious.

Maternal-fetal prothrombin time

During the past 12 years warfarin has been used in the treatment of pregnant women

Table VII. Type, duration, and complications of anticoagulant therapy

Case No.	*Heparin (wk.)*	*Warfarin (wk.)*	*Complications*	
			Maternal	*Fetal*
1	1	14*	None	None
2	1	30	None	Epistaxis, bleeding circumcision
3	2	2	Repeat embolus	Therapeutic abortion
4	1	30	None	None
5	2	10	Vaginal hematoma, postpartum hemorrhage	None
6	1	9	Aborted spontaneously	Abortion
7	2	2	Sickle cell disease	Abortion
8	1	0	Previous embolism, repeat embolism, pulmonary embolectomy, died	Died in utero
9	1	13	Late abortion	Macerated fetus, placenta infarcted
10	2	24	None	None
11	1	12	None	None
12	0	0	Died untreated in emergency department	Died in utero
13	1	1	None	None
14	1	8	None	None
15	6	0	Postpartum hemorrhage	None
16	1	2	None	None
17	½	0	Placenta previa, operative hematoma, repeat embolism	None
18	3	1	Epistaxis	Focal motor seizures, fetal distress, living and well
19	0	0	None	None
20	0	0	None	None

*Warfarin stopped at 27 weeks due to patient irresponsibility.

with pulmonary embolism, deep venous thrombosis, and in patients with artificial heart valves. On 7 occasions delivery has occurred inadvertently while the maternal prothrombin time was abnormal. The maternal and fetal values at the time of delivery are recorded in Table XI. The fetal level appears to be higher than that of the mother in most instances and fetal bleeding did not occur if the mother's level was above 20 per cent.

Comment

The incidence of antepartum pulmonary embolism has been listed from 0.0029 to 0.016.[3, 4, 5, 6] However, these were based on from 1 to 4 cases. By 1962 only 36 had been recorded in modern literature.[7] In 1965 Villa-Santa[6] collected 26 cases that had been treated with anticoagulants. Three of these cases are included in this report. The incidence of antepartum pulmonary embolism in this study is 0.067, a rate four times higher than that of Quenneville and associates[5] reported in 1959. In England and Wales[2] the death rate from antepartum pulmonary embolism has risen steadily, while deaths from postpartum pulmonary embolism has fallen. Jeffcoate and associates[8] have reported that 42 per cent of thromboembolic disease oc-

Table VIII. Maternal and perinatal mortality

Case No.	Maternal		Fetal	
	Death	*Complications*	*Death*	*Complications*
8	Yes	Repeated embolization, failed heparin, failed embolectomy	Yes	Died in utero
12	Yes	Massive embolus, died untreated, 12 years postsplenectomy for thrombocytopenic purpura	Yes	Died in utero
3	No	Recent pancreatitis, massive dose diagnostic x-ray, induced abortion	Yes	Induced abortion
9	No	Threatened early abortion	Yes	Macerated fetus, 600 grams infarcted placenta
7	No	Threatened early abortion treated with progesterone, sickle cell disease and spontaneous abortion	Yes	Necrotic villi and decidua
6	No	Missed abortion which terminated spontaneously	Yes	Macerated fetus, 100 grams, at 22 weeks

curred antepartally at the Mill Road Maternity Hospital. The particularly high incidence (50 per cent) of pulmonary embolism in the first trimester has not been documented before. Nor is there any ready explanation. However, one must admit that either the disease has not been recognized and recorded in early pregnancy or some new causative factor has appeared, which seems unlikely.

A firm diagnosis is essential in the management of this disease. Failure to treat properly with anticoagulants results in increased maternal mortality.[6] Treatment with anticoagulants also carries risk and is not justified until there is a firm diagnosis. The history of acute pleuritic chest pain, dyspnea, râles or friction rub, tachycardia over 120, and a positive chest x-ray is sufficient for a diagnosis. In our hands the electrocardiogram is of little value unless there are disorders of rhythm. The lung scan and pulmonary arteriography have had a limited use. The latter was positive in the 2 cases in which it was attempted. It should be noted that both patients had been heparinized prior to the test and both developed hematomas at the site of needle puncture.

The treatment of the antepartum patient with anticoagulants is full of potential complications for mother and fetus. However, in this study there has been no maternal mortality due to anticoagulants and the complications which followed were relatively benign compared to the expected difficulties had they not been used. Repeated embolization was noted in 4 of the 17 patients treated with anticoagulants. One patient was successfully treated with vena caval clipping. A second patient had femoral vein ligation following which she had a second and fatal embolus despite pulmonary thrombectomy. She might have survived had vena caval ligation been done. The other patient had an induced abortion and had no further em-

Table IX. Maternal complications related to anticoagulation therapy in 17 patients

Type of complication	*Complications in 5 patients treated with heparin*	*Complications in 3 patients treated with warfarin*
Re-embolization (1 death)	3	1
Postpartum hemorrhage	2	0
Wound hematoma	3	1
Abdominal 2		
Vaginal 2		
Antepartal spotting	1	2
Hematoma—arterial injection site	2	0
Epistaxis	1	0
Hematuria (mild)	1	0
Melena (mild)	1	0
Gingival bleeding	1	0
Total complications	15	4

Table X. Fetal complications possibly related to anticoagulant therapy

Type of complication	*Anticoagulant*		*Fetal prothrombin level*
	Heparin (No. of fetuses)	*Warfarin (No. of fetuses)*	
Spontaneous abortion*	0	2	—
Fetal death†	0	1	—
Neonatal epistaxis, bleeding circumcision	0	1	5% of normal
Focal motor seizures‡ which cleared, now living and well	0	1	80% of normal

*Maceration without evidence of bleeding.

†Large placental infarct, maceration without evidence of bleeding.

‡Fetal distress during labor.

Table XI. Maternal and fetal prothrombin time (per cent of normal at the time of delivery)

Case No.	*Maternal*	*Infant*	*Complications*	
			Maternal	*Newborn*
2	10	5	0	Epistaxis, bleeding circumcision
13	40	60	0	0
14	37	60	0	0
18	45	80	0	Transient seizures
3A*	15	100	0	0
5A*	30	?	0	0
6A*	20	20	0	Died, intracranial hemorrhage

*Reported in reference 10.

bolic difficulties. Re-embolization or extension of the thrombosis is an indication for ligation of the vena cava and left ovarian vein. Except for 2 patients who had postpartum hemorrhage, the amount and clinical significance of the maternal bleeding complications were small.

The effect of anticoagulant therapy on the fetus is more difficult to assess. So far as is known, heparin does not cross the placenta and has no effect upon the fetus. Warfarin does cross the placenta and may affect the fetus in several manners. First, teratogenic qualities have been ascribed to warfarin. Nine patients received warfarin during the first trimester of pregnancy. One patient aborted and the fetus was not available for examination. None of the 7 others exhibited any evidence of congenital malformations. Fillmore and McDevitt[9] have reviewed the literature and have added 36 cases of coumarin treatment during pregnancy. They conclude that "coumarin compounds, carefully administered, will usually not damage the fetus of a woman with a normal obstetric history."

Of the 6 perinatal losses, 2 died in utero at the time of maternal death and one was the result of induced abortion. One of the remaining 3 took place in a patient with sickle cell disease who threatened to abort prior to the embolism and therapy. It is unlikely that the therapy was a factor. The other 2 were delivered of macerated fetuses of 100 and 600 grams, respectively. Although there was no evidence of hemorrhage, the maceration prevents detailed pathologic examination. VillaSanta[6] found 6 cases of macerated fetuses in patients receiving warfarin during pregnancy. Only one of these revealed hemorrhage. Fillmore and McDevitt[9] reported 4 cases of stillborn macerated fetuses. This would appear to be a high incidence of intrauterine death and maceration and might suggest a toxic effect rather than hemorrhage. This complication appears to be without relation to the duration of coumarin therapy. There were no valid neonatal complications as the result of warfarin therapy. One infant had focal motor seizures for the

first year of life but has been well since, now aged 5. This infant had evidence of fetal distress during labor and the cord prothrombin value was 80 per cent, a level which is not likely to be associated with bleeding.

Two of these patients had pulmonary embolism in a previous pregnancy, which is an extraordinary rate of recurrence—2 in 20 as compared with 20 in 29,770. Patients who have had pulmonary embolism during pregnancy should be strongly discouraged from having future pregnancies—half of our patients were sterilized. If they do become pregnant, they should be under anticoagulation therapy during the pregnancy and we believe the treatment should begin early in view of the number of early pulmonary embolizations we observed.

Early recognition and treatment of deep vein thrombosis of the extremities during pregnancy is essential if we are to prevent pulmonary embolization. Such patients should be treated with anticoagulants throughout pregnancy. However, we do not use prophylactic anticoagulants for patients who have had a history of deep venous thrombosis prior to the pregnancy.

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Discussion

DR. JACK A. PRITCHARD, Dallas, Texas. A variety of most interesting and unusual observations has been presented. For example, the frequency of pulmonary thromboembolism was greater antepartum (20 cases) than post partum (16 cases). Moreover, pulmonary thromboembolism antepartum was reported to be more common than was deep venous thrombosis without thromboembolism (14 cases). This implies that pulmonary embolism commonly occurred at or before the onset of symptoms or signs of deep venous thrombosis, that either recognition of symptoms and signs or therapy was delayed until thromboembolism had occurred, or that the therapy prescribed for deep venous thrombosis was not always effective in preventing thromboembolism. How often did the first episode of thromboembolism occur while these women were being treated for deep venous thrombosis?

Medical treatment described in this report was heparin injected at 6 hour intervals in doses that raised the Lee-White clotting time to 2 to 2½ times normal. What was the rationale for administering heparin at 6 hour intervals and when in the treatment cycle was the clotting time measured? Our own experiences imply, at least, that optimal heparin therapy in women with deep venous thrombosis and pulmonary thromboembolism is, in general, 10,000 units intravenously to start followed at 4 hour rather than 6 hour intervals by 5,000 to 10,000 units intravenously so as to establish the Lee-White clotting time of blood drawn within the hour before the next dose at 2 to 3 times normal.

The authors have used sodium warfarin for long-term anticoagulant therapy, continuing its administration until term, when it was stopped and heparin therapy reinstituted. The degree of risk to the fetus and neonate from maternally administered warfarin has not been precisely defined. The risk would appear to be greatest when maternal plasma "prothrombic" activity is below 20 per cent and with premature delivery, a circumstance which in itself has been found to predispose to bleeding in the fetus and neonate. We remain reluctant to use warfarin and similar drugs antepartum. Instead, when the pregnancy

is allowed to continue, heparin would be administered chronically antepartum, usually twice a day subcutaneously. Colonel Jack Pearson (who is attending this meeting) and colleagues have described the use of an indwelling cannula for home injection of heparin intravenously. Hopefully, Dr. Pearson will comment on their experiences.

It is of considerable interest that pulmonary embolism occurred rarely during the second trimester but with about equal frequency during the first and third trimesters. The development of thromboembolism during the first trimester, but not the second, cannot be rationalized to result from mechanically induced stasis in the lower half of the body or from any known pregnancy-induced changes in the coagulation mechanism. A rather common phenomenon in our area, at least, is prohibition of further use of oral contraceptives by the woman who develops to a varying degree symptoms and signs of venous thrombosis, with one of the results being prompt conception. Had the women in this report who developed thromboembolism during the first trimester been taking oral contraceptives recently?

We, and others, have ligated the vena cava and ovarian veins as late as the thirty-first week of pregnancy with the delivery subsequently of a normal infant. Ligation in our patients was necessitated by evidence of recurring embolization. Moreover, in 2 such cases late in pregnancy we have also performed bilateral partial resection of the oviducts at the time of caval ligation while allowing the pregnancy to continue. What problems, if any, did the authors note as the consequence of caval ligation?

Effective medical management throughout the remainder of pregnancy, including delivery and the puerperium, for the woman who suffers pulmonary thromboembolism early in pregnancy may be quite difficult. Under what circumstances would the authors not advise abortion and sterilization of the woman who had an obvious pulmonary thromboembolism early in pregnancy?

Writings concerned with pulmonary thromboembolism have, for the most part, emphasized the relative rarity of this lesion during the antepartum period compared to the puerperium. This report amply demonstrates that any immunity bestowed during the antepartum period is far from complete!

DR. EDWARD C. HUGHES, Syracuse, New York. As Chairman of the Maternal Child Welfare Committee of the Medical Society of the State of New York, I would like to make a few comments to emphasize the importance of Dr. Lund's presentation this morning.

Of 735 maternal deaths in the state over a period of ten years, there were 106 maternal deaths due to pulmonary embolism of various types. The diagnosis was confirmed by postmortem examination of the patients. Sixty-two patients died from blood clot embolism, 21 during pregnancy without being delivered of their infants. There were 21 fetal deaths and 4 postmortem cesarean sections.

Thirty-seven women died from amniotic fluid embolism; 23 of these were given intravenous oxytocin for elective induction of labor. Twenty-one infants of this group were born dead or died soon thereafter.

Seven patients died from air embolism. The diagnosis was confirmed by qualified pathologists. The pelvic organs and the cardiac and pulmonary organs in these patients were dissected under water to be sure that the diagnosis was correct. Four of these patients died during pregnancy. No cause could be given to the origin of the air embolism, although lacerated vessels were found either in the pelvic organs or elsewhere. The other 3 patients died after operative procedures.

Analyzing these reports, the Committee decided that many of these were preventable. Except for the air embolism, where no cause could be found, there seemed to be a direct causative factor or factors involved. It is quite evident that the amniotic fluid emboli resulted from the increased force of the uterine contractions created by the intravenous oxytocic agent. In reviewing the group with blood clot embolism, certain clinical findings were present that, had the doctor appreciated these things, death perhaps could have been avoided by applying the treatment which Dr. Lund has so ably described. In fact, in all these patients, further dissections of the reproductive organs, thighs, and legs revealed that there had been previous thrombophlebitis or other injury to the blood vessels.

DR. RUSSELL R. DE ALVAREZ, Philadelphia, Pennsylvania. Practically each one of us is familiar with and has suffered the experiences of the relationship of deep vein thrombosis, pulmonary embolism, other thromboembolism, and their sequelae during the postpartum and the postabortal states. However, it is highly unusual to find such a large proportion of patients with

this problem existing or occurring during the first trimester of pregnancy, as reported by Dr. Lund. His report indicates that we must carefully observe early pregnant patients and anticipate the potential development of these severe coagulation processes at any duration of pregnancy. Even though we are cognizant of the pathology of thromboembolic disease and of currently appropriate directions of treatment, perhaps much more remains to be learned regarding the mechanisms of production and the pre-existing factors which form the foundation for the occurrence of thromboembolic phenomena.

Dr. Lund has mentioned, but not necessarily implicated, "the pill" in a patient who subsequently became pregnant and developed thromboembolic disease during early pregnancy. Pregnancy itself also has been mentioned as predisposing to the process. There are some similarities which do occur in both the pregnant patient and the patient ingesting the pill. In our study of the lipid changes during normal pregnancy, an increase occurs in all lipid classes and the subfractions of each class and in most of the fatty acid composition of the lipid esters beginning at or about the fourteenth week which is subsequently maintained at these high levels. These occur not only during pregnancy but also under the influence of the administration of most of the oral contraceptive steroid agents, most prominently where the steroid is high in estrogen content and particularly where the progestogens are metabolized in an estrogenic direction. Among these lipids, the phospholipids are particularly increased. Two of these multiple phosphatides, phosphatidyl ethanolamine and phosphatidyl serine, which practically substitute platelets, rise significantly.

I would be interested in learning whether Dr. Lund's data indicate any evidence of alterations in platelet count, platelet adhesiveness, or an increase in platelet spreading. Likewise, is there any evidence of an increase in the number of irreversible aggregations of thrombocytes as occurs in arteriosclerosis, myocardial infarction, and diabetes? Often, platelet disintegration, increased platelet adhesiveness, the disappearance of platelets, and a response to the platelet loss are mediated by phosphatidyl ethanolamine and phosphatidyl serine as mechanisms in the coagulation process.

Dr. Jack Pearson, El Paso, Texas (by invitation). Dr. Pritchard mentioned some of the work we have done in terms of trying to utilize intravenous heparin in the antepartum patient on a long-term basis. We had been somewhat unhappy with the subcutaneous use because of the lack of predictable effect and patient acceptance. So we have used a long-term intravenous catheter preparation. When we presented and published this work, we had treated 5 patients. Until the present time in our own series and in those reported to us by other people who have used the technique, there are some 14 cases that I am aware of in which long-term intravenous catheters have been used. All of these pregnant patients had a positive diagnosis of deep venous thrombophlebitis, usually ileofemoral. In none of the cases that I am aware of was there an associated embolic episode. None of the treated patients developed a subsequent embolic phenomenon, so I am not sure that I am talking about the exact same type of patients Dr. Lund is reporting. These women had educational levels anywhere from that of college graduate to as little as third grade. Once oriented, the patients were discharged from the hospital and administered their own intravenous heparin at home as described in our article. We consider the rationale of our approach analagous to the education of the diabetic administering her own insulin. We have had only one complication with the technique and to the present time have been quite gratified at both the maternal and fetal results.

Dr. Simon Henderson (closing). Four patients were admitted with embolism and on subsequent examination were found to have deep venous thrombosis. One of these was actually under therapy for deep venous thrombosis which subsequently extended. She was the one who had femoral ligation and subsequently died after the failure of pulmonary artery thrombectomy. Regarding our treatment, we in latter years have been using 10,000 U. of heparin intravenously after a clotting time for a base line is taken. This is repeated every 4 hours, and before each dose the clotting time is determined so that the dose can be adjusted to make the next clotting time 2½ times normal. We have mixed feelings about the value of clotting times, and some patients we treat with 10,000 U. intravenously every 4 hours the first day and then every 6 hours without determining clotting times and altering the dose, because if you give an immediate dose of heparin the clotting time goes to infinity and then slowly comes down off that peak. The question is where one catches the curve with the clotting time, and the importance of this is not really cleared up

yet. The method that we haven't used is continuous intravenous heparin drip which gives a much more constant clotting time. This needs very good nursing observation which we feel we don't have at the moment.

One patient, whom Dr. Lund did mention, fitted the question about early pregnancy and contraception. The question was asked if we would advise abortion in a patient with pulmonary embolus in early pregnancy. We certainly haven't in the past as we feel that this disease can be managed fairly well, and if the patient wants this pregnancy we allow the gestation to continue and manage the patient as has been outlined. The reason we feel rather happy about this point is that we had 3 patients who received anticoagulation therapy from 24 to 30 weeks and 5 patients who received it from 9 to 14 weeks. Our experiences with these patients were good compared with the rather poor experiences other people have reported. Although we had thought about the trans-femoral vein "umbrella" intravenous catheter and are very interested in the ease of placement, we are slightly disturbed by the recent reports of infection accompanying this procedure.

As far as platelets are concerned, we found that the platelet counts were slightly higher, which is normal for early pregnancy, and not low as they tend to be later on in pregnancy. With heparin therapy, the platelets did decrease, and this is what one expects. As far as platelet adhesiveness and stickiness, we have no data on these.