

## CASE REPORT

# Warfarin Anticoagulation and Fetal Central Nervous System Abnormalities: a Case Report

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### SUMMARY

**Background:** Anticoagulation of pregnant woman with mechanical prosthetic heart valves is associated with significant maternal and fetal risks.

**Methods:** We describe a case of dorsal midline dysplasia in a fetus at 11 weeks' gestation. The mother was receiving warfarin therapy at a dose of 7.5 mg daily following a mechanical mitral valve replacement for rheumatic heart disease.

**Results:** Histological assessment revealed a meningocele with hemorrhage. No cerebellar or cerebral tissue was present in the skull confirming anencephaly.

**Conclusions:** A multidisciplinary approach in pregnant women with mechanical prosthetic heart valves is essential in order to improve fetal outcomes.

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#### KEY WORDS

warfarin, mechanical prosthetic heart valves, central nervous system (CNS) abnormalities, pregnancy

#### INTRODUCTION

In women with mechanical prosthetic heart valves, pregnancy is associated with significant maternal and fetal morbidity and mortality [1,2]. This is related to the requirement for lifelong anticoagulation therapy, in addition to ventricular dysfunction and valvular deterioration. Risk factors such as older generation valves in the mitral position, atrial fibrillation, heart failure, and previous valve thrombosis increase the risk of thromboembolic complications [3,4]. Pregnant women and their obstetricians are faced with the difficult decision of weighing the risk and benefits of anticoagulant options during pregnancy. Vitamin K antagonists such as warfarin are associated with lower risks of valve thrombosis and maternal death [5]. However, its use is associated

with significant risks to the fetus, which is an issue of particular concern to women.

In this report, we describe central nervous system (CNS) abnormalities in the fetus of a pregnant woman with a mechanical valve replacement on lifelong warfarin therapy.

## CASE PRESENTATION

A 30-year-old African female, in a stable relationship, presented at 11 weeks' gestation for the management of a high-risk pregnancy. She had been on warfarin (Aspen Pharmacare) since 1996 following a second-generation mechanical mitral valve replacement for rheumatic heart disease. Her daily dose of warfarin was 7.5 mg to maintain an International Normalized Ratio (INR) of 2.5 to 3.5. She attended the anticoagulation clinic at Charlotte Maxeke Academic Johannesburg Hospital (CMJAH) 4 ± 2 weekly, which was associated with a time in therapeutic range of 88.8%. Additionally, on past medical history she was infected with human immunodeficiency virus (HIV) and on first line antiretroviral treatment for five years. Past obstetric history included four first trimester miscarriages and one second trimester miscarriage at 17 weeks. Warfarin was discontinued at a mean (standard deviation) of 4.4 ± 1.7 weeks' gestation and dose adjusted enoxaparin 80 mg bd (Clexane, Sanofi Aventis) was initiated. Enoxaparin was monitored weekly to achieve a therapeutic anti-Xa of 1 - 1.2 IU/mL. On investigation, there was no evidence of antiphospholipid syndrome, anatomical, chromosomal or endocrine abnormalities.

An ultrasound scan at 11 weeks' gestation in the index pregnancy revealed a crown rump length of 42.69 mm, posterior encephalocele, and dusky anterior septum. She was admitted to high care for medical termination of pregnancy. A transthoracic echocardiogram was performed. This revealed a functional trileaflet mitral mechanical valve with no valvular thromboses and no perivalvular leak. Her INR was 6.78 on 7.5 mg of warfarin with no associated signs of bleeding. Warfarin was discontinued and she received two units of fresh frozen plasma to achieve an INR of 2.75. She was bridged with enoxaparin 90 mg bd (anti-Xa 1.2 IU/mL). Oral mifepristone (Mifegyne, Exelgyn) at a dose of 600 µg was administered 48 hours prior to 400 µg of vaginal and oral misoprostol (Cytotec, Pfizer). An evacuation was performed for retained placenta and she received antibiotic prophylaxis for subacute bacterial endocarditis. Blood loss on visual inspection was 300 mL. Her post-operative hemoglobin was 88.0 g/L for which she received two units of red cell transfusion. No excessive bleeding occurred in the post-partum period. Enoxaparin was restarted six hours post-delivery at 40 mg bd (anti-Xa 0.9 IU/mL) and warfarin 2.5 mg was introduced on day two. After a week, she was transferred to the general ward. There was no cardiac decompensation in the postpartum period. She was discharged home two

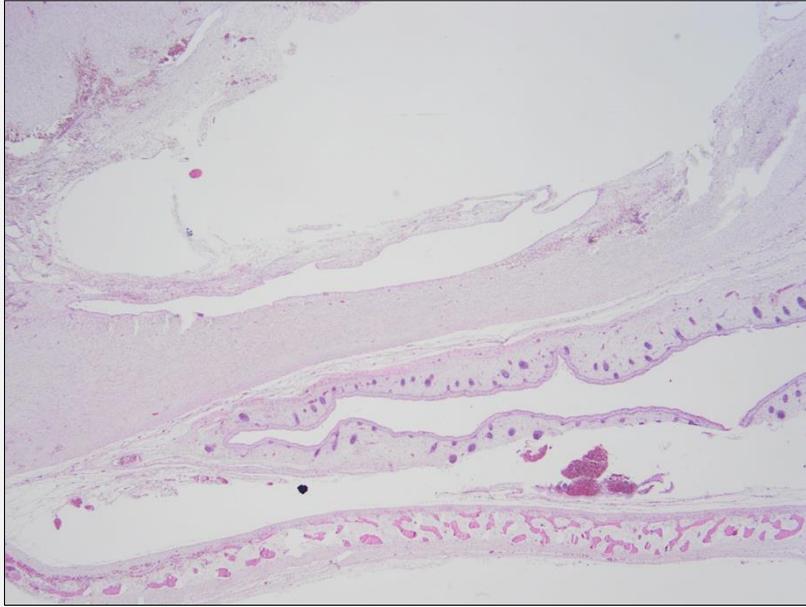
weeks after delivery in a good condition on warfarin 7.5 mg (INR 2.51).

A post-mortem examination of the male fetus showed a small flattened skull. The face, chest, abdomen and limbs showed no abnormalities. The heart was normal. Histological assessment confirmed a meningocele with hemorrhage (Figure 1). No cerebellar or cerebral tissue was present in the skull confirming anencephaly (Figure 2).

## DISCUSSION

Warfarin crosses the placenta and has the potential to cause teratogenicity, CNS abnormalities, miscarriages and stillbirths. The most commonly reported fetal anomaly is warfarin embryopathy or fetal warfarin syndrome. Systematic reviews of the literature have reported highly variable rates [6-8]. This is characterized by nasal hypoplasia, depressed nasal bridge, stippling of uncalcified epiphyses (most frequently affecting the axial skeleton, proximal femur, and calcaneus), mild hypoplasia of the nails and shortened fingers after exposure between six and twelve weeks gestation [6,9]. Low dose warfarin at doses of < 5 mg/day have been associated with a lower rate of warfarin embryopathy. However, a dose dependent relationship has not been found in all cohorts [1,10]. Therefore, in order to reduce the significant risks of embryopathy associated with warfarin, the following anticoagulant options have been recommended: dose adjusted therapeutic low-molecular weight heparin (LMWH) (to achieve a target anti-Xa levels of 1.0 - 1.2 IU/mL), dose adjusted therapeutic unfractionated heparin (UFH) (to achieve a partial thromboplastin time of twice the baseline) or warfarin in the second and third trimester with replacement by LMWH or UFH in the first trimester and close to delivery (Grade 1A).

Nevertheless, the use of sequential therapy does not obviate the risks of CNS abnormalities, miscarriages and stillbirths, which have been described following warfarin exposure during any trimester. Miscarriage rates in the literature range from 20.0 to 37.9% [3,6,10,11]. A significantly higher rate of miscarriage and stillbirth has been associated with warfarin doses of > 5 mg/day [10-12]. CNS abnormalities have been rarely described, at a rate of 0.7 - 2% [9,13]. However, most studies do not include histological assessments, thereby underestimating the numbers of anticoagulant-related fetal CNS abnormalities. Two patterns of CNS abnormalities have been described: dorsal midline dysplasia which includes agenesis of the corpus callosum, Dandy-Walker malformation, and midline cerebellar atrophy and ventral-midline dysplasia which results in optic atrophy [9,13]. The findings of this case report are consistent with anencephaly and a meningocele. Abnormal skull bone formation with partial loss in association with the meningocele was present. These fetal complications, are mainly caused by intrauterine hemorrhage, as a conse-



**Figure 1. Meningocele 2 x magnification.**

**Bone and skin with a cystic lesion. The cystic wall consists of fibrous tissue and a single layer of cuboidal cells in keeping with an arachnoid layer.**



**Figure 2. Transverse section through the skull, confirming presence of brain stem without cerebellum or cerebrum.**

quence of the immature fetal liver and low levels of vitamin K-dependent clotting factors. The skull and brain abnormalities secondary to over anticoagulation in the first trimester, add to the few case reports previously described in the literature.

In order to improve fetal outcomes, a multidisciplinary approach in pregnant women with mechanical prosthetic heart valves is essential. This should include pre-pregnancy planning, frequent pregnancy tests, early presentation or replacement of warfarin with LMWH prior to conception and contraception advice at anticoagulation clinics.

#### **Ethics Approval and Consent to Participate:**

The study was approved by the Human Research Ethics Committee of the University of the Witwatersrand (approval number M-200547).

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#### **Contributors:**

ES and RM, manuscript author; AG, HR, MM and JS, major contributor in writing the manuscript; ML, histological examination of the fetus and critical review. All authors read and approved the final manuscript.

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#### **Declaration of Interest:**

The authors have declared no conflicts of interest with respect to the authorship and/or publication of this article.

#### **References:**

1. van Hagen IM, Roos-Hesselink JW, Ruys TP, et al. Pregnancy in Women With a Mechanical Heart Valve: Data of the European Society of Cardiology Registry of Pregnancy and Cardiac Disease (ROPAC). *Circulation*. 2015;132:132-42 (PMID: 26100109).
2. Vause S, Clarke B, Tower C, Hay C, Knight M. Mechanical prosthetic heart valves (MPHV) in pregnancy are associated with a high risk of maternal and fetal morbidity and mortality. *Heart*. 2017;103:1557 (PMID: 28894012).
3. Mazibuko B, Ramnarain H, Moodley J. An audit of pregnant women with prosthetic heart valves at a tertiary hospital in South Africa: a five-year experience. *Cardiovasc J Afr*. 2012;23:216-21 (PMID: 22614667).
4. Baumgartner H, Falk V, Bax JJ, et al. 2017 ESC/EACTS Guidelines for the management of valvular heart disease. *Eur Heart J*. 2017;38:2739-91 (PMID: 28886619).
5. Ginsberg JS, Chan WS, Bates SM, Kaatz S. Anticoagulation of pregnant women with mechanical heart valves. *Arch Intern Med*. 2003;163:694-8 (PMID: 12639202).
6. 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 (PMID: 10647757).
7. Hassouna A, Allam H. Limited dose warfarin throughout pregnancy in patients with mechanical heart valve prosthesis: a meta-analysis. *Interact Cardiovasc Thorac Surg*. 2014;18:797-806 (PMID: 24595247).
8. D'Souza R, Ostro J, Shah PS, et al. Anticoagulation for pregnant women with mechanical heart valves: a systematic review and meta-analysis. *Eur Heart J*. 2017;38:1509-16 (PMID: 28329059).
9. Hall JG, Pauli RM, Wilson KM. Maternal and fetal sequelae of anticoagulation during pregnancy. *Am J Med*. 1980;68:122-40 (PMID: 6985765).
10. 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 (PMID: 10334435).
11. Soma-Pillay P, Nene Z, Mathivha TM, Macdonald AP. The effect of warfarin dosage on maternal and fetal outcomes in pregnant women with prosthetic heart valves. *Obstet Med*. 2011;4:24-7 (PMID: 27579092).
12. Ayad SW, Hassanein MM, Mohamed EA, Gohar AM. Maternal and Fetal Outcomes in Pregnant Women with a Prosthetic Mechanical Heart Valve. *Clin Med Insights Cardiol*. 2016;10:11-7 (PMID: 26884686).
13. Kaplan LC. Congenital Dandy Walker malformation associated with first trimester warfarin: a case report and literature review. *Teratology*. 1985;32:333-7 (PMID: 4082063).