The use of anticoagulants in pregnant women is problematic. Many anticoagulants cross the placenta and have the potential to be fetopathic as well as to anticoagulate the fetus. In the early 1980s, a paper by Hall et al. (1) suggested that adverse pregnancy outcomes, such as warfarin embryopathy, an increased risk of miscarriages, anticoagulation of the fetus, and possibly other abnormalities were associated with maternal use of coumarin derivatives. Warfarin embryopathy is caused by maternal warfarin exposure between 6 and 12 weeks of gestation and consists of nasal hypoplasia, underdevelopment of the upper respiratory tract, as well as stippling of the epiphyses of long bones and evidence of consequences of recurrent haemorrhage (2). When taken together, this pooled analysis of case series and case reports suggested that warfarin exposure during pregnancy was associated with a high rate of fetal loss and other poor pregnancy outcomes; the same authors came to similar conclusions about the use of unfractionated heparin (UFH) during pregnancy. Based upon these analyses, they recommended “the most prudent and advisable course of action is preconceptual counselling and, in most cases, prevention of pregnancy. Should a woman become pregnant, or should medical indications for anticoagulation arise during pregnancy, intervention in the form of a therapeutic abortion should be offered.” (1).

The report by Hall et al. had two major problems. First, UFH does not cross the placenta and it is thus unclear how it can be fetopathic, and second, many of the women using UFH had co-morbid conditions that were felt to be indications for UFH but were also associated with adverse pregnancy outcomes (hypertension, recurrent pregnancy loss, severe glomerulonephritis, etc.). When we performed a re-analysis of pregnancy outcomes, excluding pregnancies with one or more of these co-morbid conditions, the rate of adverse pregnancy outcomes with UFH (but not warfarin) was consistent with that seen in the normal population (3).

Over the last 30 years, low-molecular-weight heparins (LMWHs) have replaced UFH as the antithrombotic agent of choice in this and other settings, because they do not cross the placenta, are administered in fixed, subcutaneous doses without monitoring, and have a lower risk of causing osteoporosis (4).

It remains unknown if the direct oral anticoagulants (DOACs), also referred to as non-vitamin K antagonist oral anticoagulants (NOACs), are teratogenic. The DOACs are increasingly used in everyday clinical practice, for stroke prevention in atrial fibrillation and management of venous thromboembolism. Unlike UFH and LMWH they are likely to cross the placenta and could thus impact fetal development and they will anticoagulate the fetus. Animal models did not show consistent teratogenicity but the fidelity of such models for humans is uncertain (for example, see (5)).

The paper by Bayer-Westendorf et al. in this issue (6) is an attempt to determine the safety to the fetus of the DOACs. They exhaustively searched to find data on each of the DOACs ( dabigatran, rivaroxaban, apixaban, and edoxaban). Altogether, they identified over 200 pregnancies associated with a DOAC exposure. By the time those pregnancies associated with unknown outcomes, therapeutic abortions, and miscarriages in whom fetal outcomes could not be determined were excluded, they were left with less than 80 pregnancies for which outcomes and exposure window could be reliably known. The authors tentatively conclude that the low number of fetopathic outcomes (three) suggests the incidence of embryopathy is likely to be lower than 7% reported for warfarin. They also suggest that the data show normal live births can occur and pregnant women exposed to a DOAC should not be automatically referred for a therapeutic abortion.

The authors have made a valiant attempt to obtain fetal safety data for the DOACs, but unfortunately their conclusions are severely limited by small numbers, bias, and confounders. The usual way of establishing safety (and efficacy) of a drug is to perform an adequately powered randomised controlled trial. However, such a trial is unlikely to be performed because pregnant women are invariably excluded from nearly all pharmaceutical trials for ethical (and potentially medicolegal) reasons.

The “small numbers problem” could be solved if the drug manufacturers and regulatory agencies, alone or in partnership, established registries for pregnant women exposed to DOACs. Although a number of initiatives are underway (for example, the European Society of Cardiology Registry Of Pregnancy And Cardiac disease [ROPAC] project), to our knowledge there is no centralized effort to collect data on fetal toxicity of anticoagulant drugs. An additional problem with the DOACs is despite their use and classification collectively, each has its own structure unrelated chemically to any other and therefore needs to be evaluated separately.
In other words, safety of one of the DOACs does not necessarily imply safety of another.

The findings of this study suggest a number of conclusions. First, a better system of registering and tracking in utero exposure to drugs is required; were such a system in place we would already have substantial and reliable data on the risks of exposure to DOACs in pregnancy. Such a system will require international cooperation and data sharing. Second, better educational tools for patients and physicians and patients are required. Women of childbearing potential who may become pregnant should be counselled about the unknown risks of exposure of the fetus to DOACs, and use of these drugs should probably be avoided in patients who may become pregnant. Finally, in case of fetal exposure clinicians can take some reassurance from the results of this study that most neonates were normal.

Conflicts of interest

Dr. Crowther reports receiving honoraria from manufacturers of DOACs, as well as manufacturers of competing anticoagulant agents. Dr. Ginsberg declares no conflicts of interest.

References