

# MOTHERISK UPDATE

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## Use of warfarin during pregnancy

### ABSTRACT

**QUESTION** One of my patients, who has been taking warfarin for some time for treatment and prophylaxis of deep vein thrombosis, became pregnant due to failed contraception. I am unsure how to counsel her. Is there evidence that warfarin use during pregnancy is associated with fetal risk?

**ANSWER** If possible, warfarin therapy should be avoided during pregnancy. If warfarin therapy is essential, it should be avoided at least during the first trimester (because of teratogenicity) and from about 2 to 4 weeks before delivery to reduce risk of hemorrhagic complications. Unfractionated heparin or low molecular weight heparin could be substituted when appropriate because these agents do not cross the placenta and are considered the anticoagulant drugs of choice during pregnancy.

### RÉSUMÉ

**QUESTION** Une de mes patientes qui suit un traitement et une prophylaxie à la warfarine depuis un certain temps pour une thrombose veineuse profonde est tombée enceinte en raison de l'échec de mesures contraceptives. Je ne suis pas certain des conseils à lui donner. Y a-t-il des données probantes confirmant que l'usage de la warfarine est associé à des risques pour le fœtus?

**RÉPONSE** Si possible, il faudrait éviter une thérapie à la warfarine pendant la grossesse. Si elle est essentielle, elle devrait au moins être évitée durant le premier trimestre (en raison de la tératogénicité) et environ de 2 à 4 semaines avant l'accouchement pour prévenir les complications hémorragiques. L'héparine non fractionnée ou l'héparine à faible poids moléculaire pourrait y être substituée, lorsque indiqué, parce que ces agents ne traversent pas le placenta et sont considérés comme les médicaments anticoagulants de premier choix durant la grossesse.

Warfarin (Coumadin®) is an oral anticoagulant that inhibits synthesis of vitamin K-dependent clotting factors, including factors II, VII, IX, and X, and the anticoagulant proteins C and S.<sup>1</sup> Rats given very high doses (100 mg/kg) of warfarin have had offspring with marked maxillofacial hypoplasia and skeletal abnormalities, including abnormal calcium bridges of the vertebral and long bones.<sup>2</sup>

### Studies in human beings

Several case series and case reports of human use of warfarin during pregnancy

have been published. These reports (which range in size from one to 418 subjects) show a clear association between warfarin therapy and embryopathy. The exact risk of fetal damage from warfarin therapy during pregnancy is difficult to determine because most of the available studies are small and anecdotal.

Several reports have indicated, however, that using warfarin between 6 and 12 weeks' gestation is associated with "fetal warfarin syndrome," which is most commonly manifested by nasal hypoplasia, stippled epiphyses, limb deformities, and respiratory distress. Also, use of warfarin during the second and third trimesters has been associated sporadically with central nervous system abnormalities, including mental retardation, microcephaly, optic atrophy, and blindness.<sup>3-6</sup>

Other fetal abnormalities reported with maternal warfarin use include

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Motherisk questions are prepared by the **Motherisk Team** at the Hospital for Sick Children in Toronto, Ont. **Dr Abadi** and **Ms Einarson** are members and **Dr Koren** is Director of the Motherisk Program. **Dr Koren** is a Senior Scientist at the Canadian Institutes for Health Research, supported by the Research Leadership for Better Pharmacotherapy During Pregnancy and Lactation.

absent or non-functioning kidneys, anal dysplasia, deafness, seizures, Dandy-Walker syndrome, and focal cerebellar atrophy.<sup>7-9</sup> Use of warfarin throughout pregnancy has been associated with hemorrhagic complications, premature births, spontaneous abortions, stillbirths, and death.<sup>4,5,10-15</sup>

One study<sup>8</sup> reported on 418 cases of warfarin exposure from conception to 38 weeks after birth. About 16% of all pregnancies ended in spontaneous abortions or stillbirths, and another 15% resulted in babies with abnormalities at birth. The abnormalities included skeletal malformations (eg, stippling of cervical vertebrae, sacrum, and femurs; kyphoscoliosis; and nasal hypoplasia) bilateral optic atrophy leading to blindness, deafness, focal cerebral atrophy, respiratory distress, and seizures. Doses of warfarin ranged from 2.5 to 12.5 mg/d.

Salazar and colleagues<sup>11</sup> reported on 128 babies exposed to warfarin therapy from 0 to 38 weeks' gestation. About 8% of the 38 live-born infants displayed teratogenic effects of warfarin at birth, including nasal hypoplasia, choanal stenosis, and stippled epiphyses. When compared with 68 pregnancies where women's warfarin therapy had been replaced with 1 g of acetylsalicylic acid and 400 mg of dipyridamole daily at the onset of pregnancy, it was clear that the rate of spontaneous abortions was significantly higher in the warfarin group (28% vs 10%). The rate of neonatal deaths was also higher in the warfarin group (2.3% vs 0). The rate of stillbirths was approximately 7% in both groups. Warfarin dose was adjusted for a target prothrombin time of 2 to 2.5 times control in most women.<sup>11</sup>

Ayhan et al<sup>12</sup> reported on 64 pregnancies: 47 were exposed to warfarin, 11 were exposed to heparin, and 6 were not exposed to anticoagulation drugs. In 20

pregnancies, warfarin was discontinued after 36 weeks' gestation. Fetal wastage occurred in 25 (53%) pregnancies exposed to warfarin, four (36%) exposed to heparin, and only one (17%) with no exposure to anticoagulation drugs. Two (4%) babies were born with warfarin-related malformations, manifested by a single kidney, digit deformities, and cleft lip and palate. There were nineteen (40%) spontaneous abortions and four (9%) stillbirths with warfarin, but only one (9%) spontaneous abortion and no stillbirths with heparin. Warfarin doses were not reported in this study.

Vitali et al<sup>13</sup> reported on 98 pregnancies exposed to warfarin since conception. Warfarin was replaced with heparin in six cases 3 weeks before delivery, was discontinued in six women before term, and was maintained in 13 women throughout the whole pregnancy. There were 37 spontaneous abortions (38%) and 13 voluntary terminations (13%). Of the 47 live births, two (4%) had warfarin-associated malformations at birth, manifested by occipital bone abnormalities, nasal hypoplasia, severe choanal stenosis, and cleft palate. One baby died from respiratory insufficiency 4 hours after delivery, and four (9%) babies were born with hemorrhagic complications secondary to warfarin therapy. Warfarin doses were not specified in this study.

Vitale et al<sup>15</sup> reported on 58 exposures to warfarin throughout pregnancy until 38 weeks' gestation. Although 31 (53%) babies were reported normal at birth, 27 (47%) had fetal complications: 22 (38%) spontaneous abortions, one (1.7%) stillbirth, two (3%) warfarin embryopathies, one (1.7%) ventricular septal defect, and one (1.7%) growth retardation. Warfarin doses in this study were adjusted for a target international normalized ratio (INR) of 2.5 to 3.5. When stratified

according to dose, 22 (81%) complications occurred after exposure to doses >5 mg/d. The study concluded there was a close association between warfarin dose and fetal complications.

Finally, another study looked at 114 exposures to warfarin during pregnancy.<sup>16</sup> While 50 women took warfarin throughout pregnancy, the remaining 64 women received subcutaneous heparin during the first trimester and warfarin during the second and third trimesters. All the women's warfarin therapy was replaced by heparin 2 to 4 weeks before labour. Spontaneous abortions occurred in 22% of cases exposed to either warfarin or heparin, and stillbirths occurred in 9% of cases exposed to warfarin and 11% of cases exposed to heparin. No embryopathies were reported among the live births.

## Conclusion

The literature suggests a strong association between maternal warfarin use and fetal adverse effects. The most recent review<sup>17</sup> recommends that women receiving long-term oral anticoagulation have warfarin replaced with unfractionated or low molecular weight heparin when they become pregnant. There have, however, been case reports of unfractionated heparin being associated with adverse pregnancy outcomes, such as fetal loss and maternal thrombocytopenia, hemorrhage, and osteoporosis.<sup>15</sup> Needless to say, the women in these studies were often sick, and their complications could have been caused by underlying illness. A study of 108 women who received low molecular weight heparin for thromboprophylaxis<sup>18</sup> showed no increase above baseline for fetal deaths or malformations.

Women of childbearing age taking warfarin should be using effective birth control methods. Risks

## CLINICAL CHALLENGE



### DÉFI CLINIQUE

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and benefits of treatment should be discussed with each woman who plans to become or is pregnant while taking this drug. ♣

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