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Full Length Article

Oral contraception and menstrual bleeding during treatment of venous thromboembolism: Expert opinion versus current practice Combined results of a systematic review, expert panel opinion and an international survey

F.A. Klok [a,*], K. Schreiber [b,c], K. Stach [d], W. Ageno [e], S. Middeldorp [f], S. Eichinger [g], A. Delluc [h], M. Blondon [i], C. Ay [g]

[a] Department of Thrombosis and Hemostasis, Leiden University Medical Center, Leiden, The Netherlands
[b] Thrombosis & Thrombophilia, Guy's & St Thomas' Hospital, London SE1 7EH, United Kingdom
[c] Department of Rheumatology, Copenhagen University Hospital at Rigshospitalet, Denmark
[d] 1st Department of Medicine, University Medical Centre Mannheim, Medical Faculty Mannheim, University of Heidelberg, Germany
[e] Department of Clinical and Experimental Medicine, University of Insubria, Varese, Italy
[f] Department of Vascular Medicine, Academic Medical Center, Amsterdam, The Netherlands
[g] Department of Medicine I, Clinical Division of Haematology and Haemostaseology, Medical University Hospital, Vienna, Austria
[h] Département de Médicine interne et de Pneumologie, Hôpital de la Cavale Blanche, Brest, France
[i] Department of Angiology and Haemostasis, Geneva University Hospital, Geneva, Switzerland

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ABSTRACT

Introduction: The optimal management of oral contraception and menstrual bleeding during treatment of venous thromboembolism (VTE) is largely unknown. We aimed to elicit expert opinion and compare that to current practice as assessed by a world-wide international web-based survey among physicians.
Methods: 10 international thrombosis experts and 10 abnormal uterine bleeding experts independently completed a questionnaire containing three hypothetical patient cases each with four different scenarios, and additional queries covering different severities of VTE, patient circumstances, hormonal contraceptives and both thrombotic and bleeding complications. The consensus percentage was set a priori at ≥70%. The same questionnaire with randomized case scenarios was presented to international physicians via newsletters of the ISTH and national scientific communities. Differences between the expert groups and daily clinical care were assessed.
Results: Expert recommendations were divergent and differed in several important points from clinical practice. In contrast to common practice in which contraceptives are discontinued at the moment of a VTE diagnosis, the thrombosis experts agreed to continue oral contraception (OC) during the anticoagulation treatment period. Also, experts reached consensus on treating patients with anticoagulation-associated abnormal uterine bleeding with tranexamic acid, although this is not supported by strong evidence from the literature. No consensus was reached on the optimal anticoagulant drug class.
Conclusions: International experts' opinions on handling of contraceptives and management of anticoagulant-associated abnormal uterine bleeding in female VTE patients are divergent and management in clinical practice is heterogeneous. There is a great need of further studies on these topics.

1. Introduction

The use of hormonal contraceptives is common among women of childbearing age. The risk of venous thromboembolism (VTE) is three to six-fold higher in users of oral contraceptives (OC) than in non-users [1–4]. This excess risk is mainly determined by the estrogen dose and progestin component [1–3,5,6]. Patients with hormone-associated VTE receive anticoagulant treatment for at least three months and are instructed to discontinue OC, as the risk of VTE recurrence is low after discontinuation of hormonal therapy [7–9]. The optimal timing of OC withdrawal is however uncertain, although the only study that evaluated this issue did not find an association between active hormone therapy during treatment with anticoagulants with risk of VTE recurrence [10].

Notably, adequate contraceptive measures are required in women of childbearing age receiving oral anticoagulation for treatment of VTE, because vitamin-K antagonists (VKAs) have the potential to cross the placenta and have been associated with embryopathies and foetal

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* Corresponding author at: Department of Thrombosis and Hemostasis, Leiden University Medical Center, Albinusdreef 2, 2300 RC Leiden, The Netherlands.
E-mail address: f.a.klok@LUMC.nl (F.A. Klok).

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haemorrhage [11]. High quality clinical data on reproductive toxicity of the direct oral anticoagulants (DOACs) is still lacking [12]. According to preclinical studies this remains a major concern [13,14]. In addition, the risk of abnormal uterine bleeding in women of childbearing age treated with anticoagulant drugs is increased, and hormonal treatment with OC is often required to reduce the severity of bleeding [15].

As no clear evidence-based guidance exists for how to manage OC at the moment of a thrombotic event, i.e. when to discontinue OC and which contraceptive strategy to choose during oral anticoagulant treatment, physicians are left with a management dilemma. The World Health Organization (WHO) suggests discontinuation of all estrogen-containing OC at the moment of VTE diagnosis, but in sharp contrast, the Scientific and Standardization Committee (SSC) of the International Society on Thrombosis and Haemostasis (ISTH) recommends continuation of OC for the duration of the anticoagulant therapy [16,17].

Given the absence of clinical trials assessing the optimal management of hormonal contraception at the time of a VTE diagnosis as well as the paucity of prognostic studies addressing the outcomes associated with continuing or discontinuing OCs, we aimed to elicit expert opinion (experts included both thrombosis and abnormal uterine bleeding experts) and compare that to current practice as assessed by a worldwide international web-based survey among physicians. In addition, we performed a systematic review of the literature.

2. Materials and methods

2.1. Data sources and selection of articles for the systematic review:

A literature search was performed to identify all published studies on (1) the risks of thrombotic complications after continuing, discontinuation or initiating hormonal contraceptives at the start of anticoagulation treatment and (2) the risks of and treatment options for anticoagulant-associated abnormal uterine bleeding. Medline and EMBASE were searched using predefined search terms between January 1980 and August 2015. Search criteria included “venous thromboembolism” or “deep vein thrombosis” or “pulmonary embolism”, “contraceptive agents”, “anticoagulation treatment” and “menstrual bleeding”. The complete search string is available in Appendix B. Search results from the different databases were combined and duplicates were removed. Further, we searched the reference lists of the selected studies for additional relevant articles. Articles were limited to the English, French, German or Dutch language.

Studies were screened for relevance by six of the authors on the basis of title and abstract. Full-text articles identified by each of the six authors as potentially relevant were retrieved for further evaluation. Final decision on inclusion was based on consensus. Inclusion criteria for eligible studies were randomized controlled trials, cohort studies or case series of at least 10 patients, concerning female patients with hormonal contraceptive-associated VTE addressing the management of the contraceptive method at moment of VTE diagnosis as well as either recurrent VTE or abnormal uterine bleeding during anticoagulant treatment. In addition, randomized controlled trials, cohort studies or case series of at least 10 patients describing the management of anticoagulant-associated abnormal uterine bleeding in patients with established VTE were included as well.

2.2. Expert panel opinion

We acquired the clinical judgment of two panels of key opinion leaders by selecting and questioning 10 international clinical thrombosis experts as well as 10 international abnormal uterine bleeding experts, the latter who are all gynaecologists (names are detailed in the acknowledgement section). A questionnaire consisting of three hypothetical patient cases each with four different scenarios, and additional queries for a total of 44 questions was designed by the investigators (Appendix A). The clinical case scenario's covered different severities of VTE, different patient comorbidities/circumstances and different hormonal contraceptives, with questions regarding the management of OC and its timing. The remaining multiple-choice questions focused on the management and severity of menstrual bleeding under anticoagulation treatment and best practices with regard to choice of anticoagulant class, contraceptive method and timing of OC modification. Selected experts were contacted by email and asked to complete the survey. They were unaware of each other's answers.

2.3. International survey

To compare expert opinion to current practice patterns, we also performed an international web-based survey which was identical to the expert opinion analysis. In the survey, we randomized the four possible scenarios in each of the three hypothetical clinical cases by blocks of four. By doing so, all respondents were presented with only one of the 4 possible scenarios per clinical case (Appendix A) and this allowed us to estimate the influence of the randomized factors on physicians' management of OC. Further, this shortened the survey which might lead to a higher response rate and less potential for participation bias. The randomized factors were (1) the type of VTE (PE vs. DVT, unprovoked vs. provoked), (2) the type of contraception at the time of VTE (combined estrogen-progestin pill vs. progestin-only pill), (3) the duration of use of contraception prior to the VTE (2 months vs. 12 years) and (4) the presence of thrombophilia (factor V Leiden heterozygote and homozygote, antiphospholipid antibodies). The questionnaire was published online using survey monkey (www.surveymonkey.com) and presented to predefined groups of physicians practicing in various relevant disciplines across all ISTH members in addition to local scientific communities in the countries of the authors via newsletters. The survey was mentioned in 3 consecutive ISTH newsletters, which are distributed among ~20.000 members.

2.4. Statistical methods

With regard to the systematic review, we planned a narrative description of the results of our two primary endpoints in the identified relevant articles. We aimed to study at least 300 competed surveys in the international part of the study. Data of surveys were analysed using descriptive statistics and presented in tables and boxplots. To correct for incomplete responses, proportions were calculated based on the number of respondents per question. The consensus percentage for the expert opinion analyses was set a priori at 70% or more. Subanalysis of the international survey by specialty (internist/haematologist/angiologist, pulmonary physician, cardiologist, emergency physician, gynaecologist) and for different grades of experience were performed. We used a Chi2 test to estimate the influence of randomized factors on the management of OC by the international survey respondents, with an alpha threshold of 0.05. SPSS version 22.0 (SPSS Inc., Chicago, IL) and Stata 11 (StataCorp LP, College Station, Texas) were used to perform all analysis.

3. Results

3.1. Results of the systematic review

A total of 240 studies were identified by the literature search. Based on title and abstract, 12 papers were selected for full review (Appendix C). Of these, seven were excluded: three concerned the first timespan after anticoagulation cessation [18–20] and four included patients with an indication to anticoagulation treatment different from VTE [21–24]. Six additional relevant studies published after the completion of the literature search were additionally included, for a total of 11 relevant articles [10;25–34]. The study characteristics and results are summarized in Appendix D. Nine of eleven studies were of low quality due to an observational design and low sample size. They indicated