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Dose-Dependent Fetal Complications of Warfarin in Pregnant Women With Mechanical Heart Valves

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OBJECTIVES The purpose of this study was to assess the incidence of warfarin fetal complications and whether they are dose-dependent.

BACKGROUND Gravid patients with mechanical heart valves require long-term anticoagulant therapy. Controversy exists concerning the appropriate treatment of these patients.

METHODS Forty-three women on warfarin carrying out 58 pregnancies were studied. For each patient with full-term pregnancy a caesarian section was scheduled for the 38th week during brief warfarin discontinuation. Maternal and fetal complications were evaluated. Fetal complications were divided according to the warfarin dosage ≤5 mg and >5 mg necessary to keep an international normalized ratio (INR) of 2.5 to 3.5, and analyzed subsequently.

RESULTS A total of 58 pregnancies were observed: 31 healthy babies (30 full term, 1 premature) and 27 fetal complications (22 spontaneous abortions, 2 warfarin embryopathies, 1 stillbirth, 1 ventricular septal defect, 1 growth retardation) were recorded. Two maternal valve thromboses occurred. No fetal or maternal bleeding was observed during caesarian sections or premature vaginal delivery. Patients whose warfarin doses during pregnancy were >5 mg had 22 fetal complications, whereas those taking a dose ≤5 mg had only five fetal complications ($p = 0.0001$). For an increase of the warfarin dose there was a substantially increased probability of fetal complications ($p < 0.0001$; $\rho < 0.7316$).

CONCLUSIONS There is a close dependency between warfarin dosage and fetal complications. Patients on warfarin anticoagulation may be delivered by planned caesarian section at the 38th week while briefly interrupting anticoagulation. (J Am Coll Cardiol 1999;33:1637–41) © 1999 by the American College of Cardiology

In patients with mechanical prosthetic heart valves, long-term anticoagulation is mandatory to prevent thromboembolic phenomena. The risk of maternal thromboembolic events is heightened during pregnancy because of the patient's hypercoagulable state, which is characterized by increased levels of clotting factors and of fibrinogen and platelet adhesiveness (1).

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Warfarin provides effective protection against thromboembolism, but its use in pregnancy is associated with an augmented rate of abortion and the risk of warfarin-induced embryopathy (1–3).

It has previously been shown (4,5) that the teratogenic effect of warfarin may be prevented if this agent is discontinued from before the 6th until the 12th week of pregnancy. Several investigators have advocated substituting subcutaneous heparin for warfarin, either throughout the gestation period (2,3) or during the first trimester and the last week of pregnancy (5). In contrast, in a recent retrospective multicenter survey, the Working Group on Valve Disease of the European Society of Cardiology (6–8) concluded that heparin is neither effective nor safe for long-term use during pregnancy in patients with mechanical heart valves, bringing an increased risk of both thromboembolism and bleeding to mother and fetus. Moreover, fetal wastage in patients treated with heparin in the first trimester was similar to that observed in those patients treated with warfarin throughout the entire pregnancy (7).

Unfortunately none of these reports assessed whether the untoward effects of warfarin on the fetus are dose-

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dependent (1–9). Oral anticoagulants have a molecular weight of approximately 1,000 and readily cross the placenta to the fetus. The mother may therefore be within the therapeutic range, but the fetus is considerably overdosed because of immature liver enzyme systems and low levels of vitamin K–dependent clotting factors (1).

With this in mind we reviewed retrospectively our experience with pregnant women on oral anticoagulation with the aim of assessing the incidence of fetal complications and if these warfarin untoward effects are dose-dependent.

METHODS

Study patients. All women of childbearing age discharged from our institution after implantation of one or more valve prostheses were informed of the risks of pregnancy during anticoagulation and were asked to refer to us in case of pregnancy. From December 1987 to May 1997, 52 pregnant women were observed in our outpatient clinic. Of these 52 patients, 9 had therapeutic abortion because of unstable cardiac state in 3 cases and obstetric complications in 6. The remaining 43 patients make up our study population. All 43 patients were informed again about the fetal and maternal risks of anticoagulation with warfarin taken throughout the entire pregnancy. All patients agreed to continue their anticoagulation with warfarin with signed consent.

All patients were anticoagulated with sodium warfarin throughout pregnancy keeping the same international normalized ratio (INR) range of 2.5 to 3.5 they had before pregnancy. The doses of warfarin were recorded throughout all pregnancy, and the INR was estimated every week at our institution. To avoid any bleeding event and/or thromboembolism during delivery, caesarian section was programmed during the 38th gestational week (10). Warfarin administration was discontinued only two days before caesarian section and one day after, to be resumed after this time to reach the same INR therapeutic range. Patients underwent routine cardiac and obstetric examinations during pregnancy with fetal echo carried out in the second, fifth and eighth month.

The age of these 43 women ranged from 20 to 35 years with a mean of 28 ± 5.6 years. All patients in the study were in New York Heart Association functional class I or II; 38 were in sinus rhythm, 4 were in atrial fibrillation and 1 had a permanent pacemaker. Nineteen patients were taking digitalis and diuretics during pregnancy. Before valve implantation 11 women had 26 full-term pregnancies delivering 26 healthy babies. 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 patients' warfarin doses before pregnancy ranged between 3.75 and 8.75 mg.

Assessment of pregnancy outcome. Pregnancy outcome was divided into fetal and maternal outcome. The fetal outcome was further divided into full-term and premature healthy babies, and fetal complications. Fetal complications were considered spontaneous abortion, stillbirth and warfarin-related defects. Spontaneous abortion was defined as fetal loss before the 28th week of gestation (11). Stillbirth was fetal death after the 28th week of gestation (11).

Table 1. Distribution of the Study Population According to the Type of Prosthesis Implanted and the Valve Involved

Valve Model	Mitral	Aortic	Mitral–Aortic	Total
Starr-Edwards	8	—	—	8
Lillehei-Kaster	2	—	—	2
Bjork-Shiley	4	—	—	4
Sorin	13	5	2	20
St. Jude	1	—	1	2
CarboMedics	3	2	2	7
Total	31	7	5	43

The maternal outcome was divided into full-term and premature uncomplicated pregnancies, and maternal complications such as valve thrombosis, thromboembolism and bleeding.

To assess fetal complications in relation to warfarin dosage during pregnancy, the whole population was broken up into two groups according to the dose necessary to maintain the INR within therapeutic range. One group comprised patients for whom the warfarin dose was ≤5 mg; in the second group the anticoagulation dose was >5 mg.

Statistical analysis. The relation between warfarin doses and presence of fetal complications during pregnancy was analyzed by means of one-tail Fisher exact test, checking for association in a 2 × 2 table. Furthermore to verify if there was a correlation between doses and complications, the cograduation Spearman coefficient test was carried out.

RESULTS

A total of 58 pregnancies were observed in 43 patients; 43 patients had one pregnancy, 10 patients had a second

Table 2. Outcome of Pregnancies

Warfarin Dose (mg)	Healthy Fetuses	Fetal Complications	Total
≤5	28	5	33
	27 FT	4 SA	
	1 PR	1 GR	
>5	3 FT	22	25
		2 WE	
		18 SA	
		1 SB	
		1 VSD	
Total	31	27	58

FT = full term; GR = growth retardation; PR = premature; SA = spontaneous abortion; SB = stillbirth; VSD = ventricular septal defect; WE = warfarin embryopathy.

pregnancy and 5 patients a third pregnancy. Fetal outcome divided by warfarin dose is presented in Table 2.

All the 30 full-term healthy babies were delivered by caesarian section at the 38th week under no anticoagulation. The mean INR value at caesarian section was 1.27 ± 0.40 after two days of warfarin discontinuation. No thromboembolic or bleeding complications were observed at any time during hospitalization or in the follow-up. One patient had a premature spontaneous vaginal delivery during the 36th week; her INR at hospital admission was 2.6. No hemorrhagic complications were observed in the mother or the healthy neonate during their hospital stay.

Fetal complications. In the group of 33 gestations, with patients taking a warfarin dose ≤5 mg, there were 28 healthy babies and only five fetal complications—four spontaneous abortions in the first trimester of pregnancy and one fetal growth retardation. In this group the mean dose of warfarin, INR and INR samples were 4 ± 0.8, 2.9 ± 0.4 and 38 ± 9, respectively.

In the other group of 25 gestations, with patients taking a warfarin dose >5 mg, 22 fetal complications and three full-term pregnancies were observed. In this group the mean dose of warfarin, INR and INR samples were 7.45 ± 0.9, 3 ± 0.4 and 17 ± 11, respectively.

In both groups the doses of warfarin during pregnancy remained within the same range (i.e., ≤5 or >5 mg) as they were before pregnancy.

There was a very strong and statistically significant relation between warfarin dose and fetal complications ($p < 0.0001$). The correlation analysis confirmed the strength of such a relation ($p < 0.0001$), and indicated also that for an increase of the warfarin dose there was a substantially increased probability of fetal complications ($\rho = 0.7316$).

A total of 22 spontaneous abortions were observed; 16 occurred in the first trimester of pregnancy. Of the five abortions occurring in the second trimester, one developed at the sixth month as a consequence of reoperation on the mother for valve thrombosis; the fetus had no warfarin-related malformations. Also the other four fetuses examined after the spontaneous abortion did not present any warfarin-related malformation. One stillbirth was recorded in the third trimester of pregnancy; it was due to prematurity but not to detected fetal abnormalities.

As far as warfarin embryopathy is concerned, two fetuses spontaneously aborted at the sixth month of pregnancy, showing typical features of warfarin embryopathy with cartilage maldevelopment, nasal hypoplasia, depressed nasal bridge and bifid spine. In these patients the doses of warfarin were 6.5 and 7.5 mg, respectively.

With respect to the baby with the ventricular septal defect, a very small muscular defect was detected echocardiographically. The baby was followed up by echocardiography; eventually the defect closed in the first year of life, and he now leads an active life.

The baby born with fetal growth retardation had no skeletal abnormalities, mental or neurologic retardation. He showed catch-up growth in the first year of life and he is now fully developed.

Maternal complications. With regard to maternal complications, two cases of prosthetic valve thrombosis occurred. One patient with a 29 Bjork-Shiley mitral valve developed valve thrombosis at the fourth month of pregnancy. The INR at hospital admission was 2.7, and her warfarin dose was 3.75 mg. She had a successful emergency operation for prosthetic valve replacement with a Sorin 29 tilting disk valve. The baby survived the procedure and was delivered at full term by caesarian section according to our protocol. The other patient with a Sorin tilting disk mitral valve experienced valve thrombosis at the sixth month of pregnancy. The INR was 2.9 when she entered hospital, and her daily dose of warfarin was 7.5 mg. She was successfully operated on by prosthetic valve replacement with a Starr-Edwards 2M but, as reported previously, the fetus did not survive the procedure.

No maternal embolic or bleeding events were observed in any patient during pregnancy.

Newborn management and follow-up. All mothers were allowed to breast-feed their infants, and no hemorrhagic complications were observed.

All the healthy neonates were examined soon after birth and four and 12 months later by clinical genetist, and no signs of warfarin embryopathy were found. Mothers and babies are reported well and free of complications at the end of follow-up.

DISCUSSION

Outcome of pregnancy. In our study of 58 pregnancies, all the patients were anticoagulated with warfarin throughout pregnancy, and the fetal outcome was evaluated in relation to the warfarin dosage.

The unique and most relevant findings of our series were that fetal untoward effects of warfarin were dose-dependent. Although a previous study from our center had suggested that a warfarin dose <5 mg is safe (10), to the best of our knowledge, this is the first report to outline clearly the presence of a close relation between fetal complications and warfarin dosage. Furthermore, for an increase of warfarin dose there is a substantially increased probability of fetal complications. These findings were strongly supported by statistically significant evidence. Data of patients taking doses of warfarin <5 mg showed that in 33 gestations, 28 healthy babies were delivered and only four spontaneous abortions at the first trimester and one fetal growth retardation occurred. On the contrary, of the 25 gestations in patients whose warfarin intake was >5 mg, 22 fetal complications and only three full-term deliveries were observed.

Our observations are supported by experimental findings. Quick (12) and Krauss et al. (13) in pregnant dogs and rabbits exposed to coumarin derivatives demonstrated large

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doses of the drug given up to term to be the greatest single risk factor for fetal hemorrhage and death. Hirsh et al. (14) confirmed this result and further suggested that an additional risk factor was the trauma of spontaneous delivery.

The explanation for these findings is that oral anticoagulants have a molecular weight of approximately 1,000 and readily cross the placenta to the fetus. The mother may therefore be within the therapeutic range, but the fetus is considerably overdosed because of immature liver enzyme systems and low levels of vitamin K–dependent clotting factors (1). Reverdiau-Moalic et al., measuring blood coagulation activators and inhibitors in the healthy human fetus, found that during intrauterine life there are low levels of vitamin K–dependent clotting factors that steadily increase toward birth and then toward the adult state (15). Furthermore, also the warfarin bone and cartilage teratogenesis is very likely a dose-dependent mechanism because warfarin blocks vitamin K regeneration by inhibiting the necessary enzyme epoxide reductase (16). Vitamin K is an essential cofactor for posttranslational carboxilation of glutamic acid residues of osteocalcin and matrix Gla protein, which modulate calcium deposition (16). A failure in the synthesis of osteocalcin and Gla matrix protein results in chondrodysplasia punctata or "stippling," and nasal hypoplasia (16).

Fetal morbidity. Among the fetal complications observed in our series the most relevant one was spontaneous abortion (37.9%). Most of the abortions occurred in the first three months of pregnancy. This high abortion rate as well as its time of occurrence are common findings in other reports which recorded an abortion rate ranging between 16.2% and 44% (2,3,11). A similar incidence of abortion rate (37.5%) was found by Salazar and associates in a series of patients treated with subcutaneous heparin in the first trimester of pregnancy (9,11). It is likely that the high abortion rate could be explained by the placental hemorrhage, which may occur during effective anticoagulation with either warfarin or heparin (9). Therefore, it seems there is no advantage in the use of heparin during the first trimester of pregnancy to prevent fetal wastage. With regard to warfarin embryopathy, two cases of bone maldevelopment were observed. The cases of bone maldevelopment occurred in women in whom the daily intake of warfarin was over 5 mg. The incidence of embryopathy in our series was 3.4%, and this percentage is concordant with those reported by other authors in series of patients anticoagulated with warfarin during the entire pregnancy (8). Although the ventricular septal defect was included under the warfarin-induced congenital malformations, we believe that its occurrence was only coincidental, because in large series of fetuses affected by warfarin malformations cardiac anomalies were very rarely recorded (1,16). Also the fetal growth retardation occurring in a baby whose mother was on a daily dose of warfarin over 5 mg cannot be regarded as a consequence of warfarin intake (1). Therefore, our observations seem to confirm that among all fetal complications, spontaneous abortion is by far the most frequent one.

Maternal morbidity. In our series of 43 patients having 58 pregnancies, two cases of prosthetic valve thrombosis (3.4%) were observed. Such a rate is higher than those shown in series of nonpregnant patients with tilting disk valves (17), indicating once again that pregnancy is a prothrombotic state.

To reduce peripartum thromboembolic and bleeding complications, warfarin administration was discontinued two days before the programmed caesarian section, to be resumed the second day after surgery.

Our peripartum antithrombotic management proved successful, and no complications of any kind were experienced either by mothers or by neonates. An elective caesarian section was planned to reduce the risk of perinatal intracranial hemorrhage in the fetus, although caesarian section is a major surgery that can be associated with its own list of morbid complications and with a substantial increase in cost. Even when warfarin administration is stopped 10 days before labor, the neonate could be still at risk of bleeding by warfarin overdose (10).

Recommendations. The findings of a relevant warfarin dose-dependent mechanism of fetal complications may confidently suggest some clinical recommendations to apply to the decrease of fetal and maternal complications during pregnancy in patients taking warfarin. At the beginning of pregnancy, those patients whose warfarin intake is $\leq$5 mg with an INR within therapeutic range may continue to take warfarin during the entire pregnancy under strict medical surveillance, and consider a programmed caesarian section at the 38th week of gestation while briefly interrupting warfarin therapy. If the patient prefers to have vaginal delivery, intravenous heparin over the last two weeks of gestation should be offered as an option.

On the other hand, those patients whose warfarin doses are $>$5 mg should be made fully aware of a likely much higher risk of fetal complications during pregnancy. If they decide to carry on pregnancy with warfarin and have a bileaflet or an aortic valve prosthesis, the INR range may be lowered to 2.0 to 2.5 with the aim of bringing the warfarin intake down to 5 mg while still reaching a satisfactory antithrombotic effect. This policy may be justified by the observations by Sareli et al. (11) that the incidence of thromboembolism is low in pregnant patients with newer generation mechanical heart valves even in the presence of low anticoagulation.

If the patient refuses to carry on warfarin anticoagulation, heparin is the anticoagulant that has no effect on the fetus because it does not cross the placenta (8,9). Unfortunately long-term therapy with heparin is not safe for the mother because of an unsatisfactory antithrombotic action and dangerous side effects such as thrombocytopenia and osteoporosis (8). In those women who choose not to take warfarin and are at high thrombotic risk (mitral prostheses,

atrial fibrillation, first generation valves, previous thromboembolism), in-hospital continuous intravenous heparin treatment, at least between weeks 6 and 12 and two weeks before delivery, seems justified (4). Those patients with low thrombotic risk (aortic prostheses, sinus rhythm, newer generation valves) may adequately be treated with subcutaneous heparin (4).

Low molecular weight heparin may be an attractive drug for use during pregnancy (4), especially in patients requiring high warfarin dosage. Similar to standard unfractioned heparin, it does not cross the placenta, and at the same time, it may provide additional benefits, including reduced incidence of heparin-induced thrombocytopenia, osteoporosis and bleeding complications, and no blood test is required to monitor its safety. The drug has been used effectively and safely to treat deep vein thrombosis during pregnancy (4), but data in patients with a prosthetic valve are not available. Therefore, testing low molecular weight heparin in pregnant women with mechanical valves may be desirable. Because a small dose of aspirin is safe during pregnancy (4), it may be used in addition to anticoagulation to maximize the antithrombotic effect.

Conclusions. Although our study was carried out retrospectively, the conclusions are that there is a close dependency between warfarin dosage and fetal complications. Women in need of increased warfarin doses are going to have high risk pregnancies, but whether they are going to have an improved outcome on heparin is unknown. Above 5 mg there is an increase of fetal complications whose frequency is still dose-dependent, but our numbers are insufficient to show. The incidence of warfarin embryopathy rate was not high and similar to those reported in other series. Patients on warfarin anticoagulation may deliver by programmed caesarian section at the 38th week while briefly interrupting anticoagulation. This policy seems to reduce significantly the incidence of perinatal warfarin complications, allowing pregnancy to term in those women who maintain a stable INR within therapeutic range.

More studies are necessary to identify the best patient-specific anticoagulant management in pregnant women with a mechanical heart valve prosthesis. Regardless of their anticoagulation management all pregnant patients with mechanical heart valves should be closely monitored for anticoagulation, and for early detection of maternal and fetal complications during gestation.

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