Management of direct oral anticoagulants in women of childbearing potential: guidance from the SSC of the ISTH

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Scope and methodology

The efficacy, safety, and convenience of direct oral anticoagulants (DOACs) have led to these agents being established as therapeutic alternatives to vitamin K antagonists (VKAs) such as warfarin and becoming the standard of care for a wide range of indications. Licensed indications worldwide for the DOACs dabigatran etexilate (Pradaxa®), a direct thrombin inhibitor, and apixaban (Eliquis®); edoxaban (Lixiana®), and rivaroxaban (Xarelto®), direct factor Xa (FXa) inhibitors, are based on the results of major phase 3 prospective randomized controlled trials and detailed in their respective summary of products characteristics (SPCs) [1–4]. These indications include the treatment and secondary prevention of venous thromboembolism (VTE) [5–12], as well as the prevention of stroke and systemic embolism in patients with nonvalvular atrial fibrillation and acute coronary syndromes [1–4].

Many patients receiving oral anticoagulation for VTE are in their reproductive years, but the potential for reproductive toxicity of DOACs in humans is unknown, and there are no adequate data on the use of DOACs in pregnant women via maternal or paternal exposure. Accordingly, the DOAC SPCs recommend against their use in pregnancy and during breastfeeding [1–3]. However, patients may unintentionally become pregnant while taking DOAC therapy. A case report describes a woman taking therapeutic-dose rivaroxaban during pregnancy, identified at approximately 19 weeks’ gestation, when rivaroxaban was stopped and low molecular weight heparin (LMWH) was substituted. Pregnancy outcome was successful with no abnormalities detected on ultrasound scanning during pregnancy or in the infant [13].

This guidance document addresses the use of DOACs in women of childbearing potential, with particular focus on the preconceptual period, pregnancy and puerperium, and breast-feeding. MEDLINE and PubMed searches were carried out by using the following phrases: new oral anticoagulants, novel oral anticoagulants, direct acting oral anticoagulants, direct inhibitors of coagulation, non-vitamin K antagonist oral anticoagulants, warfarin, Coumadin, dabigatran, apixaban, edoxaban, rivaroxaban, fertility, pregnancy, childbearing age, maternal complications, fetal complications, bleeding, breastfeeding, and postpartum period. Further, information was requested from the manufacturers of the individual DOACs.

The wording ‘we recommend’ indicates a strong consensus among the panel members, whereby the clinician should consider adopting the practice in most cases; ‘we suggest’ reflects a weak guidance statement with moderate consensus among the panel members, whereby the clinician may adopt the guidance statement or use an alternative approach to manage patients; and ‘we propose’ represents a new concept based on limited theoretical knowledge, endorsed by the ISTH Guidance and Guidelines Committee panel [14].

Animal and in vitro studies on DOACs during pregnancy and lactation

Studies in rats and rabbits models have shown DOAC-associated reproductive toxicity as follows: (i) dabigatran: fetal growth restriction and anomalies, and fetal mortality
at doses corresponding to plasma exposure levels 4- to 10-fold higher than observed in patients; (ii) edoxaban: gallbladder anomalies and postimplantation pregnancy loss at approximately 50–65 times the maximum recommended human dose; and (iii) rivaroxaban: postimplantation loss, retarded/progressed ossification, hepatic multiple light-colored spots, and an increased incidence of common malformations as well as placental changes at clinically relevant plasma concentrations. In addition, there was reduced viability of the offspring at toxic doses. Animal studies with apixaban do not indicate reproductive toxicity, although the SPC recommends against apixaban use in pregnancy [1–4]. An effect on female fertility was observed with dabigatran manifested by a reduced likelihood of implantation and increased preimplantation loss at 5 times the plasma exposure level in patients. Apixaban, edoxaban, and rivaroxaban do not appear to affect male or female fertility in rats or rabbits [1–4].

Evidence for the transfer of dabigatran and its prodrug dabigatran etexilate mesylate across the term human placenta from the mother to the fetus has been obtained in a small in vitro study using a human dual perfusion placental model (n = 3) [15]. This study showed that dabigatran crosses the term placenta relatively slowly, reaching a median fetal-to-maternal concentration ratio of 0.33 after 3 h. The prodrug dabigatran etexilate mesylate had limited placental transfer as evidenced by a fetal-to-maternal ratio of 0.17 after 3 h (n = 3).

The distribution and elimination of apixaban were investigated in male, female, and pregnant female rats after a single oral dose of [14C]-labeled apixaban. In pregnant rats, the whole-body autoradiogram showed that low levels of radioactivity were present in fetal blood, liver, and kidney, although these levels of radioactivity were much lower than those in the respective maternal organs [16]. In this study, milk excretion properties in lactating rats after single oral doses of [14C]-labeled apixaban were also investigated [16]. Apixaban exhibited extensive lacteal excretion, representing greater than 96% of sample radioactivity, with the high milk–to–maternal plasma ratio possibly due to active transport into breast milk [2]. In a human placental perfusion model, unbound rivaroxaban was found to cross term placenta rapidly with a similar maternal-to-fetal and fetal-to-maternal ratio of 0.69 (n = 5 and 2, respectively) after 3 h [17].

General considerations regarding maternofetal transfer of DOACs

Extrapolation from observations on placental transfer of DOACs to the human clinical situation requires consideration of the variability of expressions of efflux transporters at different gestations and between species. The placental membrane provides a protective barrier for the developing fetus by reducing the entry of drugs from mother to fetus [18]. Efflux transporters, including breast cancer resistance protein and P-glycoprotein, can transport drugs from the fetal compartment to the maternal circulation and protect the fetus from potential toxicity [19–21].

Other factors that potentially influence the extent of placental transfer include the molecular weight (MW) of the drug and the pKa (pH at which the drug is 50% ionized). Drugs with MW greater than 500 Da achieve incomplete transfer across the human placenta. Strongly dissociated acid drug molecules should display incomplete transfer, but this does not seem to be an absolute rule. The extent of drug binding to plasma protein does not influence the type of drug transfer across the human placenta [22]. Dabigatran is highly polar and exhibits hydrogen bonding [23]; both of these factors can reduce transport across the placental barrier. Although the MW of the prodrug dabigatran etexilate of greater than 500 Da (628 Da) is likely to limit its transfer across the placenta, it is completely hydrolyzed to its active moiety dabigatran, of slightly smaller MW (472 Da), which may increase the likelihood of placental transfer from mother to fetus. The MWs of apixaban, edoxaban and rivaroxaban are 460, 548, and 436 Da, respectively [http://pubchem.ncbi.nlm.nih.gov]. As may be anticipated with these MWs and as detailed here, animal [16] and in vitro studies in a human placental perfusion model [15,17] indicate that apixaban, dabigatran, and rivaroxaban, respectively, exhibit placental transfer.

In addition, gestational age has an important impact on potential teratogenicity and fetal toxicity. In general, during the preimplantation period (from fertilization and to implantation, i.e., up to 4 weeks from the last menstrual bleeding), the effect is all or none—that is, the insult may lead to failure of implantation or a miscarriage or complete recovery, but malformation does not occur. The period of organogenesis is at an embryonic age of 4–8 weeks, which corresponds to a gestational age of 6–10 weeks. This period carries the highest risk for malformation [24]. The risk remains until 20–22 weeks as development continues in some organs such as the brain, genitalia, and palate. After 22 weeks, the risk of teratogenicity and gross structural abnormality is rare, but the risk of fetal toxicity and effect on organ function does not subside. For DOACs, there is also the potential risk of fetal bleeding at any stage of pregnancy, most importantly intracranial bleeding, due to their anticoagulant effect. On the fetomaternal side, there is, in addition, a potential risk of clinical or subclinical placental bleeding, leading to miscarriage, preterm delivery, fetal compromise, and stillbirth.

Clinical studies on DOACs during pregnancy and lactation

No systematic clinical data exist on pregnancy outcome after DOAC exposure. Current scientific literature is limited to the case report given here earlier and the
information herein. The German Embryotox Pharma-
covigilance Centre has reported on 63 pregnancies
exposed to rivaroxaban, 37 of which were ascertained
prospectively, with the outcomes of 6 miscarriages, 8 elec-
tive terminations, and 23 live births. There was one major
malformation (conotruncal cardiac defect) in a woman
with complex medication and a previous fetus with car-
diac malformation without exposure to rivaroxaban [25].
The limited cohort size does not allow ruling out an
increased malformation risk. A case report describes a
patient with new pulmonary embolism 5 days after start-
ing rivaroxaban for a deep vein thrombosis 23 days post-
delivery [26].

Guidance statements on the use of DOACs in women of
cildbearing potential

1 We recommend that all women of childbearing potential
should receive documented counseling prior to commence-
ment of DOACs, with emphasis on avoidance of preg-
nancy while on a DOAC by use of adequate and
appropriate contraception. Women of childbearing
potential should also be advised to contact the clinician
responsible for their anticoagulant care as soon as pos-
sible should there be suspicion of contraceptive failure
and a positive pregnancy test.

2 Should pregnancy be desired, we recommend that the
DOAC is switched to an alternative anticoagulant pre-
conceptually, with the main alternative anticoagulant
options VKAs (to be switched to LMWH as soon as pos-
sible when pregnant and before 6 weeks of gestation), or
LMWH, with cognizance that the latter may result in
prolonged subcutaneous injections until pregnancy is
achieved.

3 In women who unintentionally become pregnant while on
a DOAC, we recommend that the DOAC is discontinued
immediately and LMWH commenced.

4 Based on current information, we recommend that inad-
vertent exposure to a DOAC would not in itself be
regarded as medical grounds for termination of preg-
nancy. Women considering elective pregnancy termina-
tion should receive nondirective counseling, which
should include advice that based on the limited data
available in the literature, DOACs may be considered
Category C (i.e., animal reproduction studies have shown an adverse effect on the fetus and there are no
adequate and well-controlled studies in humans, but
potential benefits may warrant use of the drug in preg-
nant women despite potential risks).

5 In women who become pregnant while on a DOAC and
who decide to continue with pregnancy, we recommend
early obstetric review and fetal monitoring. This should
include discussion of the potential implications of expo-
sure to a DOAC during pregnancy and an early ultra-
sound examination to assess fetal viability and check for
evidence of subchorionic/retroplacental bleeding.

Recommended fetal monitoring includes a detailed first
trimester (11–13 weeks plus 6 days) and anomaly (18–
23 weeks) scan performed by an experienced sonologist.
For cases with DOAC exposure beyond the first trimes-
ter, further ultrasound examinations should be under-
taken to monitor for fetal growth and well-being and
evidence of intracranial bleeding. We propose that the
following are also undertaken during the anomaly scan
where possible, to obtain information on the risks and
effects of DOACs in pregnancy, which may guide man-
gement in the future: fetal echocardiogram as well as
ultrasound examination of cervical length to assess the
risk of preterm delivery, because of the theoretical risk
of anticoagulant-related bleeding, leading to increased
uterine activity and changes in cervical length.

6 We recommend that breastfeeding women should not be
treated with DOACs in the absence of evidence for their
safe use in this situation. Pending further information
on efficacy and safety, we suggest careful assessment,
with consideration of individual patient risk factors,
prior to initiation of DOACs in nonlactating women in
the postpartum period. In addition, women should be
counseled about the importance of adherence to medi-
cation and have regular follow-up to assess progress.

7 We recommend that clinicians should collect data on the
course and outcomes of pregnancy after DOAC exposure
and report findings to DOAC manufacturers and respon-
sible health and regulatory authorities, to improve knowl-
edge on potential risks and harms.

8 We recommend that all cases of DOAC exposure during
pregnancy should also be reported to the international
ISTH registry:

NOAC-use-Inclusion to ensure consistency of data col-
lection.

Addendum

H. Cohen initiated the concept of this guidance and was
involved in collecting literature, interpretation of data,
and writing and revising the manuscript. D. R. Arachchil-
lage was involved in collecting literature, interpretation of
data, and writing and revising the manuscript. S. Middel-
dorp, J. Beyer-Westendorf, and R. Abdul-Kadir were
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