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Experience with direct oral anticoagulants in pregnancy – a systematic review

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Abstract

Objectives: The experience and use of the new direct oral anti coagulants (DOACs) in pregnancy is limited, but as they offer many practical advantages compared to low molecular weight heparin (LMWH), the pursue of their safety is challenging.

Methods: Systematic review of studies in which DOACs were used during pregnancy and the puerperal period (PROSPERO registry-CRD42021237688). Searches were performed on MEDLINE, Embase, Scopus, Web of Science, and Cochrane Library databases, until July 2021 and secondary sources using the MeSH terms 'pregnancy', 'pregnancy complications', 'venous thrombosis', 'congenital abnormalities', 'Factor Xa Inhibitors,' and names of specific DOACs. Search was limited to human studies, with English or French as languages of report.

Results: Literature search yielded 1,989 results which, after duplicate exclusion, resulted in 672 publications. Studies were then screened using the specified eligibility criteria described and studies that did not meet the criteria were excluded, resulting in 21 full text studies to an in-depth analysis and data extraction. Overall, 339 cases of DOACs usage during pregnancy were reported until now. The data demonstrated 56% live births but a miscarriage rate of 22.2% and an elective termination of pregnancy in 21.8%; fetal abnormalities related to DOACs occurred in 3.6%. Our meta-analysis displayed a higher rate of fetal loss and fetal abnormalities with DOACs use compared to LMWH, notwithstanding similar bleeding complications.

Conclusions: The current information available for the 339 cases herein reported does not allow a conclusion that DOACs can be safely used in pregnancy.

Keywords: anticoagulants; direct Factor Xa Inhibitors; direct thrombin inhibitors; pregnancy.

Introduction

Pregnancy can be defined as a pro-coagulant state. As so, during pregnancy there is an increased risk of pulmonary embolism and deep venous thrombosis. Indeed, venous thromboembolism is still an important cause of maternal morbidity and mortality worldwide [1]. Thrombotic challenges during pregnancy can be managed with distinct anticoagulants.

The main therapeutic anti-thrombotic agent recommended in pregnancy is low molecular weight heparin (LMWH), which does not cross the placenta, therefore being innocuous for the fetus. Moreover, recent meta-analysis reported lower occurrence of pregnancy loss when compared with controls and similar rates of bleeding complications, with rare association with fetal anomalies [2]. Nevertheless, it can have adverse reactions, such as immune thrombocytopenia, allergic cutaneous reactions, or a reduction in bone density with extended treatments [3–5]. Also, due to its subcutaneous administration, patient treatment adhesion is often more difficult.

Recognized oral anticoagulants with proven efficiency are vitamin K antagonists such as warfarin, but these go across the placenta and anticoagulate the fetus. Hence, they are rarely used in pregnancy due to their correlation with unfavorable pregnancy outcomes including miscarriage, risk of major birth defects, prematurity, low birth weight, neurodevelopment problems, among others [1].

As so, alternate forms of anticoagulants, safer, equally effective, and simpler to use, are one of the obstetric ambitions, as well as being valuable for other specialties (primary care, cardiology, and cardiovascular surgery).

Most clinical trials have shown that new direct oral anti coagulants (DOACs) have similar efficacy to warfarin and

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LMWH [6], with the significant advantage of being administered orally.

However, the experience and use of these new anticoagulants in pregnancy is limited and needs to be balanced by the potential risk of fetal toxicity. Indeed, the usage of DOACs during pregnancy is mainly assumed by their inadvertent use, not only because their label contraindication during pregnancy, but also as pregnant women are usually not included in clinical studies [1]. Usually, when pregnancy is detected, DOACs medication is switch to LMWH.

This systematic review with meta-analysis aims to evaluate associations of DOACs use in pregnancy with adverse maternal and fetal outcomes, including thrombotic events, pregnancy-related bleeding, pregnancy loss, and fetal anomalies.

Methods

The present protocol has been registered within the PROSPERO database (registration number CRD42021237688) and is being reported in accordance with the reporting guidance provided in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (see checklist in Supplementary Material, file 1).

Eligibility criteria

The inclusion criteria strictly applied were articles concerning pregnant women taking DOACs for prophylaxis or treatment of thromboembolic events during pregnancy; data concerning thromboembolic events during pregnancy; and maternal and fetal outcomes.

Exclusion criteria used: missing data from thromboembolic events during pregnancy or/and maternal and fetal outcomes; and no information about which direct oral anticoagulants was used.

Information sources and search strategy

Searches were performed on electronic databases MEDLINE (from 1966), Embase (from 1974), Scopus, Web of Science, and Cochrane Library, until July 2021. Secondary sources of literature consisted of gray literature such as theses and dissertations, pharmacovigilance reports, case series notifications or conference papers, handsearching of the reference lists of included studies, relevant reviews, or clinical practice guidelines. The literature searches were designed and conducted by the review team ALA and AMP.

Full electronic search (Scopus)

TITLE-ABS-KEY (“pregnancy OR pregnancy complications”) OR TITLE-ABS-KEY (“venous thrombosis”) OR TITLE-ABS-KEY (“congenital abnormalities”) AND TITLE-ABS-KEY (“Factor Xa Inhibitors”).

Study selection

There was no restriction on the length of study follow-up time, country, or year of publication. However, the search was limited to human studies, with English or French as languages of report. The following Medical Subject Headings (MeSH) were used: ‘pregnancy’, ‘pregnancy complications’, ‘venous thrombosis’, ‘congenital abnormalities’, ‘Factor Xa Inhibitors,’ and names of specific anticoagulants (rivaroxaban, apixaban, dabigatran, and edoxaban).

We included all studies which reported the use of DOACs during pregnancy or one-month post-partum.

Data extraction

Analyze the titles and abstracts (two researchers); discuss differences between the choices and arrange a consensual final choice (two researchers); read the full text of the chosen articles (two researchers) and analyze the results (two researchers); disagreements were solved by debate between the two authors. An Excel file was used to register all options. Finally original authors were contacted for missing or need for extra data.

Variables for which data were sought were gestational age beginning treatment; reason for treatment; type of anticoagulant used; trimester of pregnancy with exposure to DOACs, length of treatment with DOACs, pregnancy outcome with fetal malformations; and adverse maternal or neonatal outcomes.

Results

Study selection

The PRISMA flow diagram showing the inclusion and exclusion criteria of published articles can be found in Supplementary Material, file 2.

Literature search from all databases yielded 1,989 results which, after duplicate exclusion, resulted in 672 references. Studies were then screened using the specified eligibility criteria described above and studies that did not meet the criteria were excluded, resulting in 21 full text studies to an in-depth analysis and data extraction. A review of the reference lists of these articles added also relevant citations. All levels of screening were conducted by two independent reviewers and any disputes between reviewers were solved by active discussion and unanimous agreement. None of the reviewers were blinded to titles, authors, journals, or institutions.

In total, seven articles were included in this review [1, 7–13].

Study characteristics

After thorough/exhaustive literature examination, the seven articles included in this systematic review consisted

of one previous systematic review performed in 2018 [1], one retrospective cohort study [10], two series reports [7, 8], and three case reports [11–13]. Some of the articles had intermingling cases, which made it very difficult for the authors to ascertain that there were no case duplicates. Only cases with known outcomes were included in the analysis.

After reading all articles, pharmacovigilance reports, case series notifications and excluding all repeated reports, our research disclosed 339 cases of DOACs exposure during pregnancy. These 339 cases concerned the use of rivaroxaban (263), apixaban (39), edoxaban (20), and dabigatran (17).

As for DOACs time of exposure, data were available only for 161 patients; in the majority, exposition was in the first trimester (145), leaving 11 cases in the second trimester and five cases in the third trimester or beyond.

All cases reported DOACs use for prophylaxis or treatment of venous thromboembolism, with one case report of potential failure associated with rivaroxaban therapy in the post-partum period [11] and one other report related to dabigatran use in a pregnant woman with a mechanical prosthetic heart valve [12].

There were 189 live births, 74 elective terminations of pregnancy, 74 miscarriages, and 21 fetal anomalies (Table 1).

Moreover, from the 21 fetal abnormalities reported, a possible correlation with DOACs exposure in a worst-case analysis was 3.6% (12/338) [10].

Placental changes due to DOACs could feasibly lead to growth restriction [9], but after excluding other factors (as smoking, advanced maternal age, hypertension, amongst others), all authors reported similar rates as in the general population.

There were no perinatal deaths or maternal deaths. Also, none of the reports referred major bleeding complications.

Table 1: Pregnancy outcome following DOACs exposure (total of 338 cases as one case was in the puerperium).

Outcomes n=338	Live births	Miscarriages	Elective termination of pregnancy	Fetal anomalies
Total number, n, %	**189 (56%)**	**75 (22.2%)**	**74 (21.8%)**	**12 (3.6%)**
Rivaroxaban	146	61	55	9
Apixaban	22	10	7	2
Edoxaban	15	1	4	1
Dabigatran	6	3	8	–

DOACs, direct oral anti coagulants.

Risk of bias within studies and across studies

Due to study designs a clear risk of bias evaluation could not be conducted; nevertheless, possibly reporting, selection, and publication bias need be considered.

Indeed, despite all efforts to reduce the risk of bias and to increase data quality, the presented analysis may suffer from selection bias, as other databases could have been included. Moreover, selective reporting bias could not be ruled out by including data from manufacturers. Also, we only included published studies, so the findings may not be accurate because of publication bias.

Discussion

Main findings, strengths, and limitations

Our systematic review assessed 339 cases of DOACs usage during pregnancy reported in the literature until now.

Concerning fetal outcomes, the data demonstrated 56% live births but a 22.2% miscarriage rate and an elective termination of pregnancy of 21.8%, with a 3.6% rate of fetal abnormalities associated with DOACs use.

Regarding maternal outcomes, noteworthy is the underreport of thrombotic and bleeding complications in most reports. Additionally, miscarriages could be prompted by the production of placental related bleeding that may not have been classified by any author as a bleeding complication.

Nonetheless, most authors say that current data do not raise concerns about these hurdles since most investigations had comparable bleeding complications to other studies using anticoagulation in pregnancy [1].

The most recent meta-analysis about LMWH use in pregnancy revealed a 13.9% rate of fetal loss, a 2.1% of congenital malformations and 12.2% bleeding complications [2]. As so, our meta-analysis displayed a considerably higher rate of fetal loss and fetal abnormalities with DOACs use compared to LMWH, albeit similar bleeding complications.

The main strength of the present study is the distinctiveness of the meta-analysis, since to the best of our knowledge this is the first meta-analysis conveying data from such different sources. Moreover, several strict inclusion criteria were used, and a meticulous literature review using PRISMA guidelines was conducted.

However, the quality of our systematic review was restricted by the absence of randomized studies; incomplete data since most publications are retrospective series; and selection and publication bias. Furthermore, a relevant

limitation is the overall missing information regarding the duration of DOACs treatment during pregnancy, which could represent a major influence in the outcomes.

Interpretation

Pregnant women are excluded from participation in all published trials of DOACs.

Since 2013, when the first article was published about these new anticoagulants use in pregnancy [6], that DOACs use has been pursued. DOACs seem like the optimal anticoagulation agent as can be given orally; with a fixed dosage; without the need of biologic control; acting in a specific and reversible way in coagulation factors; and having rapid effects [14]. Unfortunately, their use in pregnancy is still questionable.

Tang et al. [6] performed a systematic review about new anticoagulants in pregnancy (but not DOACs), stating that although with limited evidence, fondaparinux, hirudin, and argotroban appeared not to have adverse pregnancy outcomes.

Lameijer et al. [1] subsequently performed a systematic search reporting 236 cases of DOACs use in pregnancy but with only 140 pregnancies with full data, revealing 68% live births but 31% of miscarriages. This high miscarriage rate was related to the embryotoxic effects of DOACs, with the possibility of an even higher rate due to a possible underestimation owing to DOACs discontinuation within the first two months of pregnancy.

Also, Sessa et al. [15] evaluated cases describing DOACs-induced adverse events; their study demonstrated that there was no evidence for an increased probability of registering spontaneous abortion rather than other adverse events for rivaroxaban when it was compared to all other drugs included. On the contrary, for apixaban, there was an increased probability of reporting spontaneous or induced abortion when compared to all other drugs, warfarin, or rivaroxaban. As so, their results did not allow drawing any conclusions.

Some reports suggested potential teratogenic effects in women taking DOACs in the first trimester [1, 16], whilst others maintained the idea that DOACs use is not associated with an unbalanced reporting of spontaneous abortion [15].

More recently, un update of DOACs exposure pointed out that a proportion of birth defects and other abnormalities is low, which could be reassuring not only for a lower embryotoxicity than vitamin K antagonists (6 to 7% based in studies reported in Beyer-Westendorf et al.) but also for a miscarriage rate similar to the overall population [10].

An increased risk for bleeding complications during pregnancy and around delivery must be considered in these women. While a decrease of intracerebral bleeding events during the treatment with DOACs as compared with vitamin K antagonists is considered as an important benefit [7], specific concerns surrounding delivery are understandable. Nevertheless, most investigations had comparable bleeding problems to other studies using anticoagulation in pregnancy.

Conclusions

Our systematic review disclosed an overall 56% rate of live births but 22.2% miscarriages and 21.8% elective terminations of pregnancy, along with 3.6% fetal abnormalities rates related to DOACs use; these rates are higher than those reported for LMWH use, the therapeutic alternative currently available.

Consequently, from the gathering of the existing information available for the 339 cases herein reported, it is not possible to conclude that DOACs can be safely use in pregnancy.

Therefore, for now, DOACs prescription/use during pregnancy cannot be encouraged.

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