

MOTHERISK ROUNDS

Warfarin Embryopathy Following Low-Dose Maternal Exposure

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INTRODUCTION

Pregnant women who require antithrombotic therapy, especially those who have prosthetic heart valves, pose a therapeutic dilemma because of the relative paucity of data regarding the safety of antithrombotic agents in pregnancy.

From the maternal perspective, warfarin therapy is currently the safest and most efficacious regimen to prevent thromboembolic events; it is considered safer than heparin therapy or combined regimens.¹ However, warfarin has well-documented teratogenic effects^{2,3} and in Canada is contraindicated during pregnancy because of these fetal concerns. On the other hand, heparin has significant maternal side effects (e.g., major and minor bleeding, heparin-induced thrombocytopenia, and osteoporosis) and may be less effective than warfarin for prevention of thromboembolic events.⁴

Some experts, mostly from Europe, advocate the use of warfarin throughout pregnancy. This recommendation is based on warfarin's superiority to other anticoagulant regimens in terms of maternal safety and effectiveness and on their impression that the risk of warfarin embryopathy (WE) is overstated.^{5,6} In their opinion, there is no risk of teratogenicity in fetuses whose mothers are exposed during pregnancy to low doses of the drug (up to 5 mg/day).⁷

CASE PRESENTATION

The following is not a single case counselled by Motherisk, but a composite that illustrates a typical presentation.

A 29-year-old primigravid woman developed a sagittal sinus thrombosis and was subsequently found to have Factor V Leiden mutation, the most common genetic thrombophilic disorder. Following this thrombotic event, she was treated with warfarin 5 mg daily and her progress was monitored by a hematologist. During this time she conceived, but initially was not aware of her pregnancy. She first presented for prenatal care at 18 weeks' gestation. Warfarin therapy was discontinued at that point, and her treatment was changed to dalteparin sodium (Fragmin, Pfizer), a low molecular weight heparin, in a daily dose of 5000 units subcutaneously. The patient was given opposing opinions regarding the safety of warfarin in pregnancy.

At this point, five months after the initial thrombosis, she called Motherisk. Motherisk referred her for prenatal diagnosis, but the patient elected not to undergo an ultrasonographic evaluation and instead decided to terminate the pregnancy. The termination was performed using misoprostol induction at 21 weeks' gestation.

The postmortem examination showed a male fetus with findings consistent with WE. These included (1) flattened nasal bridge (Figures 1 and 2); (2) abnormally large tooth buds (Figure 2); (3) radiograph evidence of chondroid dysplasia (key findings were premature ossification of the hyoid bone, irregular ossification of cervical and sacral vertebrae, additional ossifications at the dorsal neural arches of the cervical and sacral vertebrae, delayed ossification of

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pubic bones, ossification abnormalities of hands, and premature ossification of the calcaneus) (Figures 2 and 4); (4) mild coarctation of the aorta; (5) bi-lobed right lung (Figure 3); (6) left ventricle non-compaction; and (7) mild maceration of lower extremities. Central nervous system examination did not reveal any abnormalities.

DISCUSSION

Warfarin sodium, a coumarin anticoagulant, has been in clinical use for more than 50 years. It depresses synthesis of vitamin K-dependent clotting factors (factors II, VII, IX, and X) by blocking reduction of the epoxide form of vitamin K. It is a potent and effective drug, used in the management of a variety of thromboembolic disorders and in patients at significant risk of thrombus formation. It has a low molecular weight and readily crosses the placenta, achieving clinically significant levels in the fetus.⁸

Warfarin is more effective than heparin in preventing thromboembolic events in the pregnant woman and has fewer bleeding complications.^{1,4,9} From the maternal perspective, using warfarin throughout pregnancy provides the lowest risk of thromboembolism from either peripheral thrombosis or a mechanical heart valve⁴ (a rate of valve thrombosis of 3.9% compared to 9.2% with use of heparin only at 6 to 12 weeks' gestation). Heparin alone is commonly used close to term (i.e., in the last two weeks of pregnancy) in order to avoid delivery of an anticoagulated newborn.¹ However, in pregnant women, the effective protection warfarin provides against thromboembolism is offset by its well-recognized teratogenicity.

Warfarin Embryopathy

A specific pattern of congenital anomalies known as WE, or congenital coumarin syndrome, is well recognized in children born to mothers who have been treated with warfarin during the first trimester of pregnancy.^{8,10-12} The two most consistent fetal anomalies in WE are nasal hypoplasia and chondroplasia punctata (epiphyseal and vertebral stippling).^{8,10} Nasal hypoplasia involves stunted growth of the septum, resulting in a depressed nasal bridge (Figures 1 and 2). Chondroplasia punctata is manifest as diffuse bone stippling seen on X-ray of the proximal epiphyseal growth area (Figures 2 and 4). The calcifications are usually seen in the axial skeleton, vertebrae, wrists, calcaneous bones, and epiphyses of the long bones, particularly of the femur.^{8,12} The malformations associated with WE are summarized in the Table.

The period of greatest vulnerability to develop the warfarin embryopathy following exposure is between the sixth and twelfth weeks of gestation.⁴ It has been suggested that WE

Malformations associated with warfarin embryopathy

Classical features

Nasal hypoplasia^{8,10}

Chondrodysplasia punctata (epiphyseal and vertebral bone stippling)^{8,10}

Common malformations

Cleft lip and (or) palate^{21,27}

Choanal stenosis/atresia^{11,32}

Less frequent malformations

Intraventricular hemorrhage^{2,14,21}

Hydrocephalus^{14,21}

Cervical spine myelopathy^{33,34}

Finger and toe defects^{21,35,36}

Rare malformations described following first trimester exposure to warfarin

Dandy Walker malformation^{11,16}

Holoprosencephaly³⁷

Schizencephaly³⁸

Solitary maxillary incisor³⁶

Situs inversus³⁹

Coarctation of aorta¹¹

Laryngeal or tracheal calcification⁴⁰

Bi-lobed right lung¹¹

Gastroschisis¹¹

Malformed ears^{10,21}

Urinary tract anomalies⁴¹

develops as a result of fetal overcoagulation, leading to fetal bleeding and WE manifestations.⁵

Additional adverse effects may develop after exclusive second or third trimester exposure to warfarin in about 3% of cases,^{8,12} presenting most frequently as central nervous system (CNS) abnormalities. They are partially related to hemorrhagic episodes and may include intraventricular hemorrhages, microcephaly, hydrocephalus, cerebellar and cerebral atrophy, eye and vision abnormalities (optic atrophy, cataracts, blindness, microphthalmia),^{8,13,14} seizures, and growth and mental retardation.^{8,10,15} Some of these CNS abnormalities were also reported after first trimester exposure. Kaplan et al.¹⁶ described a full-term infant, exposed to warfarin in utero, who developed Dandy Walker

Figure 1. Lateral view of a 21-week stillborn with warfarin embryopathy. Note the extreme nasal hypoplasia.



Figure 2. Lateral X-ray of a 21-week stillborn showing hypoplastic nasal bone, abnormally large tooth buds, abnormal early ossification of hyoid bone, and irregular ossification of cervical vertebrae.

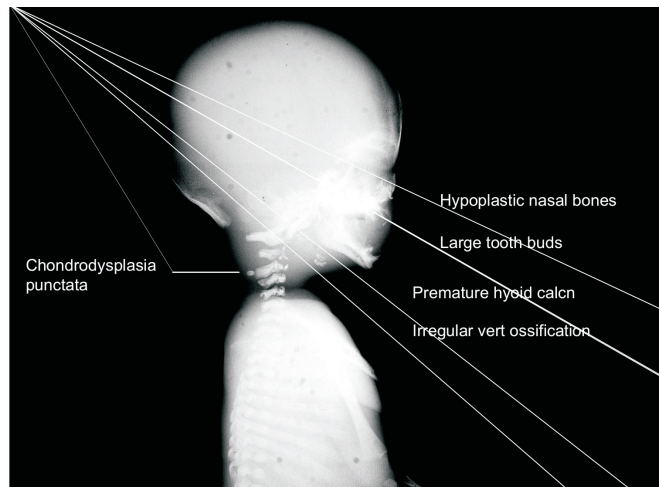
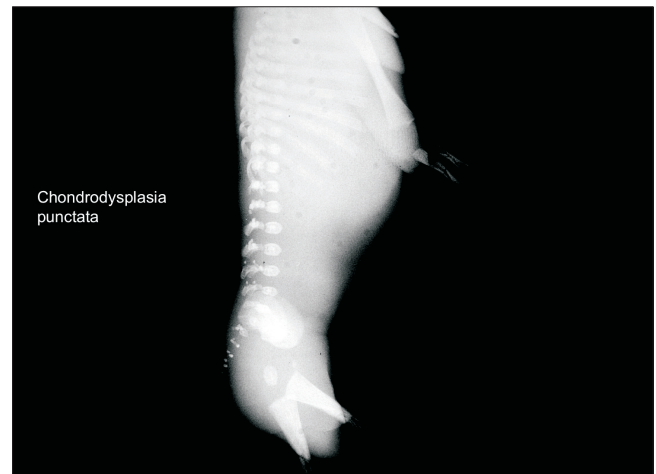


Figure 3. A bi-lobed right lung.



Figure 4. Lateral view X-ray showing calcifications and irregular ossification of lumbar and sacral vertebrae, consistent with warfarin embryopathy.



malformation, agenesis of the corpus callosum, ocular anomalies, seizure disorder and scoliosis, but no other stigmata of WE.

This report of CNS anomalies occurring as a result of first trimester exposure to warfarin may argue against the hypothesis that the CNS anomalies arising in the second and third trimester are due only to the disturbance of normal CNS development resulting from hemorrhages and fibrosis, because use of the drug was discontinued before the appearance in the fetus of clotting factors that are susceptible to vitamin K antagonists.¹⁶ Recent evidence suggests that warfarin inhibits arylsulfatase E, leading some

researchers to suggest a similar pathogenic mechanism with recessive chondroplasia punctata.¹⁷ Bone calcifications usually disappear within the first few months of life, but there may be subsequent abnormal bone development in the epiphyses and vertebrae.¹⁸

Prevalence of Warfarin Embryopathy

The reported incidence of WE ranges from 0% to almost 30% of exposed pregnancies.^{19,20} This reflects the inadequate nature of the relevant studies, most of which are retrospective with an unclear denominator. Several small studies, mostly reported in the European literature, did not find

WE cases in their series.^{5,21–23} Other series of similar size reported typical birth defects in up to 30% of fetuses exposed to coumarin derivatives.^{19,24} Two literature reviews, of 350 and 779 live births, found an incidence of WE of 5.7% and 7.4% respectively.^{20,25} A recent systematic review of prospective and retrospective cohort studies estimated the risk for WE in women with prosthetic valves who were exposed to warfarin throughout their pregnancy to be 6.4% of live births.⁴ It was found that substituting heparin for warfarin at or prior to 6 weeks' gestation, and continuing heparin until 12 weeks, appears to eliminate this risk.

Fetal Wastage

The incidence of spontaneous abortion reported in women taking warfarin throughout pregnancy varies widely, from 4.2% to almost 50%.^{4,23,26,27} The risk for fetal wastage (spontaneous abortions, stillbirths, and neonatal deaths) was estimated in women with prosthetic heart valves who took warfarin throughout their pregnancy. The risk with use of warfarin was 29.7%, compared to 16.3% in pregnant women who were switched from warfarin to heparin between 6 and 12 weeks of gestation, and 37.7% when warfarin was used beyond 6 weeks and switched to heparin later.⁴ The authors concluded that heparin substitution for warfarin between 6 and 12 weeks' gestation is pivotal, since the continued exposure to warfarin resulted in a significant risk of fetal wastage.⁴ The risk of this regimen is an increased rate of thromboembolism, compared to the protection provided by coumarin agents.⁹

Prenatal Diagnosis of Warfarin Embryopathy

Since the two most consistent effects of fetal exposure to warfarin are nasal hypoplasia and stippled vertebral and femoral epiphyses, warfarin embryopathy is likely to be identifiable on targeted ultrasonography, with special attention to the facial profile and a thorough bone survey.¹² Other common sonographic findings include brain abnormalities such as ventriculomegaly. However, even high detail ultrasonographic evaluation during the second or third trimester has diagnostic limitations and may fail to detect the prenatal defects seen in WE.¹² Moreover, some abnormalities (e.g., intraventricular hemorrhage) may develop towards the end of pregnancy.

Warfarin Dose in Pregnancy

A recent retrospective assessment of complications in 58 fetuses found a close correlation between warfarin dose and the risk of fetal complications.⁶ Of 25 fetuses whose mothers were treated during pregnancy with more than 5 mg of warfarin daily, 22 (88%) had complications (comprising 18 miscarriages, 2 WE, 1 stillbirth, and 1 ventriculoseptal defect). In contrast, of 33 fetuses whose mothers received

up to 5 mg of warfarin daily, only five (15%) had complications (comprising 4 miscarriages and 1 intrauterine growth retardation; none had WE). The women who delivered newborns with WE took 6.5 mg or 7.5 mg of warfarin daily. In a subsequent publication, the same authors concluded that "these findings may confidently suggest a clinical approach to these patients. Those patients whose (daily) warfarin intake is 5 mg with an international normalized ratio (INR) within therapeutic range may continue to take warfarin during the entire pregnancy."⁷ However, there have been other well-documented case reports of newborns with WE following maternal exposure to low doses of warfarin (2.5–5 mg/day) throughout pregnancy.^{28–30} All of these newborns had classic features of WE, such as bone stippling and nasal hypoplasia.

In contrast to the approach commonly taken in Europe^{6,7} (i.e., using warfarin as the preferred anticoagulant agent during pregnancy despite the fact that the drug monograph considers use in pregnancy to be an absolute contraindication), the American College of Chest Physicians recently issued guidelines stating that warfarin use should be avoided between 6 weeks and 12 weeks' gestation and advocating a more conservative approach from the fetal perspective.¹ The guidelines suggest using one of three optional regimens: (1) aggressive adjusted-dose therapy using unfractionated heparin; (2) low molecular weight heparin (LMWH) therapy throughout pregnancy; or (3) use of one of these two agents until the thirteenth week of pregnancy, switching to warfarin therapy until the middle of the third trimester, and then switching back to use of unfractionated heparin or LMWH.

The Society of Obstetricians and Gynaecologists of Canada (SOGC) practice guidelines on secondary prevention of venous thromboembolism during pregnancy³¹ suggest one of the following optional regimens: (1) use of unfractionated heparin (5000 units twice daily) throughout pregnancy; (2) unfractionated heparin (5000 units twice daily in the first trimester, 7500 units twice daily in the second trimester, and 10 000 units twice daily in the third trimester); or (3) use of a LMWH (dalteparin or enoxaparin) once daily throughout pregnancy.

Clinicians should bear in mind that all of the above regimens significantly reduce the risk of WE, but may subject the mother to an increased risk of a thromboembolic event.

CONCLUSION

No currently available antithrombotic regimen is optimal during pregnancy. Expert opinion varies regarding when and how to use antithrombotic agents in pregnant women.³¹ Typical manifestations of warfarin embryopathy develop after exposure to the drug in the first trimester,

even at low doses. Other fetal adverse effects, such as CNS and eye abnormalities, may occur following exposure in the second or third trimester. Fetal complications of warfarin are dose-dependent, although warfarin-induced birth malformations may develop after exposure to low doses of the drug.

Clinicians should carefully assess the risks and benefits associated with currently available antithrombotic regimens in order to provide women who require treatment with the best individualized advice. In any case, patients should be presented with the advantages and risks of each of the regimen options so they can make an informed decision about therapy.

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REFERENCES

1. Bates SM, Greer IA, Hirsh J, Ginsberg JS. Use of antithrombotic agents during pregnancy. *Chest* 2004;126:627S–644S.
2. Raivio KO, Ikonen E, Saarikoski S. Fetal risks due to warfarin therapy during pregnancy. *Acta Paediatr Scand* 1977;66:735–9.
3. Zakzouk MS. The congenital warfarin syndrome. *J Laryngol Otol* 1986;100:215–9.
4. Chan WS, Anand S, Ginsberg JS. Anticoagulation of pregnant women with mechanical heart valves. A systemic review of the literature. *Arch Intern Med* 2000;160:191–6.
5. Sbarouni E, Oakley CM. Outcome of pregnancy in women with valve prostheses. *Br Heart J* 1994;71:196–201.
6. Vitale N, De Feo M, De Santo LS, Pollice A, Tedesco N, Cotrufo M. Dose-dependent fetal complications of warfarin in pregnant women with mechanical heart valves. *J Am Coll Cardiol* 1999;33:1637–41.
7. Vitale N, De Feo M, Cotrufo M. Anticoagulation for prosthetic heart valves during pregnancy: the importance of warfarin daily use. *Eur J Cardiothorac Surg* 2002;22:656–7.
8. Hall JG, Pauli RM, Wilson KM. Maternal and fetal sequelae of anticoagulation during pregnancy. *Am J Med* 1980;68:122–40.
9. Salazar E, Izaguirre R, Verdejo J, Mutchinick O. Failure of adjusted doses of subcutaneous heparin to prevent thromboembolic phenomena in pregnant patients with mechanical cardiac valve prostheses. *J Am Coll Cardiol* 1996;27:1698–703.
10. Shaul WL, Hall JG. Multiple congenital anomalies associated with oral anticoagulants. *Am J Obstet Gynecol* 1977;127:191–8.
11. Chan KY, Gilbert-Barnes E, Tiller G. Warfarin embryopathy. *Pediatr Pathol Mol Med* 2003;22:277–83.
12. Tongsong T, Wanapirak C, Piyamongkol W. Prenatal ultrasonographic finding consistent with fetal warfarin syndrome. *J Ultrasound Med* 1999;18:577–80.
13. Quenneville G, Barton B, McDevitt E, Wright IS. The use of anticoagulants for thrombophlebitis during pregnancy. *Am J Obstet Gynecol* 1959;77:1135–49.
14. Wong V, Cheng CH, Chan KC. Fetal and neonatal outcome of exposure to anticoagulants during pregnancy. *Am J Med Genet* 1993;45:17–21.
15. Kerber JJ, Warr OS, Richardson C. Pregnancy in a patient with prosthetic mitral valve. *JAMA* 1968;203:233–5.
16. Kaplan LC. Congenital Dandy-Walker malformation associated with first trimester warfarin: A case report and literature review. *Teratology* 1985;32:333.
17. Franco B, Meroni G, Parenti G, Levilliers J, Bernard L, Gebbia M, et al. A cluster of sulfatase genes on Xp22.3: mutations in chondroplasia punctata (CDPX) and implications for warfarin embryopathy. *Cell* 1995;81:15–25.

18. 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 vitaminK metabolism. *Am J Med Genet* 1997;72:129–34.
19. Iturbe-Alessio I, Fonseca MC, Mutchinick O, Santos MA, Zajarias A, Salazar E. Risks of anticoagulant therapy in pregnant women with artificial heart valves. *N Engl J Med* 1986;315:1390–3.
20. Hung L, Rahimtoola SH. Prosthetic heart valves and pregnancy. *Circulation* 2003;107:1240–6.
21. Chen WW, Chan CS, Lee PK, Wang RY, Wong VC. Pregnancy in patients with prosthetic heart valves: an experience with 45 pregnancies. *Q J Med* 1982;51:358–65.
22. Pavankumar P, Venugopal P, Kaul U, Lyer KS, Sas B, Sampathkumar A, et al. Pregnancy in patients with prosthetic cardiac valves: a 10 year experience. *Scand J Thorac Cardiovasc Surg* 1988;22:19–22.
23. Ben Ismail M, Abid F, Trabeisi S, Tarktak M, Fekih M. Cardiac valve prostheses, anticoagulation and pregnancy. *Br Heart J* 1986;55:101–5.
24. Born D, Martinez EE, Alemida PAM, Santos DV, Carvalho ACC, Moron AF, et al. Pregnancy in patients with prosthetic heart valves: the effects of anticoagulation on mother, fetus, and neonate. *Am Heart J* 1992;124:413–7.
25. Hall JG. Embryopathy associated with oral anticoagulant therapy. *Birth Defects* 1976;12:33–7.
26. Salazar E, Zajarias A, Gutierrez N, Iturbe I. The problem of cardiac valve prostheses, anticoagulants, and pregnancy. *Circulation* 1984;70(Suppl 1):1169–77.
27. Vitali E, Donatelli F, Quaini E, Groppelli G, Pellegrini A. Pregnancy in patients with mechanical prosthetic heart valves. *J Cardiovasc Surg* 1986;27:221–7.
28. Shaul WL, Emery H, Hall JG. Chondroplasia punctata and maternal warfarin use during pregnancy. *Am J Dis Child* 1975;129(3):360–2.
29. MacLeod M. Rheumatic heart disease in pregnancy. *Lancet* 1954;267(6840):668–71.
30. Fourie DT, Hay IT. Warfarin as a possible teratogen. *S Afr Med J* 1975;49:2081–3.
31. Kent N, Leduc L, Crane J, Farine D, Hodges S, Reid GJ, et al. SOGC clinical practice guidelines: prevention and treatment of venous thromboembolism (VTE) in obstetrics. *J SOGC* 2000;22:736–49.
32. Howe AM, Hawkins JK, Webster WS. The growth of the nasal septum in the 6–9 week period of foetal development—warfarin embryopathy offers a new insight into prenatal facial development. *Aust Dent J* 2004;49:171–6.
33. Takano H, Smith WL, Sato Y, Kao SC. Cervical spine abnormalities and instability with myelopathy in warfarin-related chondrodysplasia: 17-year follow-up. *Pediatr Radiol* 1998;28:497–9.
34. 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.
35. Lamontagne JM, Leclerc JE, Carrier C, Bureau M. Warfarin embryopathy—a case report. *J Otolaryngol* 1984;13:127–9.
36. Barr M Jr, Burdi AR. Warfarin-associated embryopathy in a 17-week-old abortus. *Teratology* 1976;14:129–34.
37. Vanzieleghem BD, Lemmerling MM, Vermeersch HF, Govaert P, Dhooze I, Meire F, et al. Imaging studies in the diagnostic workup of neonatal nasal obstruction. *J Comput Assist Tomog* 2001;25:540–9.
38. Pati S, Helmbrecht GD. Congenital schizencephaly associated with in utero warfarin exposure. *Reprod Toxicol* 1994;8:115–20.
39. Barker DP, Konje JC, Richardson JA. Warfarin embryopathy with dextrocardia and situs inversus. *Acta Paediatr* 1994;83:411.
40. Taybi H, Capitanio MA. Tracheobronchial calcification: an observation in three children after mitral valve replacement and warfarin sodium therapy. *Radiology* 1990;176:728–30.
41. Hall BD. Warfarin embryopathy and urinary tract anomalies: possible new association. *Am J Med Genet* 1989;34:292–3.