Pregnancy outcome in patients exposed to direct oral anticoagulants - and the challenge of event reporting

Jan Beyer-Westendorf; Franziska Michalski; Luise Tittl; Saskia Middeldorp; Hannah Cohen; Rezan Abdul Kadir; Deepa Jayakody Arachchillage; Roopen Arya; Cihan Ay; Sandra Marten

1 Center for Vascular Medicine and Department of Medicine III, Division of Angiology, University Hospital “Carl Gustav Carus”, Technische Universität Dresden, Dresden, Germany; 2 Department of Vascular Medicine, Academic Medical Center, Amsterdam, The Netherlands; 3 Department of Haematology, University College London Hospitals NHS Foundation Trust, London, UK; 4 Katharine Dormandy Haemophilia Centre and Thrombosis Centre, Department of Obstetrics and Gynecology, The Royal Free Foundation Hospital, London, UK; 5 Department of Haematology, Imperial College Healthcare NHS Trust, London, UK; 6 King’s Thrombosis Centre, Department of Haematological Medicine, King’s College Hospital, London, UK; 7 Clinical Division of Haematology and Haemostaseology, Department of Medicine I, Medical University of Vienna, Vienna, Austria

Introduction

The use of vitamin K antagonists (VKA) in pregnant women is controversial. While VKA can be used to prevent or treat arterial or venous thromboembolism (VTE) effectively also in pregnant patients, these drugs cross the placenta and may thus harm the foetus (1, 2).

In addition to placental and fetal haemorrhage, coumarin embryopathy is a reported complication especially with VKA exposure between 6-12 weeks after last menstrual period (3, 4); abnormalities include midface hypoplasia, ocular malformations and skeletal abnormalities (5–9). Older studies suggested rates up to 30% (10) but more recent data estimate a 7% risk for coumarin embryopathy (9, 11). Consequently, women of child-bearing potential should apply effective contraceptive measures to avoid unplanned pregnancies (12) or should discontinue VKA immediately after pregnancy diagnosis.

Currently, direct oral anticoagulants (DOAC) are rapidly replacing VKA, based on the favourable efficacy and safety results seen in large phase III trials in atrial fibrillation and VTE (13, 14). Many patients receiving DOAC for VTE are of reproductive age. The approved DOAC prescribing labels around the world advise termination of pregnancy in case of DOAC exposure during the first trimester (15, 16). DOAC exposure in animals indicated a risk of reproductive embryotoxicity. To assess the risk of DOAC embryopathy, we reviewed cases of DOAC exposure in pregnancy collected from physicians, literature and pharmacovigilance systems of drug authorities and manufacturers. A total of 357 reports including duplicates were available from which 233 unique cases could be identified. Information on pregnancy outcome was available in only 137/233 cases (58.8%); 67 live births (48.9%); 31 miscarriages (22.6%); 39 elective pregnancy terminations (28.5%). In 93 cases (39.9%) no outcome data were available (including 3 cases of ongoing pregnancy). Of the 137 pregnancies with reported outcomes, seven showed abnormalities (5.1%) of which three (2.2%) could potentially be interpreted as embryopathy: live birth with facial dysmorphism; miscarriage in week 10 with limb abnormality; elective pregnancy termination due to a foetal cardiac defect in a woman who had to terminate a previous pregnancy due to Fallot tetralogy. Within its limitations (small numbers, incomplete outcome data) our results do not indicate that DOAC exposure in pregnancy carries a high risk of embryopathy or that DOAC exposure per se should be used to direct patient counselling towards pregnancy termination. Pregnancy outcome data are inconsistently captured in pharmacovigilance databases indicating the strong need for a more robust system of reporting.

Keywords
Pregnancy, direct oral anticoagulants, outcome

Correspondence to:
Jan Beyer-Westendorf
Center for Vascular Medicine and Department of Medicine III, Division of Angiology
University Hospital “Carl Gustav Carus”, Technische Universität Dresden
Fetscherstrasse 74; 01307 Dresden, Germany
Tel.: +49 351 4583659, Fax: +49 351 4584359
E-mail: jan.beyer@uniklinikum-dresden.de

Received: April 18, 2016
Accepted after major revision: May 25, 2016
Epub ahead of print: July 7, 2016
http://dx.doi.org/10.1160/TH16-04-0305
Supplementary Material to this article is available online at www.thrombosis-online.com.
in implantations, increased implantation loss, malformations, altered ossification and haemorrhagic complications (17–20).

The available data on DOAC exposure in pregnancy are very limited (17–20) and insufficient to provide clinical guidance and, consequently, counselling of patients in this situation is a challenge. Although none of the DOACs is recommended during pregnancy or breastfeeding, an unplanned pregnancy may occur during DOAC treatment, especially, if adequate contraception has not been used. Cases of healthy live-births have recently been reported (21, 22) but the current lack of information may result in patients electing to undergo a pregnancy termination for fear of DOAC embryopathy.

Since the risks potentially associated with DOAC use in pregnancy will probably never be evaluated in a prospective trial, safety assessments will be limited to the review of case series and pharmacovigilance reports. The purpose of this article is therefore to assess available data on DOAC exposure and pregnancy outcome from various sources, to provide a basis for counselling and to advocate the reporting of DOAC exposure and outcomes in pregnancy to appropriate repositories.

Methods

Data collection

The collaborative study group collected reports of DOAC exposure during pregnancy in their institutions and from gynaecologists, haematologists and vascular specialists in the county of Saxony, Germany by use of questionnaires.

Between December 2014 and December 2015, the homepage of the U.S. Food and Drug Administration (FDA) was searched for information (23). The European Medicines Agency (EMA), the German drug authority (Bundesinstitut für Arzneimittel und Medizinprodukte, BfArM) and the manufacturers of apixaban (Bristol-Myers Squibb/Pfizer), dabigatran (Boehringer Ingelheim), edoxaban (Daichii Sankyo) and rivaroxaban (Bayer Healthcare) were contacted and asked to provide access to anonymised pharmacovigilance data related to pregnancies with suspected or established exposure to DOAC.

On December 15, 2015 PubMed was searched using "apixaban and pregnancy", "dabigatran and pregnancy", "edoxaban and pregnancy" and "rivaroxaban and pregnancy" in the title and/or abstracts. Abstracts and full publications were independently reviewed by two members of the study group for potential cases of DOAC exposure in pregnancy. Authors of relevant publications were contacted to obtain further information on DOAC therapy, pregnancy details and outcome.

Data from all sources (see Suppl. Table 1, available online at www.thrombosis-online.com) were evaluated by two independent physicians and transferred to a study database with missing values left blank. Given the nature of the data, only descriptive statistics were applied.

Ethics

The data collection from physicians was approved by the local ethics committee at the Technical University Dresden (EK190042015).

Results

Literature search

The literature search in PubMed resulted in a total of 31 separate publications, of which two articles related to cases of DOAC exposure in pregnancy: a case series of 39 pregnancies with rivaroxaban exposure (22) and a case report from Austria on the pregnancy outcome of a VTE patient treated with rivaroxaban (21). Two unpublished cases of apixaban exposures were identified through the FDA homepage (23).

Pregnancy outcome data provided by study group

The collaborative study group collected 15 well-documented cases of DOAC exposure in pregnancy (15 rivaroxaban), which included eight cases from questionnaires sent to gynaecologists, haematologists and vascular specialists in Germany.

Pharmacovigilance data provided by EMA

EMA provided relevant passages from periodic safety update reports (PSUR) provided by DOAC manufacturers to EMA: five PSUR for apixaban (with information on 21 exposures in pregnancy), seven for dabigatran (26 exposures) and five for rivaroxaban (148 exposures).

Pharmacovigilance data provided by BfArM

On February 27, 2015 the German drug authority BfArM accessed their pharmacovigilance system, which provided a total of 13 cases (1 apixaban, 12 rivaroxaban).

Pharmacovigilance data provided by DOAC manufacturers

Bayer Healthcare (manufacturer of rivaroxaban) provided available information on 148 cases of rivaroxaban exposure during pregnancy. Data were extracted from the Bayer pharmacovigilance system, from the WHO VigiBase and from the FDA Adverse Event Reporting System (FAERS) and provided in aggregated form.

Boehringer Ingelheim (manufacturer of dabigatran) provided detailed information including anonymised physicians reports for 26 cases.

Daichii Sankyo (manufacturer of edoxaban) provided information for 10 cases of edoxaban exposure. Details for these 10 cases could also be extracted from the edoxaban SmPC (20). Details on the pharmacovigilance systems are presented in Suppl. Table 1 (available online at www.thrombosis-online.com).
Table 1: Data quality according to data source (including duplicate reports).

<table>
<thead>
<tr>
<th>Data source (n)</th>
<th>DOAC indication available</th>
<th>DOAC dosage available</th>
<th>DOAC pregnancy exposure duration available</th>
<th>Pregnancy outcome available</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case collection; n=15</td>
<td>15/15 (100 %)</td>
<td>15/15 (100 %)</td>
<td>15/15 (100 %)</td>
<td>12/15 (80.0 %) + 3 ongoing</td>
</tr>
<tr>
<td>Pharmacovigilance database of DOAC manufacturers; n=83</td>
<td>Bayer:34/47 (72.3 %)</td>
<td>Bayer:11/47 (23.4 %)</td>
<td>Bayer:0/47</td>
<td>Bayer:28/47 (59.6 %)</td>
</tr>
<tr>
<td>Pharmacovigilance database BfArM; n=13</td>
<td>Bayer: 1/1 (100 %)</td>
<td>Bayer:1/1 (100 %)</td>
<td>Bayer: 1/1 (100 %)</td>
<td>Bayer:28/47 (59.6 %)</td>
</tr>
<tr>
<td>Summaries from manufacturers PSUR from EMA; n=195</td>
<td>Bayer: 9/148 (6.1 %)</td>
<td>Bayer:5/148 (3.4 %)</td>
<td>Bayer: 0/148</td>
<td>Bayer:58/148 (39.2 %)</td>
</tr>
<tr>
<td>SmPC(20) (edoxaban); n=10</td>
<td>10 (100 %)</td>
<td>0/10</td>
<td>0/10</td>
<td>10 (100 %)</td>
</tr>
<tr>
<td>Literature search</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FDA(23); n=2</td>
<td>Apixaban: 1/2 (50 %)</td>
<td>Apixaban: 1/2 (50 %)</td>
<td>Apixaban: 2/2 (100 %)</td>
<td>Apixaban:2/2 (100 %)</td>
</tr>
<tr>
<td>Embryotoxic cases (22); n=39</td>
<td>Apixaban: 1/2 (50 %)</td>
<td>Apixaban: 1/2 (50 %)</td>
<td>Apixaban: 2/2 (100 %)</td>
<td>Apixaban:2/2 (100 %)</td>
</tr>
<tr>
<td>case report(21)</td>
<td>Apixaban: 1/2 (50 %)</td>
<td>Apixaban: 1/2 (50 %)</td>
<td>Apixaban: 2/2 (100 %)</td>
<td>Apixaban:2/2 (100 %)</td>
</tr>
</tbody>
</table>

DOAC, direct oral anticoagulants; DS, Daiichi Sankyo; BI, Boehringer Ingelheim; FDA, U. S. Food and Drug Administration; EMA, European Medicines Agency; BfArM, Bundesinstitut für Arzneimittel und Medizinprodukte (German drug authority).

Figure 1: Overview on pregnancies exposed to different DOACS, duplicate cases and pregnancy outcomes for definitely unique cases. SLE, systemic lupus erythematoses.
Pfizer declined to provide details on cases of apixaban exposure in pregnancy.

When combining the data from all sources, a total of 357 reports were available, including potentially duplicate reports. The main limitation was the lack of detail in the datasets provided by the DOAC manufacturers and authorities (Table 1). By use of unique patient identifiers in some datasets, trial subject numbers and several pregnancy- or DOAC exposure-related information (listed in Suppl. Table 2, available online at www.thrombosis-online.com) 64 duplicate reports could be identified and merged. If duplicity could neither be established nor ruled out due to insufficient data, these reports (n=60) were not included in further analysis.

This resulted in 233 definitely separate cases of DOAC exposure in pregnancy which could be identified from the various sources (Table 1).

<table>
<thead>
<tr>
<th>Drug</th>
<th>Total exposures reported n=233</th>
<th>No outcome data available n=93</th>
<th>Pregnancy ongoing n=3</th>
<th>Outcome available n=137</th>
<th>Live birth n=67</th>
<th>Miscarriage n=31</th>
<th>Elective termination of pregnancy n=39</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apixaban; n (%)</td>
<td>21</td>
<td>9/21 (42.9)</td>
<td>0/21 (0)</td>
<td>5/21 (23.8)</td>
<td>4/21 (19)</td>
<td>3/21 (14.3)</td>
<td></td>
</tr>
<tr>
<td>Dabigatran; n (%)</td>
<td>26</td>
<td>14/26 (53.8)</td>
<td>0/26 (0)</td>
<td>3/26 (11.5)</td>
<td>2/26 (7.7)</td>
<td>7/26 (26.9)</td>
<td></td>
</tr>
<tr>
<td>Edoxaban; n (%)</td>
<td>10</td>
<td>0/10 (0)</td>
<td>0/10 (0)</td>
<td>6/10 (60)</td>
<td>1/10 (10)</td>
<td>3/10 (30)</td>
<td></td>
</tr>
<tr>
<td>Rivaroxaban; n (%)</td>
<td>176</td>
<td>70/176 (39.8)</td>
<td>3/176 (1.7)</td>
<td>53/176 (30.1)</td>
<td>24/176 (13.6)</td>
<td>26/176 (14.8)</td>
<td></td>
</tr>
</tbody>
</table>

Table 3: Overview of reported pregnancy outcomes during DOAC exposures.

For 137/233 (58.8 %) of the DOAC pregnancy exposures outcome data were available (Figure 1, Table 3). In another three cases, the pregnancy was still ongoing by December 15, 2015. For the remaining 93 cases (39.9 %) no outcome data were available.

Of the 137 pregnancies with available outcome data, 67 (48.9 %) resulted in live birth, 31 (22.6 %) resulted in miscarriage (10 in 1st and 5 in 2nd trimester; 16 without details) and 39 (28.5 %) were electively terminated (reasons available for 13 cases only: 7 for social reasons, 3 for fear of DOAC embryopathy and three for medical reasons not related to DOAC exposure) (Table 3).

Details on duration of DOAC exposure and pregnancy outcome were available for 75 cases (Figure 2) and in 61 cases (81.3 %) DOAC exposure was restricted to the first two months of pregnancy. Live-births were the most common outcomes across the spectrum of DOAC exposure time (Figure 2).

Patient and pregnancy characteristics of live-births and miscarriages according to exposure to different DOAC are provided in Suppl. Table 3 (available online at www.thrombosis-online.com).

Patient characteristics

The characteristics of the final study cohort of 233 pregnancies are presented in Table 2.

Patients were exposed to rivaroxaban in 176 (75.5 %), dabigatran in 26 (11.2 %), apixaban in 21 (9.0 %) and edoxaban in 10 (4.3 %) cases. Indications for DOAC therapy were VTE in 86 (36.9 %) patients and atrial fibrillation in four (1.7 %) patients, thrombosis prophylaxis in 4 (1.7 %) patients, thrombophilia in one (0.4 %) patient, other reasons in three (1.3 %) patients and unknown in 135 (57.9 %) patients. Congenital and/or acquired thrombophilia was reported in 18 women (Suppl. Table 2, available online at www.thrombosis-online.com; Table 2).

Based on available data, the mean duration (SD) of DOAC exposure could be calculated for 75 pregnancies and was 6.2 ± 4.4 weeks.

Outcome of pregnancies during DOAC exposure

For 137/233 (58.8 %) of the DOAC pregnancy exposures outcome data were available (Figure 1, Table 3). In another three cases, the pregnancy was still ongoing by December 15, 2015. For the remaining 93 cases (39.9 %) no outcome data were available.

Of the 137 pregnancies with available outcome data, 67 (48.9 %) resulted in live birth, 31 (22.6 %) resulted in miscarriage (10 in 1st and 5 in 2nd trimester; 16 without details) and 39 (28.5 %) were electively terminated (reasons available for 13 cases only: 7 for social reasons, 3 for fear of DOAC embryopathy and three for medical reasons not related to DOAC exposure) (Table 3).

Details on duration of DOAC exposure and pregnancy outcome were available for 75 cases (Figure 2) and in 61 cases (81.3 %) DOAC exposure was restricted to the first two months of pregnancy. Live-births were the most common outcomes across the spectrum of DOAC exposure time (Figure 2).

Patient and pregnancy characteristics of live-births and miscarriages according to exposure to different DOAC are provided in Suppl. Table 3 (available online at www.thrombosis-online.com).
There were no reports of fetal bleeding. Congenital abnormalities were reported in three cases of live-birth (renal pelvis dilatation and facial dysmorphism in 1 case with rivaroxaban exposure in 1st trimester, mild hip dysplasia in an otherwise uneventful pregnancy with rivaroxaban exposure until week 7 and a septum pellucidum cyst diagnosed at week 32 after rivaroxaban exposure in 1st trimester, which was not confirmed post-delivery of a healthy male in week 39). In three cases of miscarriages defined abnormalities were reported (limb abnormality with miscarriage in week 10; anhydramnios and miscarriage in week 14, IUGR and miscarriage in week 20). Finally, one pregnancy was electively terminated due to a fetal cardiac defect. Of note, a previous pregnancy of this woman with systemic lupus erythematosus treated with multiple drugs had also been terminated after prenatal diagnosis of tetralogy of Fallot.

**Discussion**

With increasing use of DOAC the number of potential pregnancies exposed to this new class of oral anticoagulants is expected to rise. Data on the reproductive risks associated with DOAC intake during pregnancy are scarce, and systematic assessments of pregnancy outcomes and in particular risk of embryopathy after DOAC exposure in pregnant women have not yet been performed. Here, we present a comprehensive analysis of data on DOAC exposure and pregnancy outcome available from a variety of sources. This evidence provides the first evidence base for prenatal counselling.

Our data collection indicates that DOAC exposure in pregnancy does occur mostly to patients treated for VTE, probably the commonest indication for DOAC in women of reproductive age. The mean duration of exposure of 6.2 weeks indicated that most women seek medical advice immediately after pregnancy has been
established and that physicians seem to be aware of the fact that current recommendations suggest that DOAC therapy should not be continued during pregnancy.

Our findings also indicate that effective forms of contraceptions are underused in DOAC-treated women. An ACOG bulletin on “the use of hormonal contraception in women with coexisting medical conditions” recommends combined oral contraceptives as long as the patient is anticoagulated (level A) (24). However, in daily practice a reluctance to continue prescription of hormonal contraception is often seen, based on the consideration that the hormone may have caused the VTE and continuation of hormonal contraception could potentially increase the risk of thromboembolic complications during or after the end of anticoagulation therapy (25, 26). Furthermore, the World Health Organization (WHO) 2010 guidelines stated that use of oestrogen-containing contraceptives poses an “unacceptable health risk” during anticoagulant treatment for VTE (27). By contrast, the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis (ISTH) recommends that women should continue oral contraceptive and oestrogen-replacement therapy until they discontinue anticoagulant therapy (12) because any prothrombotic effect of hormonal therapy is likely to be suppressed by anticoagulation. Importantly, a recent post-hoc analysis from the pooled EINSTEIN DVT and PE studies did not find an increased risk for VTE complications for hormone treatment during anticoagulation (28), which supports the statement from the ISTH to continue hormonal contraception during anticoagulation for VTE, if necessary (12).

The ISTH recently issued a guidance document on the issue of DOAC exposure during pregnancy (29). This guidance document recommends that DOAC should be stopped immediately after confirmation of pregnancy and, if indicated, replaced by low-molecular-weight heparin, which does not cross the placenta and is safe for the foetus (30, 31). Furthermore, the writing panelists agreed that DOAC exposure in itself should not be regarded as medical reason for termination of pregnancy. Women considering elective pregnancy termination should receive non-directive counselling and, if decision to continue with pregnancy is made, early obstetric review and pregnancy surveillance.

In our cohort we found a rate of miscarriage of 22%, which is comparable to the miscarriage rate in the overall population (32–34). Furthermore, the rate of miscarriage after DOAC exposure compares favourably with data from VKA exposure in pregnancy, where a miscarriage rate as high as 30% and an increased risk of premature delivery was demonstrated (9, 11).

Of the 137 pregnancies with reported outcomes, seven anatomical abnormalities were observed, of which three could be potentially interpreted as drug-related embryopathy. However, there were no recurring patterns of abnormalities, which would be expected in the case of embryotoxicity in the first or second trimester. Anatomical abnormalities are also frequent findings in pregnancies not exposed to DOAC (35, 36). The one case of severe fetal cardiac abnormality occurred in a women with a history of Fallot tetralogy in a previous pregnancy during which she was not exposed to a DOAC (22). Based on these numbers, the risk of embryopathy after DOAC exposure seems to be at least numerically lower than the 7% reported for VKA exposure. Furthermore, the risk of malformations in the newborn is estimated to be about 3.5% (37), which puts the number of three potential cases of embryopathy after DOAC exposure into perspective. However, it is important to highlight that for 93 DOAC exposures the outcome was not reported and that for 16 cases of miscarriage and 26 elective pregnancy terminations no details were available. Therefore definitive conclusions or an accurate determination of embryopathy risks cannot be drawn from our series of 233 documented DOAC exposure cases. Another limitation of our study was the pooling of data for all DOAC, which are chemically different compounds that may have different embryotoxic potentials. Therefore, the safety assessment of DOAC needs to continue and, with larger numbers of pregnancy exposure reports, a more differentiated evaluation is warranted in the future.

The quality of documentation of DOAC exposures in pregnancy needs to be improved: exposed pregnancies were inconsistently reported, most cases were only documented in one or two data sets of the various sources and we suspect that the majority of cases are not reported at all. If reported, data contained in pharmacovigilance databases from health authorities or DOAC manufacturers are incomplete (in contrast to the very detailed documentations obtained directly from physicians), which further impairs the interpretation of risks. Defined criteria and measures should be implemented to improve the reporting of DOAC exposure and pregnancy outcomes. The ISTH recently started an international registry to prospectively collect cases of DOAC exposure in pregnancy (38).

Finally, in the context of DOAC exposure in pregnancy it is important to point out that animal models demonstrated secretion of some DOAC into breast milk (20, 39–41). Consequently, breastfeeding is a contraindication for DOAC use and anticoagulant therapy should be changed to LMWH or VKA or breastfeeding should be stopped if DOAC needs to be used post-partum (31).

**Conclusion**

Existing data do not allow the conclusion that DOACs can be safely used in patients planning to conceive or during pregnancy and DOAC exposure in pregnant or breast-feeding women is strongly discouraged at present.

Pregnancy outcome data were available only on 58.8% women exposed DOAC during pregnancy indicating the need for a more robust system of reporting. However, even within the limitation of our data set, our careful review of the available data does not indicate that the risk of embryopathy from DOAC exposure is higher than the 7% reported for VKA exposure. Therefore, as with VKA exposure, cases of DOAC exposure should be counselled in a non-directive manner and, if the decision is to proceed with the pregnancy, the well-being of mother and child should be carefully monitored. Our data do not support to direct patient counselling towards pregnancy interruption and it is of concern that pregnancies are being electively terminated for fear of DOAC embryopathy suggesting that the lack of data and the consequent lack of guidance in this situation may have medical and ethical consequences.
What is known about this topic?

- Exposure to vitamin K antagonists (VKA) is associated with a considerable risk for coumarin embryopathy, manifesting as placental and fetal haemorrhage, midface hypoplasia, ocular malformations and skeletal abnormalities.
- Direct oral anticoagulants (DOAC) are currently replacing VKA. DOAC are small molecules that have been shown to cross the placenta but the clinical risk of embryopathy is currently unknown.
- Cases of healthy live-births after DOAC exposure have recently been reported but the current lack of systematic data and guidance for prenatal counselling may result in patients electing to undergo a pregnancy termination for fear of DOAC embryopathy.

What does this paper add?

- In our review of 233 cases with DOAC exposure during pregnancy, outcome data were missing in approximately 40%, indicating the need for more robust system of reporting. As a consequence, existing pharmacovigilance data do not allow the conclusion that DOACs can be safely used in patients planning to conceive or during pregnancy.
- In the 137 pregnancies with reported outcomes, three anatomical abnormalities were observed that could be potentially interpreted as drug-related embryopathy, even though there were no recurring patterns of abnormalities. Therefore, within the limitations of our data set, the risk of embryopathy after DOAC exposure seems to be at least not higher than the approximately 7% rate reported for VKA related embryopathy.
- Therefore, as with VKA exposure, cases of DOAC exposure should be counselled in a non-directive manner and, if the decision is to proceed with the pregnancy, the well-being of mother and child should be carefully monitored. Our data do not support to direct patient counselling towards pregnancy interruption for fear of DOAC embryopathy.

To improve risk assessment, pregnancy outcomes after exposure to oral anticoagulants should generally be reported to the DOAC manufacturer and to the responsible health authority. With a more rigorous reporting policy, expanding sets of safety data should improve patient counselling and treatment in the future.

Conflicts of interest

No funding was obtained for this study and no author received honoraria or research support in relation to the submitted work. The authors report the following unrelated support: JBW received honoraria and institutional research support from Bayer HealthCare, Boehringer Ingelheim, BMS/Pfizer, CSL Behring, Daiichi Sankyo and LEO Pharma, FM, LT, RAK and CA have nothing to disclose. SMi reports personal fees from Aspen, Bayer Pharma, Boehringer Ingelheim, Daiichi Sankyo, GSK, and BMS/Pfizer, and grants from Aspen, GSK, BMS/Pfizer, Sanquin and Daiichi Sankyo. HC reports grants from Bayer Pharma. DJA reports non-financial support from Bayer, personal fees and non-financial support from Pfizer, grants from Covidien. SMA reports honoraria from Daichi Sankyo, Bayer HealthCare.

References


