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Failure of Adjusted Doses of Subcutaneous Heparin to Prevent Thromboembolic Phenomena in Pregnant Patients With Mechanical Cardiac Valve Prostheses

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Objectives. **This report describes our experience with the use of an anticoagulant regimen of adjusted doses of subcutaneous heparin during pregnancy in women with cardiac valve prostheses.**

Background. **Gravid patients with prosthetic heart valves require long-term anticoagulant therapy. To avoid the increased incidence of fetal morbidity and mortality associated with the use of coumarin agents in such patients during pregnancy, anticoagulation with subcutaneous heparin has been suggested. Controversy exists concerning the appropriate treatment of these patients.**

Methods. **Forty pregnancies in 37 women with prosthetic heart valves were prospectively followed up. Subcutaneous heparin was administered from the 6th until the end of the 12th week and in the last 2 weeks of gestation. Heparin was given every 8 h in the first 36 cases and every 6 h in the last 4 cases, and the dose adjusted to maintain the activated partial thromboplastin time at 1.5 to 2.5 times the control level. Acenocoumarol was used at other times.**

Results. **The incidence rate of spontaneous abortions was 37.5%; there was one neonatal death (2.5%) due to cerebral hemorrhage. No signs of coumarin-induced embryopathy were found in any of the 16 live-born infants studied by the geneticist. One mother died of gastrointestinal bleeding while receiving oral anticoagulant agents. There were two cases of fatal massive thrombosis of a mitral tilting-disk prosthesis during heparin therapy. The study was interrupted after the last of these two cases.**

Conclusions. **The regimen of adjusted doses of subcutaneous heparin used in this study is not effective to prevent thrombosis of mechanical valve prostheses during pregnancy. The use of heparin from the 6th to the 12th week of gestation does not decrease the high incidence of fetal wastage associated with anticoagulant therapy. Coumarin agents provide adequate protection against thromboembolism during pregnancy in patients with mechanical valve prostheses.**

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In patients with mechanical prosthetic heart valves, long-term anticoagulant therapy is mandatory to prevent thromboembolic phenomena. Anticoagulation is also necessary in patients with a bioprosthesis who have atrial fibrillation and a large left atrium. The risk of maternal thromboembolic events is heightened during pregnancy because of the patient's hypercoagulable state, which is characterized by increased levels of certain clotting factors and of fibrinogen and platelet adhesiveness (1).

Coumarin derivatives provide effective protection against thromboembolism, but their use in pregnancy is associated with an augmented rate of abortion and the risk of coumarin-induced embryopathy (2–4). It has previously been shown (5) that the teratogenic effect of coumarin derivatives may be prevented if these agents are discontinued from before the 6th until the 12th week of pregnancy. Several investigators have advocated substituting subcutaneous heparin for oral coumarin derivatives, either throughout the gestation period (6–9) or during the 1st trimester and the last weeks of pregnancy (2,5,10–12). However, neither the efficacy of heparin in preventing thromboembolism nor its safety with respect to fetal wastage has been fully evaluated. Moreover, the exact dosage and the proper method of monitoring remain unclear.

For pregnant women with mechanical prosthetic heart valves or bioprostheses and either atrial fibrillation or previous thromboembolic events, Ginsberg and Barrón (13) recently recommended the use of adjusted doses of subcutaneous heparin every 12 h between the 6th and 12th weeks of gestation and close to term, with the use of coumarin derivatives at other times. In contrast, in a recent retrospective multicenter survey, the Working Group on Valve Disease of the European Society of Cardiology (14,15) concluded that heparin is neither effective nor safe for long-term use during pregnancy in patients

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Table 1. Prostheses Used in Study Patients

Prosthesis	Pregnancies
Aortic	
Total	4 (10%)
Medtronic-Hall	2 (5%)
Björk-Shiley*	2 (5%)
Aortic and mitral	
Total	1 (2.5%)
Björk-Shiley*	1 (2.5%)
Mitral	
Total	35 (87.5%)
Björk-Shiley*	11 (27.5%)
Starr-Edwards†	11 (27.5%)
Bovine pericardium (biologic)	13 (32.5%)

*Standard model. †Models 6120, 6310, 6320 and 6400. Data are presented as number (%) of pregnancies.

with mechanical heart valves, bringing an increased risk of both thromboembolism and bleeding to mother and fetus. It appears, therefore, that arguments continue as to whether such patients are best managed with oral anticoagulant agents or with heparin. We therefore report our experience with the use of adjusted doses of subcutaneous heparin in the first trimester and the last 2 weeks of gestation in 40 pregnancies in 37 women with prosthetic heart valves.

Methods

Study patients. We prospectively followed up 40 pregnancies in 37 women with prosthetic heart valves. The age of the patients at the beginning of pregnancy ranged from 18 to 40 years (mean ± SD 27.7 ± 6.2 years). All women in the study were in New York Heart Association functional class I or II; 17 (42.5%) had sinus rhythm and 23 (57.5%) had chronic atrial fibrillation. Thirty-three patients (82.5%) received treatment with different combinations of digitalis and diuretic drugs.

Prosthetic valves. The different types of valve prostheses used and their sites of implantation are shown in Table 1. The valve model inserted depended on the preference of the surgeon and reflected common usage at the time of operation. The 13 patients with bioprostheses were receiving long-term anticoagulant therapy because of atrial fibrillation and a large left atrium.

Method of anticoagulation. When the diagnosis of pregnancy was established by a gynecologist, at or before the 6th week of pregnancy, the mother was admitted to the National Institute of Cardiology. The administration of acenocoumarol was discontinued and treatment with subcutaneous heparin, 7,500 U every 8 h, was begun. The dose of heparin was adjusted until the activated partial thromboplastin time, determined 4 h after the last dose, was between 1.5 to 2.5 times the control level (kaolin-cephalin reagent, Pathromtin, Behring). The patient was then discharged from the hospital and was followed up every 2 weeks at the anticoagulant clinic. An average dose of 8,055 ± 1,308 U every 8 h was given to the first 36 mothers in the study. In the last 4 cases, the interval between injections was reduced and the mothers received an average of 5,125 ± 1,030 U of subcutaneous heparin every 6 h, again to maintain the activated partial thromboplastin time between 1.5 to 2.5 times the control level. Treatment with acenocoumarol was resumed in all cases after the end of the 12th week to maintain an international normalized ratio (INR) of 3.0 to 3.5. In this period the patients were seen at the anticoagulant clinic at least every 4 weeks. All mothers were referred for delivery to an obstetric hospital specializing in high risk pregnancies, where subcutaneous adjusted heparin was again administered, as described, during the last 2 weeks of pregnancy. Heparin was discontinued at the onset of labor and reinitiated 24 h after delivery. Acenocoumarol therapy was begun as soon as possible and heparin discontinued once the prothrombin rates were within the therapeutic range. In some patients who had early labor, acenocoumarol was not discontinued until immediately before delivery. The anticoagulant regimen used in these patients was that thought best at the time. Nevertheless, the fetal and maternal risks were thoroughly discussed with every patient and her husband, and written informed consent was obtained. Those patients who refused or could not comply with the heparin regimen, or whose pregnancy was detected after the 6th week, received acenocoumarol during all 3 trimesters and are not included in this study. Sixteen of the 22 live-born babies were examined by a geneticist.

Results

Pregnancy outcomes. There were 15 spontaneous abortions (37.5%; 95% confidence interval [CI] 22.7% to 54.2%); all occurred in the first trimester of gestation. Pregnancy resulted in live births in 22 cases (55.0%). There were 16 vaginal deliveries (16 [72.7%] of 22; 95% CI 49.8% to 89.3%); a cesarean section was performed in 6 patients (6 [27.3%] of 22; 95% CI 10.7% to 50.2%) because of obstetric indications or because labor developed while coumarin therapy was still in effect.

Maternal mortality and morbidity. There was a minor episode of cerebral embolism in the 1st trimester of pregnancy in a patient with a mitral Starr-Edwards prosthesis while heparin treatment was still in effect. Three women died (7.5%; 95% CI 1.6% to 20.4%) during the course of the study. One of the three (Case 2 in the series) arrived at a different hospital in profound shock secondary to upper gastrointestinal bleeding and died in the 14th week of pregnancy. Acenocoumarol had been substituted for heparin at the end of the 12th week of gestation and the INR had been adequate 1 week before her death. In the second patient (Case 36 in the series), massive thrombosis of a Björk-Shiley aortic prosthesis developed, and she died 1 h after the onset of symptoms in the 8th week of gestation. She had been receiving 9,500 U of subcutaneous heparin every 8 h since the end of week 4. This unfortunate

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result was of serious concern and we therefore changed the guidelines for heparin administration to delivery of the dose every 6 h instead of every 8 h, with adjustment of the dose, as before, until the activated partial thromboplastin time was 1.5 to 2.5 times the control level. The third patient (Case 40 in the series) had thrombosis of a Björk-Shiley mitral prosthesis in the 12th week of pregnancy while receiving 6,500 U of subcutaneous heparin every 6 h. She died in the immediate postoperative period. Both patients with thrombosis had strictly followed their heparin treatment, and the careful monitoring of the activated partial thromboplastin time had shown values in the target therapeutic range (55 to 95 s; control 30 to 35 s). After this death, it was concluded that the regimen of subcutaneous heparin employed was not effective to prevent thromboembolic phenomena in pregnant patients with mechanical cardiac valve prostheses. After consultation with the Institute's Bio-Ethics Committee, the study was ended earlier than planned.

No thromboembolic accidents were observed in any of the mothers while they were receiving acenocoumarol. There was no maternal morbidity in the patients with bovine pericardium bioprostheses.

A woman with a mitral Björk-Shiley prosthesis experienced heart failure with pulmonary congestion during the 13th week of gestation. She was successfully treated with furosemide and had a full-term pregnancy and normal vaginal delivery. All other patients remained in hemodynamically stable condition throughout pregnancy and delivery. One patient had severe vaginal bleeding during delivery and puerperium requiring blood transfusions. Two other mothers had minor peripartum hemorrhagic complications. One had an inguinal hematoma and the other had transient hematuria. No cases of osteoporosis or thrombocytopenia were detected.

Fetal outcomes. Eight (36.4%; 95% CI 17.2% to 59.3%) of the 22 neonates were born prematurely (before the 37th week of gestation). Three of these eight infants had low birth weight (<2,500 g). One additional infant had a myelomeningocele. There was one neonatal death due to cerebral hemorrhage. In this case, labor had begun in the 35th week of pregnancy while the mother was still under treatment with coumarin agents and it had progressed for some time before the patient arrived at the obstetrics hospital where a cesarean section was performed. Except for this infant and one other infant who was born at the 28th week of gestation with a birth weight of 1,000 g, the 22 live-born neonates had normal Apgar scores. There were no signs suggestive of coumarin-induced embryopathy in any of the 16 live-born infants studied by the geneticist. No cases of central nervous system abnormalities or optic nerve atrophy were observed.

Discussion

Outcome of pregnancy. Coumarin compounds and their derivatives cross the placental barrier, and their use by the mother results in an increased incidence of fetal mortality and morbidity. Treatment with these agents during pregnancy is associated with a high spontaneous abortion rate ranging between 16.2% and 44% (2,3,5,16–20). It was thought that heparin could be an effective alternative method of anticoagulation because it has a high molecular weight and does not cross the placental barrier. Ginsberg et al. (9) reported a low incidence of spontaneous abortion (3 [8.8%] of 34) in patients who were given subcutaneous heparin therapy for the prevention or treatment of venous thromboembolism within the 1st 20 weeks of pregnancy. In a review of reported studies, Ginsberg and Hirsh (21) concluded that, when pregnancies associated with comorbid maternal conditions that could independently cause adverse fetal outcomes were excluded, the rate of these adverse outcomes in heparin-treated mothers was similar to that found in a normal population. Unfortunately, in the present study, the incidence rate of spontaneous abortion was 37.5%, which is comparable to that observed in mothers treated with coumarin derivatives during the first trimester. Likewise, using adjusted doses of heparin in the first trimester, Lee et al. (11) found nine spontaneous abortions in 18 cases (50%). The high fetal wastage rate observed in the present study may be related to an underlying high baseline risk of the patients. In fact, all patients conceived while receiving coumarin and were treated with this agent for 4 to 6 weeks before the initiation of heparin therapy. It is also probable that these abortion rates could be explained by placental hemorrhage, which may occur during effective anticoagulation with either coumarin agents or heparin.

Fetal morbidity. Fetal exposure to coumarin agents during the first trimester may result in an embryopathy whose features are telecanthus, hypoplasia of the nose, small nasal bones, depressed nasal bridge, hypoplastic alae nasi, choanal stenosis with upper airway obstruction and punctate dysplasia of the epiphyses of the long bones, as well as of the cervical and lumbar vertebral end plates. Previous studies from this institution looked for congenital malformations after maternal coumarin therapy. The typical form of coumarin embryopathy among the infants exposed to coumarin derivatives between the 6th and 12th weeks of gestation was found in 1 of 38 infants studied in one of our series (2) and in 2 of 35 infants in a second study (5), for a combined total of 4.1%. In these previous reports from our institution, some additional infants, 10 (13.7%) of 73, had minor abnormalities, such as a slight hypoplasia of the nasal bones and of the alae nasi, suggesting less severe examples of the syndrome. Recent studies by Sareli et al. (16) and by Born et al. (17) found an incidence rate of 5.9% (2 of 34) and 10.0% (3 of 30), respectively, in neonates born of mothers who were treated with coumarin derivatives throughout pregnancy. It has been shown (5) that the teratogenic effects of the coumarin agents may be prevented if these agents are discontinued from before the 6th until the end of the 12th week of gestation (5). Thus, in the present study, none of the 16 infants examined by the clinical geneticist had any of the features of coumarin-induced embryopathy.

It has been reported (4,21) that central nervous system abnormalities may occur in the offspring in association with

maternal coumarin therapy during any trimester. However, no cases of neurologic abnormalities were observed in this series or in our previous studies (2,5). The presence of myelomeningocele in one infant cannot be attributed to the use of oral anticoagulant agents. Finally, the neonatal death due to cerebral hemorrhage underlines the fact that the trauma of labor, when it develops while the mother is still receiving coumarin therapy, may be a major factor in the production of perinatal intracraneal bleeding. Other cases of neonatal death due to intracranial hemorrhage have been reported (2,16,17) in infants of mothers who were given warfarin until term. The relative immaturity of the fetal clotting system renders the fetus hypersensitive to the usual doses of coumarin agents (22). Thus, the fetus may continue to have effective anticoagulation for 7 to 10 days after cessation of warfarin therapy. There is an increased risk if labor begins prematurely while the mother is still taking coumarin agents, and emergency cesarean section may be needed to protect the fetus against the danger of cerebral hemorrhage associated with the trauma of vaginal delivery.

Maternal mortality and morbidity. Gravid women who have mechanical prostheses require prophylaxis against thromboembolism. The omission of effective anticoagulant therapy during pregnancy considerably increases the danger of prosthetic thrombosis and of systemic embolization. In 68 pregnant patients with mechanical cardiac valve prostheses treated with dipyridamole and aspirin in the early part of our experience (2), there were three instances of massive thromboses that occluded a mitral or aortic caged-ball valve prosthesis and a 25% incidence rate of cerebral embolism. Because of the high incidence of fetal wastage and the risk of teratogenic effects when the fetus is exposed to coumarin derivatives, the substitution of heparin for oral anticoagulant agents during pregnancy has been advised (2,5–12). In a previous study from our institution (5), the use of fixed low doses of subcutaneous heparin, 5,000 U every 12 h, administered from the 6th to the 12th week and the last 2 weeks of gestation, did not protect against prosthetic valve thrombosis. There were three cases of thrombosis of a tilting-disk mitral prosthesis in a group of women treated with these small doses of heparin. Likewise, Wang et al. (10) and Thomas et al. (23) found that this regimen was not efficacious to prevent thromboembolic phenomena in their patients.

The possibility that larger and adjusted doses of subcutaneous heparin with monitoring of the activated partial thromboplastin time might be effective has been suggested (11–13,21). Lee and co-workers (11) adjusted the dose of subcutaneous heparin, administered every 8 h to prolong the activated partial thromboplastin time at 1.5 times the control value, during the 1st trimester and last 3 weeks of gestation, in 18 pregnancies in 16 women with cardiac valve prostheses. There were no thromboembolic complications in the nine pregnancies that were continued to term. In the present study subcutaneous heparin was administered from the 6th to the 12th week and in the last 2 weeks of gestation. In the first 36 cases the dose was given every 8 h and it was adjusted to maintain an activated partial thromboplastin time at 1.5 to 2.5 times the control level. Under this regimen, Patient 36 had a fatal massive thrombosis of a Björk-Shiley standard aortic valve. In an attempt to avoid possible periods without anticoagulant effect, we shortened the interval between doses of subcutaneous heparin to every 6 h in the last four cases of the study, again to maintain an activated partial thromboplastin time at 1.5 to 2.5 times the control level. Unfortunately, Patient 40 also had a massive thrombosis of a mitral standard Björk-Shiley valve. In both these cases and in the episode of cerebral embolism observed in the present study, there was strict adherence of the patients to the protocol and careful monitoring had shown anticoagulation in the target activated partial thromboplastin time therapeutic range. From our data it is clear that the dosage of subcutaneous heparin employed does not provide adequate protection against thromboembolism in pregnant patients with mechanical prostheses and its use has been abandoned at our institution.

Cases of thromboses of mechanical cardiac valves related to heparin treatment have been reported (5,10,14,20,23–28). Sbarouni and Oakley (14) recently reported a retrospective multicenter survey from major European centers. The information was obtained by questionnaire. There were 13 cases of thrombosis of a prosthetic valve and eight major embolic events in 151 pregnancies observed in 133 women with mechanical valves. Ten of the 13 women with thrombosed valves and 5 of the 8 patients with arterial embolism were taking heparin. Subcutaneous heparin was administered throughout the duration of pregnancy in several reported cases (9,25,29). Among 34 pregnancies in patients with mechanical valves treated with this regimen, Sbarouni and Oakley (14) reported that 24% were complicated with valve thrombosis and 12% by embolic events. It has been suggested (13) that the different and perhaps inadequate heparin dosing and target therapeutic range employed in these studies may explain the high rates of thromboembolic phenomena. It is possible that subcutaneous heparin may be effective if given in a larger dose, i.e., 35,000 U daily. It has been suggested (13) that subcutaneous heparin should be initiated in doses of 17,500 to 20,000 U every 12 h, with dose adjustment to a minimum target activated partial thromboplastin time ratio of at least twice control level. However, these regimens have not been tested. Similarly, no experience with the use of low molecular weight heparin has been reported.

In this series, the mechanical prostheses in which thrombosis developed were of the Björk-Shiley standard type. Newer generation mechanical heart valves are known to have a relatively low thromboembolic profile (30,31). Sareli et al. (16) found no thromboembolic complications in 39 patients with Medtronic-Hall prostheses or 7 women with St. Jude Medical models treated with warfarin throughout pregnancy. The use of these valves may result in a lower incidence of thromboembolic events in pregnant patients treated with heparin, but the available data are scarce. In a retrospective cooperative study, Hanania et al. (27) recently reported two cases of prosthetic thrombosis during pregnancy in 22 patients with St. Jude

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Medical prostheses who were being treated with calciheparin. In addition, González-Santos et al (28) described prosthetic thrombosis in a patient with a Medtronic-Hall valve who was also receiving calciheparin. Because bioprostheses are less thrombogenic than mechanical prostheses, it seems probable that adjusted doses of heparin may be adequate therapy in the 1st trimester and the last 2 weeks of pregnancy in patients with these valves who require anticoagulation because of atrial fibrillation, large left atrium or a history of previous systemic embolism. In this study, there was no maternal morbidity in the patients with bovine pericardium cardiac valves who received heparin.

Coumarin derivatives are effective to prevent thromboembolic complications during pregnancy in patients with mechanical valves (14–16). There were no thromboembolic accidents in the present study during treatment with these agents. In one of our previous reports there was a 2.3% incidence of systemic embolism in 128 gravid women treated with acenocoumarol throughout pregnancy (2). In addition, in a second study (5) there were no thromboembolic accidents in 72 pregnancies while the mothers received coumarin agents in the 2nd and 3rd trimesters. Born et al. (17) reported a 7.5% incidence rate (3 of 40) of mechanical valve thrombosis in patients being treated with coumarin derivatives. However, two of these thrombotic accidents occurred in patients with inadequate anticoagulation.

Recommendations. In women with mechanical heart valves no method of anticoagulation during pregnancy is entirely free of risk, and all management policies must be based on an estimate of risk benefit ratio. There is a 4.1% risk of embryopathy when coumarin compounds or derivatives are used from the 6th to the 12th week of gestation. However, the obvious alternative, subcutaneous heparin, with the doses adjusted to increase the activated partial thromboplastin time from 1.5 to 2.5 times the control value, does not provide adequate prophylaxis against thromboembolism in these patients. Moreover, there would seem to be no advantage in the use of heparin during the second half of the 1st trimester to prevent fetal wastage because the incidence of spontaneous abortion is similar to that observed when the mothers are treated with coumarin agents. Therefore, maternal risks and neonatal morbidity should be the major causes for concern in these patients. Because coumarin derivatives provide effective protection against thromboembolic phenomena during pregnancy, they should be used in patients with mechanical prostheses until the 38th week of gestation. To avoid the delivery of an anticoagulated infant, it has been recommended (17,32,33) that the mother be admitted to the hospital and be given intravenous heparin, in full anticoagulant doses, instead of the coumarin agent in the last 2 weeks of gestation. The use of heparin may be avoided by elective cesarean section in the 38th week (34). As noted before, because of the risk of perinatal intracranial hemorrhage in the fetus, emergency cesarean section is indicated if labor develops while the mother's coumarin therapy is still in effect. In these cases oral anticoagulation may be immediately reversed and the prothrombin time promptly corrected with administration of vitamin K and fresh-frozen plasma.

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