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ORIGINAL PAPER

Pregnancy outcome after exposure to the novel oral anticoagulant rivaroxaban in women at suspected risk for thromboembolic events: a case series from the German Embryotox Pharmacovigilance Centre

M. Hoeltzenbein[1,2] · E. Beck[1,2] · K. Meixner[1,2] · C. Schaefer[1,2] · R. Kreutz[1,2]

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Abstract
Background New oral anticoagulants are increasingly used in women of childbearing age, but apart from one case report there is no published experience with rivaroxaban exposure during pregnancy.
Methods From October 2008 to December 2014, the German Embryotox Pharmacovigilance Centre identified 63 exposed pregnancies among 94 requests concerning rivaroxaban use during childbearing age. Follow-up included paediatric checks until 6 weeks after birth.
Results All pregnancies with completed follow-up were exposed at least during the first trimester. Treatment indications included venous thromboembolism, knee surgery, and atrial fibrillation. 37 pregnancies were prospectively ascertained and resulted in six spontaneous abortions, eight elective terminations of pregnancy, and 23 live births. All women had discontinued rivaroxaban after recognition of pregnancy, mostly in the first trimester, but in one woman treatment continued until gestational week 26. There was one major malformation (conotruncal cardiac defect) among the 37 prospectively ascertained pregnancies in a woman with complex medication and a previous foetus with cardiac malformation without exposure to rivaroxaban. Only one case of bleeding concerning a retrospective report of surgery for missed abortion was observed in our case series.
Conclusion Our results might give reassurance to those women, who were inadvertently exposed to rivaroxaban in early pregnancy. However, our limited cohort size does not allow ruling out an increased malformation risk and does not support the use of rivaroxaban during pregnancy. In all cases of (inadvertent) rivaroxaban exposure during 1st trimester, anticoagulation regimen should be reconsidered and a detailed ultrasound assessment recommended to confirm normal foetal development.

Keywords Pregnancy · Rivaroxaban · New oral anticoagulants · Non-vitamin K antagonist oral anticoagulants · Venous thromboembolism

Introduction

The risk of venous thromboembolism (VTE) during pregnancy is increased by factor 4–5 compared to non-pregnant women of the same age and VTE is a major cause of maternal morbidity and mortality during pregnancy or after delivery [9]. Indications for treatment with anticoagulants during pregnancy include women with a high risk for VTE, valvular atrial fibrillation, or mechanical prosthetic heart valves [7, 9, 20, 24, 33, 40, 44]. The use of vitamin K antagonists (VKA) as established oral anticoagulants is limited during pregnancy due to their teratogenic effects. Consequently, low molecular weight heparins (LMWH) are the preferred treatment option in pregnancy today and use of VKAs is limited to high risk situations (e.g., mechanical heart valves) [4, 10, 19, 33, 39]. However,

C. Schaefer and R. Kreutz contributed equally to this article.

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✉ M. Hoeltzenbein
maria.hoeltzenbein@charite.de

[1] Berlin Institute for Clinical Teratology and Drug Risk Assessment in Pregnancy, Charité-Universitätsmedizin Berlin, Augustenburger Platz 1, 13353 Berlin, Germany

[2] Institute of Clinical Pharmacology and Toxicology, Charité-Universitätsmedizin Berlin, Charitéplatz 1, 10117 Berlin, Germany

heparins are parenteral drugs requiring daily s.c. injections and delayed-type hypersensitivity skin reactions are frequent during pregnancy [37, 38]. One study reported that in almost every second pregnancy women had to switch at least once to another anticoagulant due to the development of hypersensitivity skin reactions on LMWH [37]. In most cases (77 %) skin reactions did not recur on the second preparation of LMWH but for the remaining patients there are limited treatment options [37, 38].

During the last years non-vitamin K antagonist oral anticoagulants (NOACs) as selective and direct inhibitors of either thrombin (factor IIa) or factor Xa have been developed as an alternative to the established anticoagulants that are also considered during pregnancy, e.g., VKA, unfractionated heparins (UFH) and LMWH [9, 33]. Meanwhile NOACs have been approved in many countries for prophylaxis of VTE in adult patients after hip or knee replacement surgery, for the treatment of acute deep vein thrombosis (DVT) and acute pulmonary embolism (PE), and for the prevention of recurrent DVT and PE [21]. In addition, in Europe the direct factor Xa inhibitor rivaroxaban has been approved for the prevention of atherothrombotic events in adult patients with elevated cardiac biomarkers after an acute coronary syndrome (ACS) [1]. NOACs were considered to be similarly effective as VKAs with a lower risk for intracranial bleedings [43]. Therefore, they have been recommended as an alternative to VKAs for patients with VTE and non-valvular atrial fibrillation [6, 14, 17, 18, 27, 31, 35, 41]. However, experience so far is largely derived from clinical studies and has to be confirmed in the "real world" [45].

Due to their physical and chemical properties, mostly based on the rather low molecular weight and data on placental transfer in rats, NOACs including the direct thrombin inhibitor dabigatran and the factor Xa inhibitors apixaban, edoxaban and rivaroxaban are expected to cross the placenta [9]. Except for one case report on rivaroxaban [26], there are no published studies on use of NOACs in pregnancy. The increase in prescription rates of NOACs in many countries around the world [11] will probably cause an increase in women with unplanned pregnancy while being on NOACs. Accordingly, raising numbers of information requests on NOACs during pregnancy are received by the German Embryotox Pharmacovigilance Centre. Therefore, we decided to present our observations of the outcome of 39 pregnancies exposed to rivaroxaban at least during the first trimester.

Materials and methods

The German Embryotox Pharmacovigilance Centre offers risk assessment on drug use in pregnancy to health care professionals of all specialities and pregnant women. On behalf of the German Federal Institute for Drugs and Medical Devices, more than 10,000 exposed pregnancies per year are documented through risk consultation. Using a structured questionnaire or phone interview at the first contact, all relevant data with respect to drugs, exposures to other agents, maternal characteristics as well as obstetric and family history are documented with the permission of the patient. Approximately 8 weeks after the expected date of delivery, follow-up is conducted by a questionnaire mailed to the woman or her physician and covers at least the first three paediatric examinations from birth up to the age of 4–6 weeks. In addition, information on complications during pregnancy such as infections, gestational diabetes, pre-eclampsia, details in case of pregnancy loss, gestational age at birth, sex, birth weight, length, head circumference, pH, and Apgar scores are obtained. On average, 85 % of our clients return their follow-up questionnaires. The main reasons for non-response are relocation, change of the physician, and very rarely refusal to answer.

Weeks of gestation are calculated from ultrasound during the first trimester or, if not available, from last menstrual period. Pregnancies are classified as prospective when the first contact to our Institute occurred before the outcome of pregnancy or prenatal diagnostic findings were known. Pregnancies that were reported because of pathological findings or after birth are considered as retrospective and evaluated separately. Further details of patients and methods have been described elsewhere [28].

Our survey includes all requests on rivaroxaban to our Institute from October 2008 (approval of the drug in Germany) until December 2014. All requests were analysed with regard to indication for treatment and pregnancy outcomes with special focus on miscarriage and on major malformations, defined as structural abnormalities of medical, surgical or cosmetic relevance [29, 32].

Results

From October 2008 to December 2014 our Institute received 94 requests for information on rivaroxaban. Most requests were on maternal exposure during pregnancy (86 %) followed by requests on use during lactation (11 %) or paternal exposure (3 %); further details are given in Fig. 1. In comparison 427 requests with 273 (64 %) concerning maternal exposure during pregnancy were received for phenprocoumon, the preferred VKA in Germany, during the same period. The number of requests on rivaroxaban increased over time, especially after its approval for treatment and prophylaxis of DVT and PE in Germany in November 2012. Treatment indications among our requests in relation to time of approval are shown in Fig. 2. Of

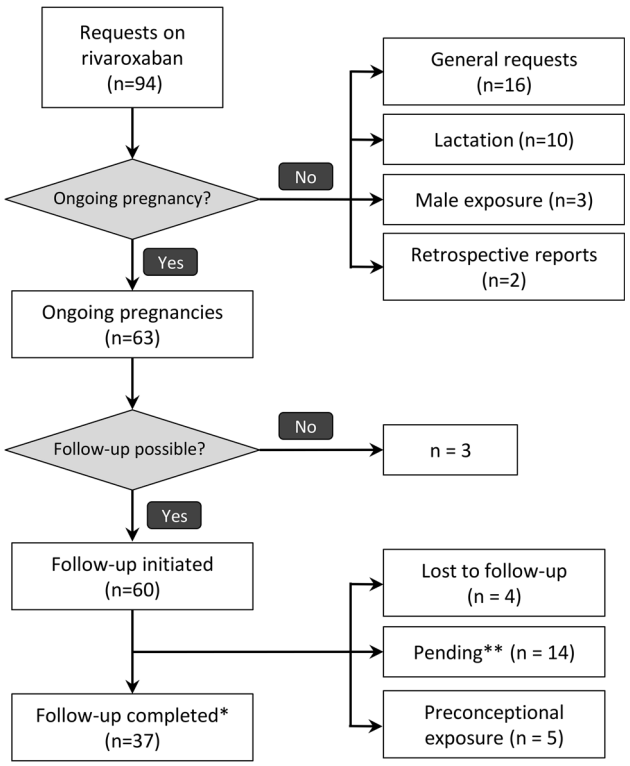

Fig. 1 Flow chart of requests for information on rivaroxaban exposure to the German Embryotox Pharmacovigilance Centre from October 2008 until December 2014 with number of completed follow-ups. *Asterisk* indicates that two pregnancies with elective termination have been reported before the scheduled follow-up date. *Double asterisk* indicates that the estimated date of birth of all pending pregnancies is in 2015, follow-up at 8 weeks after estimated date of birth is not yet available

interest, before the respective approval rivaroxaban was already used off-label for treatment or secondary prophylaxis of VTE and other indications such as minor surgery procedures and thrombophlebitis (Fig. 2). Moreover, inappropriate dosing was observed in at least 12 (13 %) of the 94 requests. Nine patients received a daily dose of only 10 mg, one patient received 5 mg daily after an initial 3 weeks regimen of 10 mg daily, and two patients were treated with higher doses (40 and 50 mg daily); all for prophylaxis of recurrent VTE.

The outcome of rivaroxaban exposed pregnancies will be presented separately for prospectively ascertained cases and retrospective case reports.

Outcome of prospective cases ($n = 37$)

Follow-up was completed in 37 prospectively ascertained pregnancies with treatment at least during the first trimester. Maternal characteristics are summarised in Table 1. Further details of maternal and obstetric history are presented as supplementary material (Supplementary material online File Table 1). In 34 patients, treatment indication was prophylaxis of recurrent VTE, among these were one woman with systemic lupus erythematosus, one with antiphospholipid syndrome and one with homocystinuria (#2, #14 and #25 in Fig. 3 and Supplementary material online File Table 1). Further indications were prophylaxis of VTE after knee surgery (#1) and long distance flight after previous DVT (#4 and #16). The median pre-pregnancy BMI was 24.7, while eight patients had a BMI > 30. Median gestational age at study enrolment was 7 weeks. Rivaroxaban treatment had been initiated before pregnancy in 33 (89 %) of the 37 women and median treatment discontinuation in these women was in week 7. Of interest, in one woman (#19) treatment was continued until her pregnancy was recognised in week 26. In four cases therapy was started before pregnancy recognition, in gestational week 4, 5 and 7 (#1, #4, #6, and #22), respectively. Rivaroxaban exposure intervals and pregnancy outcomes are shown in Fig. 3. Median rivaroxaban dose was 20 mg/day (range 5–50 mg).

After discontinuation of rivaroxaban, all 26 women in whom anticoagulant treatment was continued were switched to LMWH (Fig. 3). However, in four patients there was a gap of up to 5 weeks (#6, #10, #17, and #26), before treatment with LMWH was initiated and in three patients rivaroxaban and LMWH were given concomitantly for 1–3 days. Two patients had to switch from one LMWH to another, one in week 10 and the other in week 29 (#25 and #26). One patient received low dose acetyl salicylic acid for VTE prophylaxis after discontinuation of rivaroxaban (#34). Five patients did not receive further anticoagulation: one patient after knee surgery, two patients for VTE prophylaxis because of long distance flights, two patients with a history of PE, four patients after DVT.

Pregnancy outcomes were six spontaneous abortions, eight elective terminations of pregnancy and 23 live births. The group of pregnant women with spontaneous abortions included one woman with antiphospholipid syndrome (#14; week 10), one with a prosthetic heart valve and opiate co-medication (#11; week 15), one with premature rupture of membranes and histologically confirmed ascending infection (#10; week 16), one with a twin pregnancy (#27, missed abortion in wk 10), one in a women with bicornuate uterus (#32) and only one without known risk factors (#9; week 8). Six pregnancies were terminated for social reasons, one for fear of malformations after rivaroxaban exposure and one after diagnosis of a complex foetal heart defect (#2, see below).

Overall, 23 pregnancies were carried to term; in eight of these pregnancies Caesarean section was performed (#15–19, #24, #26, #30, #31). Mild thrombocytopenia was observed in two women (#5, #17) and interpreted as pregnancy related. Neonatal characteristics are summarised in Table 2.

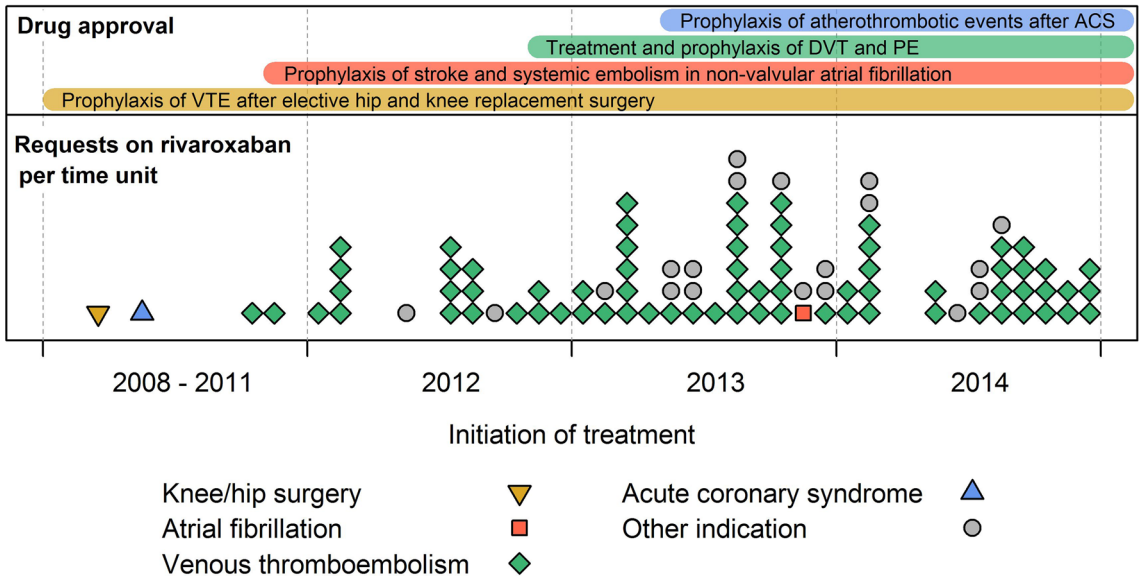

Fig. 2 Treatment indication for rivaroxaban and date of treatment start in 94 patients in relation to the approval status for rivaroxaban indications in Germany over time. For each patient the reported time (month and year) of treatment start is shown. (*ACS* acute coronary syndrome with elevated biomarkers)

There was only one case with a congenital malformation among the 37 prospectively reported pregnancies: a conotruncal cardiac defect leading to termination of pregnancy (case #2). The first pregnancy of this woman 1 year before was not exposed to rivaroxaban, but had also been terminated after prenatal diagnosis of tetralogy of Fallot. She had systemic lupus erythematosus with recurrent VTE necessitating treatment with multiple drugs: tacrolimus, hydroxychloroquine, prednisolone, pantoprazole, ramipril, torasemide, simvastatin, ezetimibe, acetyl salicylic acid, and salbutamol were used throughout her current pregnancy. In addition, she took metamizole and aliskiren during the first trimester. Rivaroxaban was discontinued because of suspected inefficiency and replaced by LMWH, when inferior vena cava and renal thrombosis were diagnosed in week 5 of the—at that time—unknown pregnancy. Preconceptionally, she had been exposed to rituximab and cyclophosphamide.

This patient was the only one in our case series developing thrombosis during pregnancy. No further patients with pregnancy complications were reported that could be attributed to thromboembolic events. Postpartum VTE was not reported in any woman during a median follow-up of 17 weeks after birth.

Outcome of retrospectively reported cases ($n = 2$)

Two pregnancies were reported retrospectively. Treatment with 10 mg rivaroxaban daily had been started in a 37-year-old mother with tetralogy of Fallot after a first episode of atrial fibrillation 8 days before conception and was stopped by the patient 1 week after conception. Pregnancy was complicated by recurrent atrial fibrillation necessitating electric cardioversion at gestational weeks 17 and 20, respectively. Only after the second episode in week 17, anticoagulation was started again with 60 mg enoxaparin twice daily. Intrauterine growth retardation was diagnosed in week 31 and a girl was delivered by Caesarean section at week 33 + 6 days. Neonatal birth weight was 1830 g (35th percentile). After mild hypoglycaemia and episodes of apnoea-bradycardia the infant developed normally.

In another 37-year-old woman rivaroxaban was prescribed 4 months following her first pregnancy complicated by DVT at gestational week 26. Still being on 10 mg rivaroxaban once daily, she got pregnant again. At week 10 a missed abortion was diagnosed necessitating uterine evacuation which was followed by unusually severe bleeding. The embryo was described as having abnormal ("crumpled") limbs. No further details are available for this case.

Discussion

Our case series presents the first data on pregnancies exposed to rivaroxaban including detailed documentation of exposure related to gestational age. Rivaroxaban is an oral factor Xa inhibitor currently approved for several indications [36]. Whereas indications such as VTE prophylaxis in elective hip and knee replacement surgery, stroke prevention in non-valvular atrial fibrillation, and

Table 1 Maternal characteristics of prospective pregnancy cohort ($N = 37$)

	Number (%) or median (interquartile range)
Age ($n = 37$)	29 (25–34)
BMI ($n = 32$)	24.7 (22.8–29.0)
Maternal education ($n = 17$)	
No leaving exam	0 (0)
9 years exam	6 (35.3)
10/11 years exam	7 (41.2)
Secondary school exam	2 (11.8)
Academic study	2 (11.8)
Smoking ($n = 33$)	
No	24 (72.7)
≤5 cigarettes/day	3 (9.1)
>5 cigarettes/day	6 (18.2)
Alcohol ($n = 34$)	
No	32 (94.1)
≤1 drink/day	2 (5.9)
>1 drink/day	0 (0)
Social drugs ($n = 32$)	
Yes	0 (0)
No	32 (100)
Previous pregnancies ($n = 36$)	
0	13 (36.1)
1	10 (27.8)
2 or more	13 (36.1)
Previous parities ($n = 36$)	
0	17 (47.2)
1	8 (22.2)
2 or more	11 (30.6)
Previous miscarriages ($n = 36$)	
0	31 (86.1)
1	4 (11.1)
2 or more	1 (2.8)
Previous elective terminations ($n = 36$)	
0	33 (91.7)
1	3 (8.3)
2 or more	0 (0)
Previous children with birth defect ($n = 36$)	
0	34 (94.4)
1	1 (2.8)
2 or more	1 (2.8)
Week at first TIS contact ($n = 37$)	7.0 (5.9–9.3)

n number of women with available information

prevention of atherothrombotic events after ACS are more prevalent in older patients, the most frequent indication for use of rivaroxaban or other NOACs in women of child-bearing age is treatment and prophylaxis of recurrent VTE [36]. Accordingly, we have noticed a significant increase in rivaroxaban exposures in pregnant women after the approval for the treatment of acute DVT and PE, and for the prevention of recurrent DVT and PE in Germany in November 2012 (Fig. 2). While case reports or smaller case series on the selective and parenteral factor Xa inhibitor fondaparinux totalling at least 65 pregnancies have been published [12, 25, 30], there is only one case on a pregnant patient treated with rivaroxaban published so far [26].

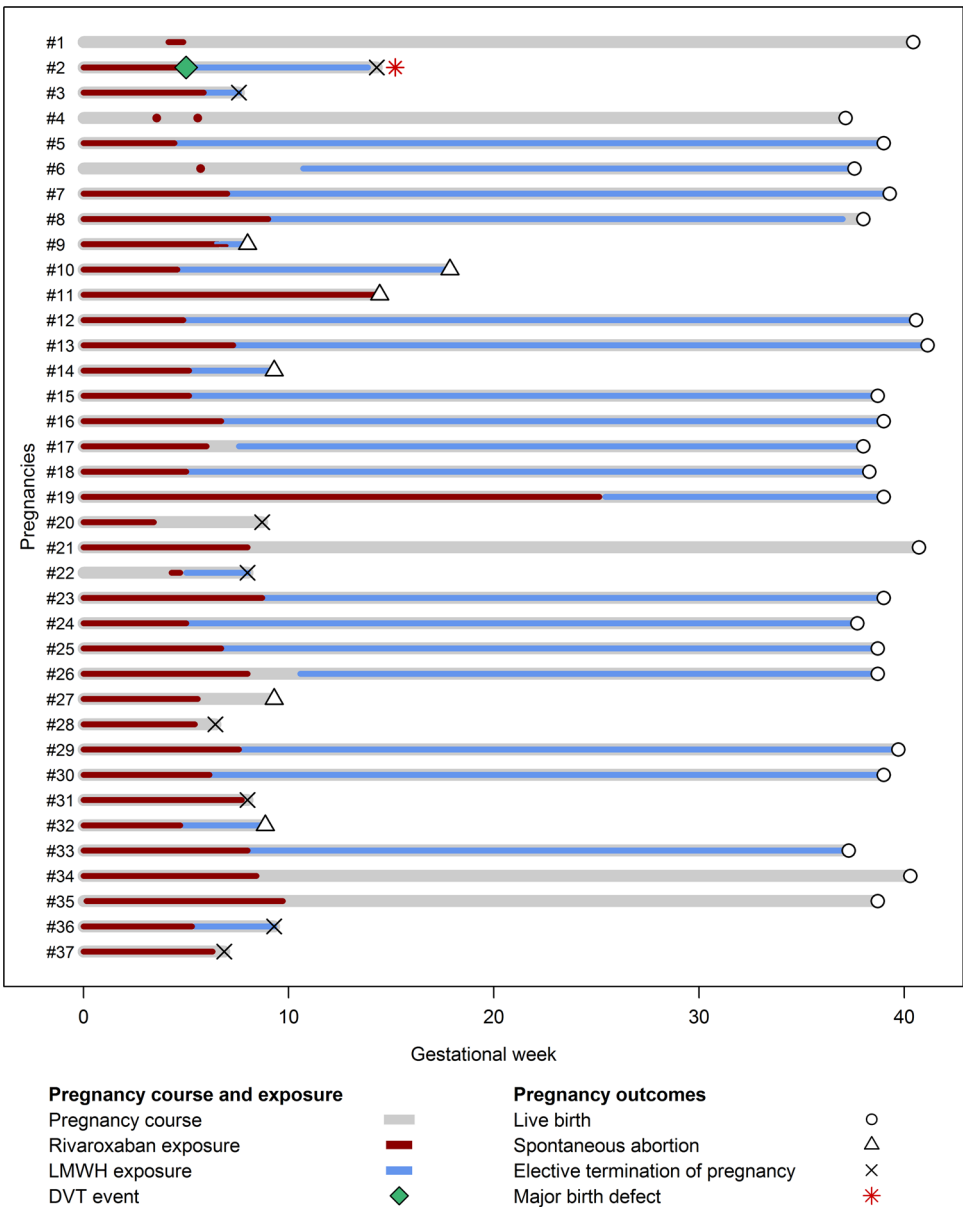

Fig. 3 Exposure to rivaroxaban during pregnancy, continuation of anticoagulation with LMWH and pregnancy outcome in 37 prospectively ascertained pregnancies

Table 2 Neonatal characteristics from prospective cohort ($N = 23$)

	Number (%) or median (interquartile range)
Gestational week at birth ($n = 23$)	39 (38.1–39.5)
Preterm birth ($n = 23$)	
Preterm	0 (0)
Term	23 (100)
Sex ($n = 22$)	
Female	13 (59.1)
Male	9 (40.9)
Birth weight ($n = 22$)	3320 (3035–3580)
Length ($n = 22$)	51 (50–52)
Head circumference ($n = 21$)	34.5 (34–35)

n number of neonates with available information

Compared to established anticoagulants, practical experience with rivaroxaban is still limited and as with any new drug, responsible use of NOACs within the label of approval is an important issue [42]. Whereas a recent study did not observe important off-label use of rivaroxaban in Germany [23], our case series demonstrates that inappropriate dosing and off-label treatment (Fig. 2) occur even during pregnancy although the European Medicines Agency (EMA) has labelled rivaroxaban as contraindicated during pregnancy due to its potential reproductive toxicity and the intrinsic risk of bleeding (product information Xarelto® [13]). According to this product information, embryo-foetal toxicity (post-implantation loss, retarded/progressed ossification, hepatic multiple light-coloured spots) and an increased incidence of common malformations as well as placental changes were observed at clinically relevant plasma concentrations in animal studies with rats and rabbits.

In contrast, the US Food and Drug Administration (FDA) stated that there is no increased malformation risk in rats or rabbits but a decrease in viable rat foetuses after exposure to 41 times the human dose based on surface area. Increased resorption rates and decreased number of live foetuses and decreased foetal body weight were observed when pregnant rabbits were given oral doses that are about four times the human exposure of unbound drug, based on AUC comparisons at the human dose of 20 mg/day [22]. However, animal experiments did not provide evidence of teratogenicity, i.e., an increase of structural malformations [15]. Consequently, the FDA has assigned rivaroxaban to pregnancy category C [22] indicating that animal reproduction studies have shown an adverse effect on the foetus and, although no adequate and well-controlled studies in humans are available, potential benefits may warrant use of the drug in pregnant women despite potential risks [16].

In the more restrictive European approval of rivaroxaban, it is recommended that women of childbearing potential should avoid becoming pregnant during treatment with the drug and should, therefore, practise reliable contraception [13].

In the current case series, we observed only one major malformation documented in the prospective cohort. The mother suffered from severe systemic lupus erythematosus and recurrent VTE and had several co-medications, some of which are insufficiently studied during pregnancy (e.g., aliskiren, ezetimibe) or definitely fetotoxic (e.g., ramipril). Her obstetric history with a previous foetus affected by tetralogy of Fallot (without rivaroxaban exposure) suggests other risk factors or a genetic contribution to the cardiac malformation in both foetuses. Interestingly, Elsaigh et al. [12] reported a foetus with tetralogy of Fallot and Dandy–Walker syndrome after maternal exposure to the parenteral selective factor Xa inhibitor fondaparinux (started in week 7 of pregnancy), but we would consider this as a coincidence, as tetralogy of Fallot is the most frequent cyanotic cardiac defect [3]. Our retrospective case report of an aborted embryo with crumpled limbs might still represent a normal phenotype at that early developmental stage with a body size of 1.5 cm.

The rate of spontaneous abortions of 16 % lies within the expected range in the general pregnant population [5, 8].

Finally, it is noteworthy that one woman receiving rivaroxaban until week 26 delivered a healthy infant. The mother reported two previous spontaneous abortions while being on phenprocoumon, in weeks 22 and 11, respectively.

There was one pregnancy with mild preeclampsia, but no preterm birth reported in the prospective cohort and

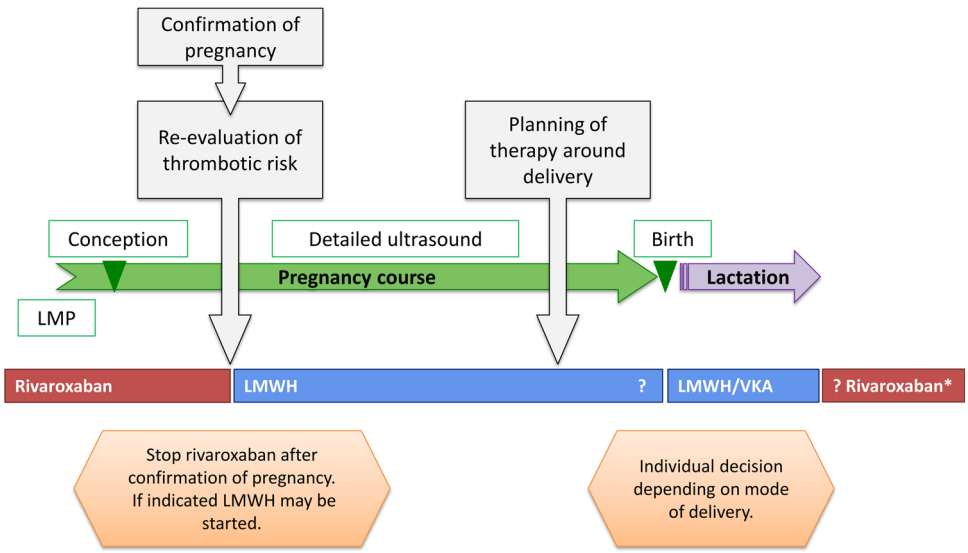

Fig. 4 Proposed procedure after inadvertent treatment with rivaroxaban during pregnancy. Switch from rivaroxaban to LMWH should be decided upon individual risk assessment. The first dose of the replacement anticoagulant (e.g. LMWH) can be given at the time the next dose of rivaroxaban would have been due. LMP, last menstrual period. *Asterisk* indicates individual decision about re-initiation of rivaroxaban after lactation period

only one infant was born preterm among the two retrospective case reports (Table 2).

An increased risk for bleeding complications during pregnancy and around delivery has to be considered in women treated with any anticoagulant including NOACs. While a reduction of intracerebral bleeding events during the treatment with NOACs as compared with VKA is considered as an important advantage of these drugs [34, 43] they may expose specific patient groups to a higher risk for gastrointestinal bleeding events [34]. Moreover, bleeding complications have been observed more frequently in women than in men [2]. In late pregnancy, similar to VKA, rivaroxaban might cause cerebral bleeding in the foetus. Except for one case with an evacuation of a missed abortion we did not observe (maternal) bleeding complications in our case series. However, rivaroxaban exposure was limited to the first trimester in most of the cases. All women of the current case series discontinued rivaroxaban after discovering their pregnancy. A delay of initiation of conversion to LMWH as observed in some of our pregnancies should be avoided in high risk pregnancies, since the switching from rivaroxaban to LMWH therapy can be easily conducted in clinical practice [42] (Fig. 4).

In summary, our observations do not provide evidence of a substantial embryotoxic risk for rivaroxaban during early pregnancy. Therefore, our results may be used to reassure those women, who were inadvertently exposed to rivaroxaban in early pregnancy. These women should be carefully counselled to prevent overestimation of embryotoxic risks. Apart from reconsidering the need of continuous anticoagulation a detailed ultrasound should be recommended to confirm normal foetal development (Fig. 4).

The available data are still insufficient to document safety and to recommend the use of rivaroxaban during pregnancy. Before prescribing rivaroxaban to women of childbearing age they should be advised to use effective birth control. According to the European labelling of rivaroxaban (EMA) as contraindicated during pregnancy, rivaroxaban should be discontinued in unplanned pregnancies. More observational studies on rivaroxaban and other NOACs during pregnancy are required because it appears likely that the number of pregnant women exposed to these drugs will increase in the future.

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Compliance with ethical standards

Conflict of interest MH, EB, KM, CS declare no conflict of interest. RK has been a consultant or participated in advisory boards for Bayer HealthCare, Berlin-Chemie Menarini, Bristol-Myers-Squibb, Daiichi Sankyo and Servier.

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