

## Case Report

# Fetal Warfarin Syndrome

Achara Sathienkijkanchai MD\*,  
Pornswan Wasant MD\*

*\*Division of Medical Genetics, Department of Pediatrics, Faculty of Medicine, Siriraj Hospital,  
Mahidol University, Bangkok, Thailand*

---

*Fetuses exposed to Warfarin in the first trimester of pregnancy have an increased risk of embryopathy which consists of nasal hypoplasia and stippled epiphyses, known as fetal warfarin syndrome or warfarin embryopathy. We herein report a first case of an infant with fetal warfarin syndrome in Thailand. The patient was an offspring of a 34-year-old mother with history of SLE and arterial embolism for several years. She had an unplanned pregnancy while taking warfarin. The patient developed difficulty breathing in the first few hours after birth from severe nasal hypoplasia. He also had short limbs, brachydactyly, nail hypoplasia, and calcifications in the epiphyseal regions of humeri, femora and vertebrae radiographically. The patient eventually died from respiratory failure at 6 months of age.*

**Keywords :** *Fetal warfarin, Warfarin, Warfarin embryopathy, Teratogen*

**J Med Assoc Thai 2005; 88(Suppl 8): S246-50**

**Full text. e-Journal:** <http://www.medassocthai.org/journal>

---

Warfarin, a coumarin derivative, is a low molecular weight oral anticoagulant which has been in clinical use for 50 years. Prior to introduction as an anticoagulant drug in human, warfarin was a useful rodenticide, which acted by inducing fatal hemorrhage in rats<sup>(1)</sup>. Oral anticoagulants, warfarin and its derivatives, have both advantages and disadvantages in term of safety, efficacy, and cost. There were several reports of congenital anomalies in human relating to warfarin exposure during pregnancy. Therefore, the manufacturers have issued warning against using warfarin during pregnancy since the late 1970s<sup>(2-4)</sup>.

In 1966, DiSaia reported the first case of multiple congenital anomalies in an infant associated with maternal ingestion of warfarin during pregnancy<sup>(3)</sup>. In 1980, Hall et al reviewed 418 pregnancies in which warfarin derivatives were used, and estimated that one-sixth of pregnancies resulting in abortion and stillbirth; one-sixth of infants abnormal, and two-thirds resulted in apparently normal infants<sup>(4)</sup>. It is therefore a well

known fact that fetuses who are exposed to warfarin in the first trimester of pregnancy have an increased risk of embryopathy consists of nasal hypoplasia and stippled epiphysis, which is known as "Fetal warfarin syndrome" or "Warfarin embryopathy"<sup>(1-4)</sup>.

There were numerous reports of multiple congenital anomalies associated with warfarin exposure during pregnancy from all over the world<sup>(2,5-15,17)</sup>.

In Thailand, a report from Chiang Mai University demonstrated a case of prenatal sonographic diagnosis of fetal warfarin syndrome in 1999. This case was diagnosed at 25 weeks of gestation and delivered vaginally as stillborn fetus at 26 weeks of gestation<sup>(14)</sup>. We herein report a first case of postnatal alive infant with fetal warfarin syndrome in Thailand.

### Case Report

A baby boy was the third offspring of a 34-year-old woman with SLE and secondary antiphospholipid syndrome. She had digital gangrene, which was diagnosed 2 years prior to pregnancy. Consequently, she regularly received warfarin 3 mg/day, prednisolone, nifedipine, colchicine and chloroquine at the Rheumatology clinic at Siriraj Hospital. She had an unplanned pregnancy while taking warfarin. The pregnancy was alert at 29 weeks of gestation because

---

*Correspondence to: Pornswan Wasant MD, Professor of Pediatrics, Division of Medical Genetics, Department of Pediatrics, Faculty of Medicine Siriraj Hospital, Mahidol University, 2 Prannok Road Bangkok, Thailand. Tel. 66-2-419-8414, 66-2419-7000 extension 5944, Fax: 66-2-419-8414., Email: sipws@mahidol.ac.th*

she had bloated. Her internist and obstetrician discontinued warfarin, and since then subcutaneous fraxiparin, a low molecular weight heparin, was administered. She developed premature rupture of the membrane at 30 weeks of gestation, 8 hours prior to normal delivery. The baby was born with APGAR scores of 7 and 8 at 1 and 5 minutes respectively. One hour after birth he developed tachypnea and cyanosis. He was intubated and transferred to our Neonatal Intensive Care Unit.

Physical examination revealed a baby boy at 35 weeks of gestation by Ballard score. His birth measurements were weight 1,460 gm, length 37 cm and head circumference 29 cm all of which were below the third percentile for 35 weeks of gestation. He had short trunk and limbs, short neck, marked nasal hypoplasia, deep groove between alar nasi and nasal tip, brachydactyly and hypoplasia of all distal phalanges (Figure 1-4). Neonatal radiographs revealed epiphyseal stippling of sacrum, spines and proximal humeri and femurs (Figure 5).

The patient was not able to wean off oxygen therapy and was intubated due to severe upper respi-



1



2

**Fig. 1 and 2** Abnormal facial features: nasal abnormality, small nose with markedly depressed nasal bridge



**Fig. 3** Severe shortening of lower extremities



**Fig. 4** Brachydactyly, hypoplasia of all distal phalanges



**Fig. 5** Epiphyseal stippling of the sacrum, spines, proximal humeri and femurs

ratory tract obstruction from severe nasal abnormality. He eventually developed respiratory failure and expired at 6 months of age.

## Discussion

Warfarin is used for the prevention of systemic thromboembolism. However, it is known to possess some teratogenic effects in human. Warfarin prevents the recirculation of vitamin K leading to vitamin K deficiency, which results in decrease of vitamin K-dependent clotting factors synthesis. It is used in the treatment of thromboembolic disorders<sup>(15-16)</sup>. Moreover, warfarin interferes in vitamin K epoxide reductase activity, which plays a role in the synthesis of some vitamin K-dependent proteins such as osteocalcin and Gla matrix protein, two essential components of bone and cartilage development<sup>(15-16)</sup>.

Warfarin is a relatively small molecule with molecular weight about 1,000 daltons. Its unbound fraction easily crosses the human placental barrier to reach the fetal blood circulation<sup>(17,18)</sup>. Since warfarin readily crosses the placenta, it is implicated in two major adverse effects. First, it inhibits vitamin K recycling in the embryo resulting in hemorrhage in every fetal organ<sup>(2,10)</sup>. Second, it interferes in vitamin K reductase activity which leads to a decrease in the production of vitamin K-dependent mineralization inhibitors in cartilage resulting in ectopic calcium deposits in epiphysis and nasal septum called epiphyseal stippling. In addition, premature closure of growth plate and shortening extremities could ensue<sup>(9)</sup>. Franco et al, suggested that warfarin may inhibit arylsulfatase enzyme activity, the cause of X-linked recessive chondrodysplasia punctata, which has a phenotype identical to warfarin embryopathy<sup>(19)</sup>.

In 1966, Di Saia reported the first case of fetal warfarin syndrome<sup>(3)</sup>. Anomalies include nasal hypoplasia, choanal atresia, laryngeal abnormalities, upper airway obstruction, short neck, hypoplasia of distal phalanges, brachydactyly, and short limbs. The most striking radiographic finding is pronounced epiphyseal stippling of vertebrae, sacrum and long bones during early childhood and disappears with age<sup>(20,21)</sup>. All the above results are from exposure to warfarin in the first trimester of pregnancy. Other teratogenic effects in fetuses exposed to warfarin after second or third trimester include optic atrophy, blindness, corneal opacity, deafness, microcephaly, hydrocephalus, epilepsy, Dandy-Walker malformation and mental retardation<sup>(4)</sup>. The greatest susceptible period for developing warfarin embryopathy is between the 6<sup>th</sup> to 9<sup>th</sup> weeks of gestation<sup>(9)</sup>.

Hall et al (1980) reviewed 418 pregnancies with maternal warfarin derivatives usage and concluded that spontaneous abortions occurred in 8.6%,

live births in 83.7%, stillbirths occurred in 8.4%, premature deliveries in 4.6%, neonatal deaths occurred in 2.9%, and warfarin embryopathy in living infants occurred in 4.6%<sup>(4)</sup>. Blickstein et al collected seven case series of warfarin usage during pregnancy published after 1980, and compared with the data compilation of Hall et al<sup>(2)</sup>. The data reveal similar frequencies of still birth, neonatal deaths and warfarin embryopathy but higher with respect to spontaneous abortion (24.1 vs. 8.6%) and premature deliveries (13.9 vs. 4.6%) and lower with live births (73.3% vs. 83.7%), neonatal death in 4.5% and warfarin embryopathy in 2.4%<sup>(2)</sup>.

Warfarin can cross the placental barrier, but heparin, which has molecular weight about 20,000 daltons, can not reach the fetus by crossing the placental barrier<sup>(17,22)</sup>. Therefore, pregnant women should switch from warfarin to heparin throughout the pregnancy in order to reduce the incidence of stillbirths and warfarin embryopathy. Low-molecular-weight heparin can be the alternative regimen for these pregnant women<sup>(12)</sup>.

This case report should alert clinicians and, in particular, obstetricians to the teratogenic effects of warfarin. Any female patient in the child-bearing age who is taking warfarin should be warned against pregnancy. Furthermore, pediatricians should keep in mind for the possibility of the congenital warfarin syndrome in the newborn with the history of maternal warfarin usage, and can prevent the tragedy of an avoidable recurrence of birth defects in subsequent pregnancies.

## Acknowledgements

The authors would like to thank Professor Kriangsak Jirapaet, Associate Professor Thrathip Kolatat, Assistant Professor Pimol Srisuparp, Assistant Professor Sopapan Ngernecham, Dr. Ratchada Kitsommart, and personnels in Neonatology Division, Department of Pediatrics, Faculty of Medicine Siriraj Hospital, Mahidol University for taking care of this patient.

## References

1. Zakzouk MS. The congenital warfarin syndrome. *J Laryngol Otol* 1986;100:215-9.
2. Blickstein D, Blickstein I. The risk of fetal loss associated with warfarin anti-coagulation. *Int J Gynaecol Obstet* 2002;78:221-5.
3. DiSaia PJ. Pregnancy and delivery of a patient with a Starr-Edward mitral valve prosthesis. *Obstet Gynecol* 1966;28:496-72.

4. Hall JG, Pauli RM, Wilson KM. Maternal and fetal sequelae of anticoagulation during pregnancy. *Am J Med* 1980;68:122-40.
5. Chan Ky, Gilbert-Barness E, Tiller G. Warfarin embryopathy. *Pediatr Pathol Mol Med* 2003; 22:277-83.
6. Ginsberg JS, Greer I, Hirsh J. Use of antithrombotic agents during pregnancy. *Chest* 2001;119 (1 Suppl):122S-131S.
7. Bony C, Zyka F, Tiran-Rajaofera I, Attali T, De Napoli S, Alessandri JL. Warfarin fetopathy. *Arch Pediatr* 2002;9:705-8.
8. Wellesley D, Moore I, Heard M, Keeton B. Two cases of warfarin embryopathy: a re-emergence of this condition? *Br J Obstet Gynaecol* 1998; 105:805-6.
9. Van Driel D, Wesseling J, Rosendaal FR, Odink RJ, Van der Veer E, Gerver WJ, et al. Growth until puberty after in utero exposure to coumarins. *Am J Med Genet* 2000;95:438-43.
10. Howe AM, Lipson AH, de Silva M, Ouvrier R, Webster WS. Severe cervical dysplasia and nasal cartilage calcification following prenatal warfarin exposure. *Am J Med Genet* 1997;71:391-6.
11. Nagai T. Fetal warfarin syndrome. *Ryoikibetsu Shokogun Shirizu*. 2001;33:706-7.
12. Lee HC, Cho SY, Lee HJ, Kin CJ, Park JS, Chi JG. Warfarin-associated fetal intracranial hemorrhage: A case report. *J Korean Med Sci* 2003;18:764-7.
13. Wong V, Cheng CH, Chan KC. Fetal and neonatal outcome of exposure to anticoagulants during pregnancy. *Am J Med Genet* 1993;45:17-21.
14. Tongsong T, Wanapirak C, Piyamongkol W. Prenatal ultrasonographic findings consistent with fetal warfarin syndrome. *J Ultrasound Med* 1999;18:577-80.
15. Menger H, Lin AE, Toriello HV, Bernert G, Spranger JW. Vitamin K deficiency embryopathy: a phenocopy of the warfarin embryopathy due to a disorder of embryonic vitamin K metabolism. *Am J Med Genet* 1997;72:129-34.
16. Pauli RM. Mechanism of bone and cartilage maldevelopment in the warfarin embryopathy. *Pathol Immunopathol Res* 1988;7:107-12.
17. Cotrufo M, De Feo M, De Santo LS, Romano G, Della Corte A, Renzulli A, et al. Risk of warfarin during pregnancy with mechanical valve prostheses. *Obstet Gynecol* 2002;99:35-40.
18. Yacobi A, Udall JA, Levy G. Serum protein binding as a determinant of warfarin body clearance and anticoagulant effect. *Clin Pharmacol Ther* 1976;19:552-8.
19. Franco B, Meroni G, Parenti G, Levilliers J, Bernard L, Gebbia M, et al. A cluster of sulfatase genes on Xp22.3: mutations in chondrodysplasia punctata (CDPX) and implications for warfarin embryopathy. *Cell* 1995;81:15-25.
20. Mason JD, Jardine A, Gibbin KP. Foetal warfarin syndrome — a complex airway problem : Case report and review of the literature. *J Laryngol Otol* 1992;106:1098-9.
21. Shaul WL, Hall JG. Multiple congenital anomalies associated with oral anti-coagulants. *Am J Obstet Gynecol* 1977;127:191-8.
22. Baillie M, Allen ED, Elkington AR. The congenital warfarin syndrome: a case report. *Br J Ophthalmol* 1980;64:633-5.

---

## กลุ่มอาการฟีตล วาร์ฟาริน: รายงานผู้ป่วย 1 ราย

อัจฉรา เสถียรกิจการชัย, พรสวรรค์ วสันต์

หญิงตั้งครรภ์ในช่วง 3 เดือนแรกที่ได้รับยา warfarin จะทำให้ทารกในครรภ์มีความเสี่ยงต่อความพิการที่เรียกว่า Fetal warfarin syndrome หรือ Warfarin embryopathy โดยมีลักษณะเด่นได้แก่ ตั้งจุกแบนและจุกมีขนาดเล็ก กระดูกอ่อนมีแคลเซียมเกาะเป็นหย่อมๆ

ผู้วิจัยได้รายงานผู้ป่วยโรค fetal warfarin syndrome ที่มีชีวิตอยู่หลังเกิดรายแรกของประเทศไทย มารดาผู้ป่วยอายุ 34 ปีมีประวัติป่วยเป็นโรค SLE และเส้นเลือดแดงอุดตัน มารดาตั้งครรภ์โดยไม่ได้คาดคิด ขณะได้รับการรักษาด้วยยา warfarin ผู้ป่วยมีอาการหายใจลำบากหลังคลอดเมื่ออายุได้ 2 - 3 ชั่วโมงจากจุกผิดปกติ เล็กกว่าปกติ นอกจากนี้ผู้ป่วยยังมีแขนขาสั้นผิดปกติ นิ้วมือนิ้วเท้าสั้น เล็บไม่เจริญ และเอกซเรย์กระดูก พบปลายกระดูกอ่อนของกระดูกแขนท่อนบน กระดูกขาท่อนบน และกระดูกสันหลังมีแคลเซียมเกาะเป็นหย่อมๆ ผู้ป่วยเสียชีวิตเมื่ออายุ 6 เดือนจากภาวะหายใจล้มเหลว

---