

Warfarin-associated Fetal Intracranial Hemorrhage : A Case Report

A 27-yr-old woman who had been taking warfarin for 10 yr after mitral valve replacement became pregnant. After knowing her pregnancy, she received heparinization for nine weeks instead of warfarin, and took oral anticoagulant again. At 24 weeks of gestation, fetal ultrasound and MRI showed a left subdural hematoma, and the pregnancy was terminated. Subdural hematoma was demonstrated on autopsy. Fetal bleeding of the fetus is a rare complication of maternal warfarin medication, occurring mostly in the second or third trimester. There is no alternative regimen available, so that regular monitoring by fetal ultrasound and strict control of warfarin dose with regular measurement of prothrombin time are the best way to prevent intrauterine fetal death due to bleeding.

Key Words : Fetus; Heart Valve Diseases; Intracranial Hemorrhages; Pregnancy; Warfarin

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INTRODUCTION

Antenatal intracranial hemorrhage is a rare cause of intrauterine fetal death, with the incidence of 4.6-5.1% in autopsy study of stillborn fetuses (1, 2). Sherer et al. performed a literature survey on predisposing factors of antenatal intracranial hemorrhage from 1966 to 1998, and maternal factors included hematologic disorders (alloimmune and idiopathic thrombocytopenia, and von Willebrand's disease), seizures, abdominal trauma, cholestasis of pregnancy, drug abuse, and specific medication including warfarin (3).

Warfarin-associated fetal bleeding event is a rare problem, with the incidence of 4.3% in the literature review by Hall et al. (4). Some authors reported fetal intracranial hemorrhages confirmed by prenatal ultrasound (Table 1) (5, 6).

The present case is a rare example of warfarin-associated fetal intracranial hemorrhage which stresses the importance of warfarin as a cause of fetal intracranial bleeding.

CASE REPORT

A 27-yr-old woman had been taking warfarin (7.5 mg per day) for 10 yr since mitral valve replacement and obliteration of patent ductus arteriosus in 1991. She was found to be pregnant at five weeks of gestation. She received heparinization

instead of warfarin medication by subcutaneous nadroparin (one of low-molecular-weight heparin) 3,800 IU/mL twice a day for nine weeks, and then took oral anticoagulant again, 7 mg per day. Prothrombin time by international normalized ratio (INR) was maintained between 2.3 and 3.0.

At 24 weeks of gestation, fetal ultrasound revealed echogenic subdural mass in the left cerebral hemisphere associated with mild ventricular enlargement (Fig. 1A). In addition, there was an arachnoid cyst in the posterior cranial fossa along with cerebellar atrophy. On MRI, this intracranial mass showed mixed low and high signal intensity, suggesting active bleeding (Fig. 1B). Maternal TORCH test was negative and fetal karyotype was 46,XX. The fetus was delivered by labor induction one week later, and died three hours after delivery.

At autopsy, the fetal body weight was 800 g, and the measurements including head circumference of 24.5 cm were appropriate for those of 25 weeks of gestation. There was no congenital anomaly. Cerebrospinal fluid was bloody, and the left cerebral hemisphere showed a subdural hematoma over the left Sylvian fissure with compression of underlying brain parenchyma (Fig. 2). No other significant findings were seen in brain and spinal cord. The thoracic and abdominal visceral organs were generally pale, but revealed no hemorrhagic foci. The liver, spleen, adrenal glands, and kidney showed exaggerated extramedullary hematopoiesis.

Table 1. Cases of warfarin-associated fetal hemorrhage confirmed by imaging study

	Robbins et al. (5)	Ville et al. (6)		Present case
		Case 1	Case 2	
Maternal disease	VHD* with prosthetic valve	Pulmonary embolism	VHD* (aortic, mitral)	VHD* (mitral) with prosthetic valve
Warfarin exposure in pregnancy	1st week -	26th week -	15th week -	1st-5th week 14th-23th week
Warfarin dose (mg)	NA [†]	6 to 3 [‡]	5-6	6-7
Prothrombin time (INR [§])	NA [†]	8.6 to 1.7-2.5 [‡]	0.7-1.9	2.2-3.0
Gestational age at diagnosis (weeks)	32	32	29	23
Hemorrhage site	Subdural, bilateral	Intraventricular	Intraventricular	Subdural, left
Fetal outcome	Spontaneous delivery at 34 weeks, died 3 hr later	Stillborn at 36 weeks	Stillborn at 29 weeks	Delivery by labor induction at 25 weeks, died 3 hr later

*VHD: Valvular heart disease; [†]NA: Not available; [‡]: On the 10th day of warfarin with the dose of 6 mg per day, INR was elevated to 8.6. When the dose was decreased to 3 mg, the INR level was maintained between 1.7 and 2.5; [§]INR: International normalized ratio.

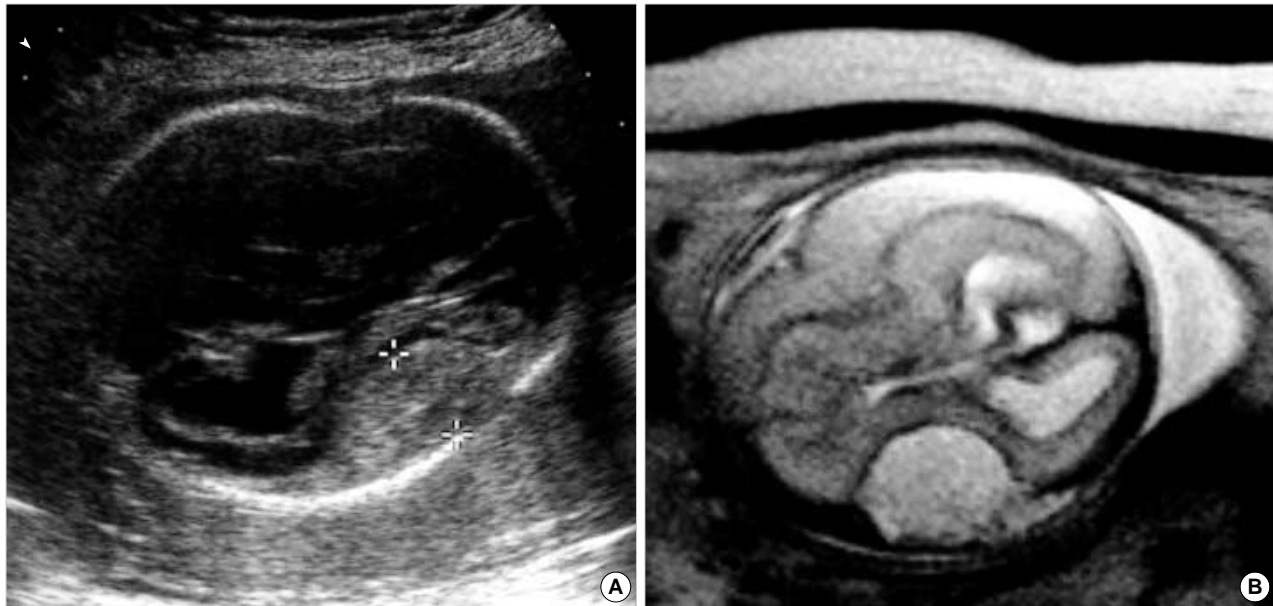


Fig. 1. Prenatal imaging study of fetus. (A) There is an echogenic mass at the subdural area of left temporoparietal area on ultrasonography. (B) In T2-weighted MRI image, the mass shows mixed low and high signal intensity, suggesting an active bleeding. The brain at this site is compressed, and the left lateral ventricle is slightly larger than the right.

DISCUSSION

Warfarin is used for the prevention of systemic thromboembolism in patients having prosthetic heart valves or atrial fibrillation, of myocardial infarction or stroke, and for the treatment of deep vein thrombosis (7). Unfortunately, warfarin is known to have some teratogenic effects. Warfarin embryopathy, characterized by nasal hypoplasia and/or stippled epiphyses, is associated with the exposure to warfarin in the first trimester (4). It is thought to be related to inhibition of post-translational carboxylation of vitamin K-dependent calcium-binding proteins, including osteocalcin and some bone matrix

proteins (8). Central nervous system anomaly, i.e., agenesis of corpus callosum, Dandy-Walker syndrome, and midline cerebellar atrophy, and optic nerve atrophy are associated with the warfarin exposure in the second or the third trimester (4). Pathogenesis of these brain anomalies are not yet evaluated.

In fetal bleeding event, like central nervous system anomaly, warfarin exposure during the second or the third trimester was noted in most of these cases (4). It has also been proven that warfarin can induce fetal hemorrhage by experimental study. Howe and Webster demonstrated that an excessive dose of warfarin could induce fetal intracranial hemorrhage in spite of vitamin K injection (9).

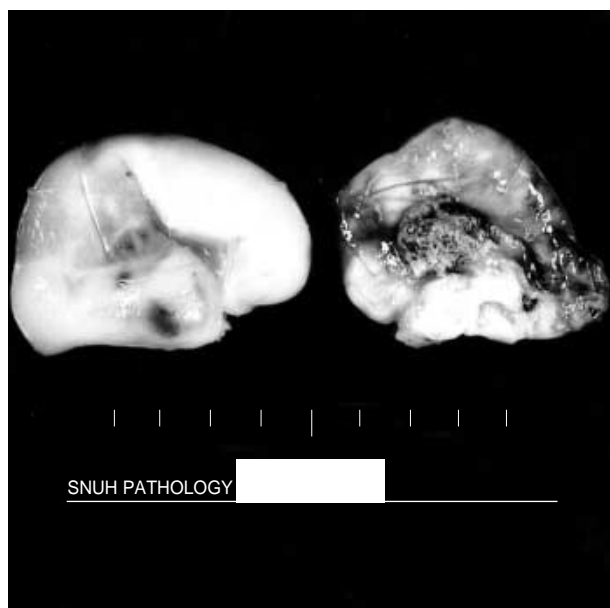


Fig. 2. Gross picture of cerebral hemisphere. Left cerebrum (right side) revealed a residual hemorrhage in Sylvian fissure with parenchymal compression and degeneration. There was some blood-tinged area in the right cerebrum (left side), but no hematoma was shown.

The fetal subdural hemorrhage in our case is most likely due to the maternal warfarin exposure based on the following assumptions; (a) warfarin can cross the placental barrier to reach the fetal blood circulation, (b) the exposure was occurred during the second trimester, and (c) no hemorrhagic foci were found until the beginning of the second oral anticoagulant therapy.

A question to be addressed is why the brain is the most frequent site of fetal hemorrhage. Although some of the reported cases had hemorrhage other than the brain (10, 11), majority of the cases had intracranial hemorrhage only. The pathogenesis is still unknown, but it may be different from that of neonatal intraventricular or periventricular hemorrhage in prematurity, which is suggested to be associated with the fragile germinal matrix of the brain (12). In warfarin-associated fetal intracranial hemorrhage, intraventricular or periventricular area is not so frequent bleeding region and prematurity is not a risk factor.

Warfarin-induced fetal intracranial hemorrhage is a fatal condition. Including our case, most were stillborn or died within one day after delivery. A baby with intraventricular hemorrhage was managed with shunt insertion and actually alive, but the baby showed subsequent mental retardation and blindness (13). Therefore, prevention is very important.

As for the best management of pregnant women with prosthetic heart valves to prevent fetal hemorrhage, discontinuation of warfarin and use of only heparin throughout the pregnancy seems ideal, because it is well known that heparin cannot cross the placental barrier. Indeed, no case has been report-

ed on fetal hemorrhage with maternal heparin injection. However, the mothers treated with heparin were more prone to spontaneous abortion or stillborn fetuses than control group (4, 14). In addition, some studies revealed that unfractionated heparin was more dangerous than warfarin for the mother with mechanical heart valves (14). Low-molecular-weight heparin can be the alternative regimen for those mothers, but no randomized studies about full-time use of low-molecular-weight heparin have yet been available. It is only used during the first trimester and some weeks before delivery, in which warfarin is contraindicated.

Second, reduction of warfarin dose may be considered. According to Table 1, however, prothrombin time levels by INR are 3.0 or less, as suggested by Hirsh *et al.* (7). Therefore, these hemorrhages may not be associated with excessive dose of warfarin. And if the dose is reduced, maternal complication may increase. So, reduction of warfarin dose will not be helpful.

Vitamin K can be used as additional treatment. However, its effectiveness is doubtful, because vitamin K cannot cross the placental barrier freely. In one case, fetal coagulation factors II, VII, X, and XII were severely decreased in spite of maternal vitamin K injection (6). In maternal and fetal blood tests, the average neonatal vitamin K level was less than one tenth of the average maternal level, and the differences are wider after vitamin K injection to their mother before the delivery (15). And it is well documented that vitamin K can induce anaphylactoid reaction (16). So, its administration should be carefully considered.

In conclusion, warfarin-associated fetal hemorrhage is a fatal event. Unfortunately, there is no alternative regimen that can replace warfarin for pregnant women with mechanical heart valves yet. Regular monitoring of fetal ultrasound study and strict control of warfarin dose with regular measurement of prothrombin time are the best way to prevent intrauterine fetal death due to bleeding, although there is no direct way to prevent fetal intracranial hemorrhage so far.

REFERENCES

1. Sims ME, Turkel SB, Halterman G, Paul RH. *Brain injury and intra-uterine death.* *Am J Obstet Gynecol* 1985; 151: 721-3.
2. Squier M, Keeling JW. *The incidence of prenatal brain injury.* *Neuropathol Appl Neurobiol* 1991; 17: 29-38.
3. Sherer DM, Anyaegbunam A, Onyeije C. *Antepartum fetal intracranial hemorrhage, predisposing factors and prenatal sonography: a review.* *Am J Perinatol* 1998; 15: 431-41.
4. Hall JG, Pauli RM, Wilson KM. *Maternal and fetal sequelae of anticoagulation during pregnancy.* *Am J Med* 1980; 68: 122-40.
5. Robinson MJ, Cameron MD, Smith MF, Ayers AB. *Fetal subdural haemorrhages presenting as hydrocephalus.* *Br Med J* 1980; 281: 35.
6. Ville Y, Jenkins E, Shearer MJ, Hemley H, Vasey DP, Layton M, Nicolaidis KH. *Fetal intraventricular haemorrhage and maternal warfarin.* *Lancet* 1993; 341: 1211.

7. Hirsh J, Dalen J, Anderson DR, Poller L, Bussey H, Ansell J, Deykin D. *Oral anticoagulants: mechanism of action, clinical effectiveness, and optimal therapeutic range. Chest* 2001; 119: 8S-21.
8. Shearer MJ. *Vitamin K. Lancet* 1995; 345: 229-34.
9. Howe AM, Webster WS. *Exposure of the pregnant rat to warfarin and vitamin K1: an animal model of intraventricular hemorrhage in the fetus. Teratology* 1990; 42: 413-20.
10. Gordon RR, Dean T. *Foetal deaths from antenatal anticoagulant therapy. Br Med J* 1955; 2: 719-21.
11. Raivio KO, Ikonen E, Saarikoski S. *Fetal risks due to warfarin therapy during pregnancy. Acta Paediatr Scand* 1977; 66: 735-9.
12. Donn SM, Stuck KJ. *Neonatal germinal matrix hemorrhage: evidence of a progressive lesion. J Pediatr* 1981; 99: 459-61.
13. Oakley C, Doherty P. *Pregnancy in patients after valve replacement. Br Heart J* 1976; 38: 1140-8.
14. Chan WS, Anand S, Ginsberg JS. *Anticoagulation of pregnant women with mechanical heart valves: a systematic review of the literature. Arch Intern Med* 2000; 160: 191-6.
15. Shearer MJ, Rahim S, Barkhan P, Stimmler L. *Plasma vitamin K1 in mothers and their newborn babies. Lancet* 1982; 2: 460-3.
16. Fiore LD, Scola MA, Cantillon CE, Brophy MT. *Anaphylactoid reactions to vitamin K. J Thromb Thrombolysis* 2001; 11: 175-83.