

Editorial Focus

Vitamin K antagonists in pregnancy: An overestimated risk?

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Warfarin and other coumarin derivatives acting as vitamin K antagonists (VKA) are teratogenic and may induce the well-defined coumarin or warfarin embryopathy. There is no doubt about the developmental toxic potency of this drug group. However, as with many other drugs it took years or decades to find out more precisely when and how and to what extent a suspected drug acts as a developmental toxicant. Valproic acid for example was first seen as a novel antiepileptic without teratogenic effects in humans until spina bifida (1) and other birth defects were found to be associated with its exposure 25 years ago, and finally it became clear that it is the strongest teratogen among antiepileptic drugs (2), including mental effects in the child. *Vice versa*, lithium was suspected to be a strong teratogen decades ago, while today it is evident that less than one of 100 exposed fetuses develop teratogenic defects, like Ebstein anomaly of the heart (3). A similar change in risk estimation can be observed with coumarin derivatives. In handbooks of pharmacology one may still find a risk rate of 15–30% for birth defects after its use in the 1st trimester, more recent studies summarize some 5%. The “teratogenic window” is usually defined in the early 1st trimester during weeks 6–9, allowing the interpretation that the high-risk phase starts four weeks after conception, and a restart of anticoagulation may be safe four weeks later.

The difficulties with analyzing drug effects during human pregnancy are due to the fact that we do not investigate in a laboratory setting, neither before licensing nor post marketing, since there are ethical obstacles against enrolling women of reproductive age in randomized controlled pregnancy outcome studies to test the embryotoxic potential of a drug. Therefore, we need other data sources, and these are very rare.

To put it simply, there are two options: i) Data from birth (defect) registries with (retrospective) drug exposure ascertainment allowing case-control studies valuable for quantifying the relative risk for a particular birth defect in association with a particular drug exposure. However, this approach is useless to study abortion risk. ii) Prospective observational studies of exposed pregnancies identified before the outcome is known. One important source for the latter approach are follow up-data from “Teratology Information Services” (TIS). Data collection by TIS

has the advantage of low costs and motivated responders, because the counselling is offered free of charge. Most callers to a TIS are highly satisfied and grateful for the information they received, so that they are willing to respond to a questionnaire sent to them to report on pregnancy outcome. TIS studies use an already existing infrastructure that selects “cases” with potentially teratogenic drugs, because the majority of TIS users mainly ask about insufficiently tested or potentially problematic drugs and not about those with evidence for low or no risk. In other words, TIS users and TIS research focus on the same spectrum of agents.

In this issue of *Thrombosis and Haemostasis*, Schaefer et al. (see pages 949-57) (4) compared in a multi-centre TIS study 666 pregnant women to a non-exposed control group. It is the largest prospective cohort study on VKA in pregnancy and the first presenting large case numbers apart from acenocoumarol and warfarin or phenprocoumon and fluindione as well. Furthermore, in contrast to other published data almost all pregnancies were exposed from the beginning. The rate of major birth defects after 1st trimester exposure was significantly increased (OR 3.86, 95% CI: 1.86–8.00). However, there were only two coumarin embryopathies among 356 live births (0.6%). Apart from two children with diaphragmatic hernias – one was exposed beyond the sensitive period and therefore definitely unrelated to VKA exposure – the majority of birth defects were heterogeneous and neither indicative of well established symptoms of coumarin embryopathy nor resembling to one of the various published case reports discussing additional defects in context with coumarins. One could argue that a higher proportion of prenatally exposed newborns diagnosed as normal develop VKA-induced health problems only later in life, and are therefore missed by this study. However, other investigations suggest that the risk is remote that a healthy newborn develops late onset teratogenic effects from 1st trimester VKA exposure (5).

Schaefer et al. correctly point out that the increased rate of spontaneous abortions they observed may indicate a drug-related (embryotoxic) effect which requires careful further investigation and evaluation. What is unique about this study is the introduction of the proportional hazard model for calculating the

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rate of spontaneous abortion. In contrast to the usually calculated ratio number of miscarriages / number of exposed pregnancies, the proportional hazard model considers the varying number of cases at risk of abortion (6). The crude ratio ignores the “delayed” entry of pregnancies to the study population due to the individual time of pregnancy or (drug) problem recognition (leading to study enrolment). Applying the methodology of survival analysis and proportional hazard, Schaefer et al. found an abortion rate of 14% in the control group, and 42% in the VKA group. The percentage in the control group corresponds well to the expected prevalence in the general population (approximately 15%).

Some publications have focused on the shortcomings of pregnancy outcome studies performed with material collected in TIS. Mainly differences in the population contacting a TIS or not and differences in cases, where follow-up information failed to be obtained (non-responders), were discussed as possible biases (7, 8). Johnson et al. (9) compared all subjects who enrolled in the California-TIS pregnancy outcome study for prenatal exposure to carbamazepine and valproic acid and compared these to patients with the same exposure who had not enrolled in the study. There were no significant differences between the groups on any one of 14 pregnancy risk factors; however, a notably higher proportion who did not enrol in a study were smokers or had a positive family history of congenital disorders. Medical information obtained from a telephone interview during a counselling process may be incomplete. Einarson et al. (10) checked the reproducibility of information obtained in a telephone interview and a (later) personal interview. They found a high reproducibility for the primary drug of concern but low consistence in additional drugs and alcohol consumption. As with any medical care, patients of low social status or poor education have less access to medical programmes, and morbidity and mortality rates are higher compared with more educated patients. It is the experience of many TIS that women with better education are over-represented. On the other hand, lower social status/education is associated with higher risk for reproductive failure, and in particular for congenital or developmental malformations.

Therefore, one cannot rule out that TIS data lead to underestimation of risk, e.g. of major malformations. On the other hand, the above mentioned biases are probably not specifically related to the drug under study, since a risk-promoting co-factor only plays a role in the presence of a potentially harmful drug (and not in the control cohort). Also, it is not plausible that selection criteria (for patients contacting a TIS) are different between exposed and non-exposed (control) patients. As the infant’s examiners were not blinded to the prenatal exposure, one can assume that the well known teratogenicity of the coumarin derivatives encouraged careful examination of exposed infants and made underreporting less probable compared to the control group. As there are no alternatives for pregnancy outcome studies in association with drug exposure, all efforts have to be made to enable TIS to optimize evaluation of these data “goldmines”, a unique byproduct of risk counselling (11).

In summary, the VKA study does not confirm a particular high risk in early pregnancy, i.e. before completed eight weeks after the last menstrual period. Although the results allow by no means the exclusion of any teratogenic effect in early pregnancy, they may reassure pregnant women to carry out their pregnancy in case of (inadvertent) exposure during early pregnancy. On the other hand, the results of the study further weaken earlier recommendations to restart coumarin therapy at the end of the 1st trimester, suggesting a safe interval from weeks 12 to 14 until the very end of pregnancy. Based on this study and the other coumarin-studies published during the last five years, two treatment options for pregnant women with high risk for thromboembolism may be concluded: i) Discontinuation of VKA therapy and replacement by alternative anticoagulants like heparins when a pregnancy is planned, or at the latest at recognition until the end of pregnancy; ii) Interruption of continuous VKA therapy only before delivery, if severe maternal conditions like prosthetic heart valves speak against alternative anticoagulants.

The high rate of “Elective termination of pregnancies” in the exposed group (almost 30%; the majority decided to interrupt for non-medical reasons) underlines the necessity of a rational approach in risk communication with respect to VKA therapy.

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