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Communication from the ISTH SSC Subcommittee on Women's Health Issues in Thrombosis and Haemostasis: A Survey on Anticoagulation for Mechanical Heart Valves in Pregnancy

Recommendations and guidelines

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1. Introduction

Patients with mechanical heart valves (MHV)s require life-long anticoagulation to prevent thromboembolic complications (TECs). Women with MHVs in pregnancy experience an increased risk of severe maternal morbidity and mortality from both thrombotic and bleeding complications. A large international registry of pregnancies with MHVs revealed that valve thrombosis and maternal mortality occurred in 4.7% and 1.4% of women, respectively, and hemorrhage complicated 23% of pregnancies [1]. Of importance, only 58% of women with MHVs were free from serious adverse events during pregnancy compared with 79% of women with bioprosthetic valves and 78% of women with cardiac disease and no prosthetic valves [1].

Vitamin K antagonists (VKAs), such as warfarin, are the standard anticoagulation modality for non-pregnant patients with MHVs. However, VKAs readily traverse the placenta and are teratogenic. Indeed, warfarin-associated embryopathy may occur with first-trimester VKA exposure consisting of developmental anomalies affecting bones and cartilage [2,3]. Moreover, administration of VKAs in the second and third trimesters can lead to a warfarin-associated fetopathy, characterized by central nervous system anomalies potentially from microhemorrhages in brain tissue [2,3].

Alternative options to VKAs are low molecular weight heparins (LMWHs). However, LMWHs have been associated with higher frequency of maternal valvular thrombosis and mortality, and their use for anticoagulation of MHVs remains off-label [4]. The main options for anticoagulation regimens have been described in pregnancy with the aim of reducing maternal fetal risks include (a) VKAs throughout pregnancy, (b) LMWH throughout pregnancy, (c) LMWH in the first trimester and VKAs in the second and third trimester (sequential treatment), and (d) unfractionated heparin (UFH) throughout pregnancy [5,6]. Outcomes associated with these strategies have predominantly been described by observational studies, which are inherently at increased risk of bias [4]. In addition, society guidelines have mostly issued recommendations regarding the choice of anticoagulation modality [5], and practices regarding adjunctive antiplatelet therapy in pregnancy are not well described. The optimal anticoagulation management strategy for pregnant women with MHVs thus has not yet been determined. Assessing current anticoagulation practice is a necessary step for planning of future prospective studies. Thus, we sought determine practice patterns for anticoagulation therapy for pregnant women with MHVs by conducting an international survey.

2. Methods

2.1. Survey development

We conducted a cross-sectional study using online questionnaires to be administered and filled out by respondents. The survey was sent to hematologists, cardiologists, obstetric medicine physicians, and obstetricians internationally in collaboration with the Subcommittee on Women's Health Issues in Thrombosis and Haemostasis of the ISTH. Approvals were obtained from the institutional review

boards of Mount Sinai Hospital in Toronto, Ontario (IRB#19-0045-E), and the McGill University Health Centre in Montreal, Quebec (IRB#2020-5819), for this survey.

An electronic questionnaire was developed according to previously published techniques [7]. The final survey instrument included two case scenarios: a patient with a mitral MHV and a patient with an aortic MHV, as these are the two most common MHVs. Partially close-ended questions addressed (a) type of anticoagulation (ie, LMWH, VKA, UFH, dosing of LMWH) on the basis of a previous reviews of anticoagulation regimens for MHV in pregnancy [4]; (b) low-dose ASA use because low-dose ASA may improve outcomes, yet has been associated with an increased bleeding risk [1]; (c) peripartum management (including regional anesthesia and mode of delivery) because minimal data on peripartum management are available; and (d) postpartum anticoagulation regimens because increased bleeding risk with early transition to VKAs postpartum has been described [8]. To gauge whether additional clinical factors could potentially affect decisions for anticoagulation selection during pregnancy, a partially close-ended question listed several characteristics including an option to select other characteristics. Because a dose-dependent teratogenic effect of VKAs has been suggested [9], we aimed to assess whether anticoagulation choices depended on the equivalent of a warfarin dose of ≤5 mg orally daily [5].

To permit for an analysis of potential physician variables that may be associated with decisions regarding anticoagulation, the following physician characteristics were gathered: years of practice, physician specialty, type of practice (primary, secondary, or tertiary health care center), and continent of practice. The survey instrument was pilot tested by investigators, resident physicians, and members of the ISTH for validity and clarity. Modifications to the survey were made based on this feedback. The complete survey instrument can be found in the Supplementary Appendix.

2.2. Study participants

Potential participants included all members of the ISTH, the North American Society of Obstetric Medicine, and the International Society of Obstetric Medicine. These societies were selected because they were believed to represent worldwide physicians most likely to be primarily managing anticoagulation for pregnant women with MHVs. In addition, researchers who published studies on the use anticoagulation for MHVs in pregnancy previously identified by the investigative team in a systematic review of the use of anticoagulation in pregnant patients with MHVs were also invited to participate. All potential respondents were asked to participate by email invitation sent out by their respective societies. The following screening question assessed their eligibility to participate: «Do you manage anticoagulants in pregnant patients with mechanical heart valve replacements?»

2.3. Survey administration

The survey was administered using the REDCap software platform [10], hosted by ISTH. We adopted several strategies to try to maximize the response rates by developing a respondent-friendly questionnaire and making several contacts with each subject [1]. The survey was open to respondents from September 24, 2019, to April 20, 2020.

2.4. Statistical methods

The numbers and proportion of physicians selecting response categories was described for each case scenario. We hypothesized that responses could potentially vary according to physicians' training experience, and location of practice. Thus, we assessed the association between physician characteristics (ie, specialty, years of practice, and continent of practice) and the respondents' choice of anticoagulation modality and dose adjustment practices for LMWH using chi-squared test or Fisher's exact test, as appropriate. The proportion missing for these analyses were less than 5%; thus, complete case analysis was used. All statistical analyses were performed using IBM SPSS version 26, 2019. Significant associations were defined if P values were less than .05.

3. Results

3.1. Characteristics of respondents

A total of 121 potential participants answered the initial survey screening question for eligibility, and 84 (69%) were involved in anticoagulation management of these patients. Respondents were from

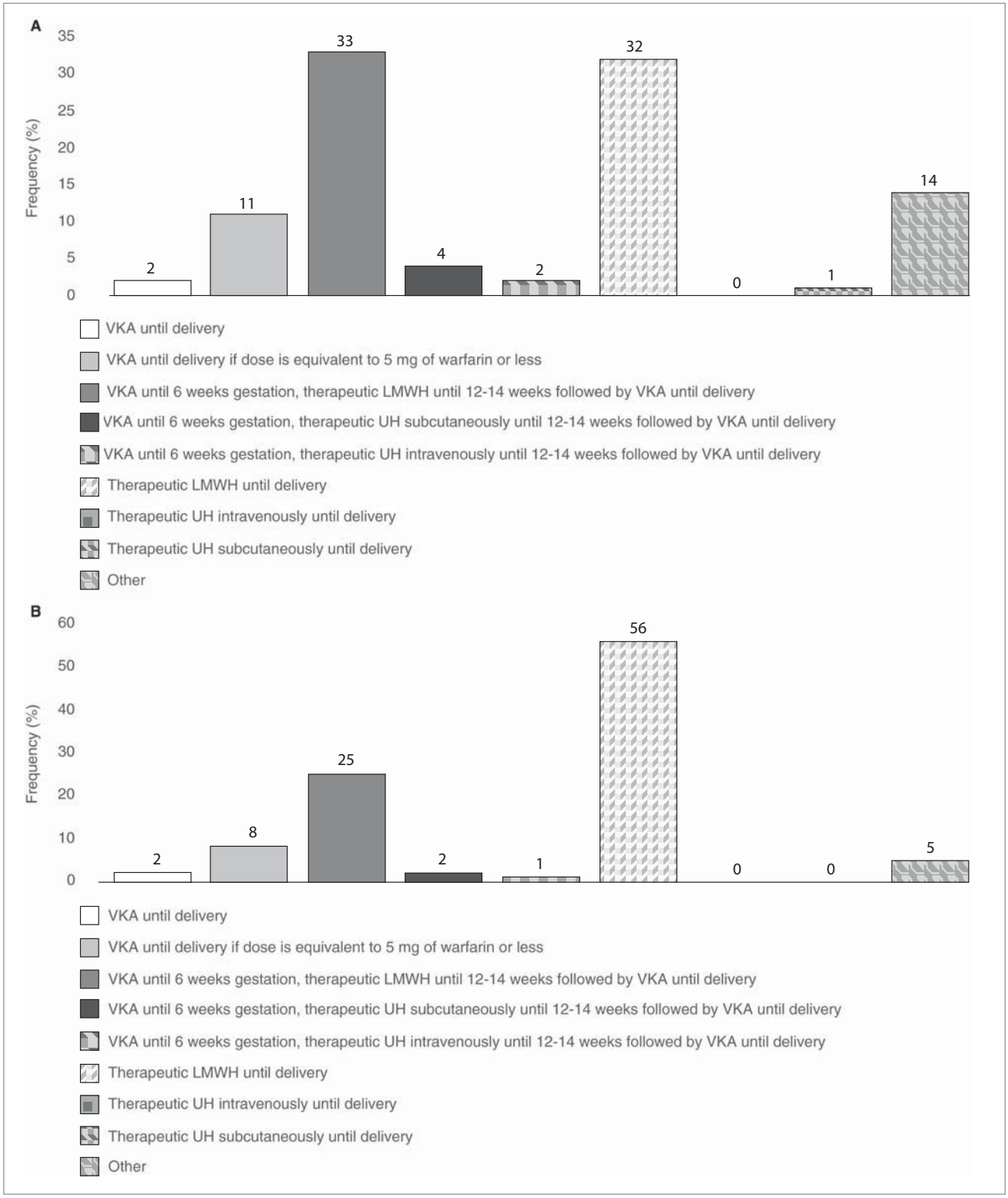

Fig. 1. A — Distribution of practices for anticoagulation among women with mitral mechanical heart valves; B — Distribution of practices for anticoagulation among women with aortic mechanical heart valves. LMWH, low molecular weight heparin; UFH, unfractionated heparin; VKA, vitamin K antagonists

the specialties of hematology/thrombosis (n=49; 61%), obstetric medicine (14; 17.5%), cardiology (n=8; 10%), and maternal fetal medicine (n=3; 3.8%). They almost exclusively practiced in tertiary referral hospitals (n=74; 89%), and were in mid-late career, having practiced for >11 years after completion of training (n=55; 65%). Participants were clinicians from Europe (n=35; 42%), North America (n=31; 37%), Asia (n=8; 10%), South America (n=5; 6%), Africa (n=3; 4%), and Australia and

Table 1

Factors considered when choosing anticoagulation modality

Factors Considered	Respondents n (%)
Type of valve	59 (70)
Location of the replacement valve	54 (64)
Previous embolic event	53 (63)
Patient preference	50 (60)
Presence of atrial fibrillation	41 (49)
Availability of anti-Xa testing if LMWH used	39 (46)
Number of valves	37 (44)
Clinical guidelines	33 (39)
Dose of warfarin	28 (33)
Availability of LMWH	23 (27)
Presence of left ventricular dysfunction	21 (25)
Presence of left atrial dilatation	19 (23)
Cost	14 (17)
I use only one anticoagulant in all patients	8 (10)

Note: Abbreviations: LMWH, low molecular weight heparin.

New Zealand (n=2; 2%). Most centers (n=48; 62%) saw fewer than 5 pregnant patients with MHVs per year, and therefore most respondents (n=61; 78%) reported managing fewer than 5 cases per year.

3.2. Choice of anticoagulation modality

The most commonly used anticoagulation regimens for mitral MHVs in pregnancy were sequential therapy with therapeutic LMWH at 12 to 14 weeks followed by a VKA through the remaining pregnancy (n=28; 33%), therapeutic LMWH throughout pregnancy (n=27; 32%), and VKAs throughout pregnancy if the dose was equivalent to ≤5 mg of warfarin daily (n=9; 11%) (Fig. 1A). No respondents chose UFH as the anticoagulant of choice for women with mitral MHVs. The most commonly used anticoagulation regimens for pregnant women with aortic MHVs were therapeutic LMWH throughout pregnancy (n=47; 56%), therapeutic LMWH until 12 to 14 weeks followed by a VKA throughout remaining pregnancy (n=21; 25%), and VKAs throughout pregnancy if the dose was equivalent to ≤5 mg of warfarin daily (n=7; 8%) (Fig. 1B). Aspirin was selected by 31 (37%) participants, predominantly from the first trimester onward (n=25/31; 80%), among women with either mitral or aortic MHVs receiving LMWH in 14/31 (47%), and women with either mitral or aortic MHVs regardless of anticoagulation modality in 9/31 (30%).

Factors considered when choosing the anticoagulation modality are described in Table 1. Four characteristics were selected by the majority (>60%) of respondents, the type of valve, the location of the replacement valve, previous embolic event, and patient preference. Cost was selected by 17% of respondents. Anticoagulation selection for mitral MHVs varied according to specialty, but not according to years or continent of practice (Table S1 of the Supplementary Appendix). Anticoagulation selection for aortic MHVs varied according to specialty and continent of practice (Table S2 of the Supplementary Appendix).

3.3. Antithrombotic selection and dosing

Seventy-seven (92%) respondents reported LMWH use in pregnancy. Although most respondents decided on the initial LMWH dose based on pregnancy weight (n=52; 68%), some used prepregnancy weight (n=22; 29%). Adjustments to LMWH dosage were made according to pregnancy weight, peak anti-Xa (n=22; 29%), peak and trough anti-Xa (n=20; 26%), peak anti-Xa only (n=20; 26%), or pregnancy weight only (n=11; 14%). Hematology/thrombosis specialists predominantly used peak anti-Xa (n=15; 31%). Dosage adjustments did not vary according to a respondent's characteristics (Table S3 of the Supplementary Appendix).

Fifty (60%) respondents reported VKA use in pregnancy. Most reported aiming for an international normalized ratio (INR) of 2 to 3 for pregnant women with aortic MHVs and 2.5 to 3.5 for mitral MHVs (n=33; 66%). Some respondents, however, aimed for INR of 2.5 to 3.5 (n=5; 10%) and INR of 2 to 3, (n=8; 16%) regardless of valve position.

3.4. Antithrombotic management during labor and delivery

Epidural anesthesia was the preferred mode of peripartum analgesia (n=35; 44%). The preferred mode of delivery was based on obstetrical indications for most respondents (n=44; 55%), whereas vaginal and a cesarean delivery was specified for 29 (36%) and 7 (9%) individuals, respectively. VKAs were resumed 24 to 72 hours following delivery in 38 (48%) respondents, and within 24 hours (n=15; 19%) or 7 days after delivery (n=15; 19%) for others.

Aspirin was either discontinued 5 to 10 days before delivery and it was not restarted postpartum (n=7; 23%), discontinued 5 to 10 days before delivery and restarted following delivery until at least

6 to 12 weeks postpartum (n=4; 13%), or discontinued at delivery (9; 30%). Certain respondents, however, did not discontinue aspirin before delivery and continued it until 6 to 12 weeks postpartum (n=7; 23%).

4. Discussion

We surveyed physicians' strategies of anticoagulation for women with MHVs during pregnancy. We found that sequential therapy and LMWH throughout pregnancy were the anticoagulation strategies most commonly chosen for women with mitral and aortic MHVs, respectively. Although weight in pregnancy was used to determine the starting dose of LMWH, anti-Xa peak and trough levels were used to guide further dosing adjustments in most instances. Aspirin was often prescribed concomitantly with LMWH and discontinued 5 to 10 days before delivery. Delivery mode was guided by obstetrical indications.

We observed considerable variations in practice in the choice of anticoagulation modality for pregnant patients with mitral MHVs. The choice of anticoagulant was made predominantly according to patient-specific factors, whereas published guidelines were only used by a minority of participants. This may reflect the paucity of clinical data to guide the optimal method of anticoagulation for these women [5,6]. Sequential therapy and LMWH alone were reported to be more frequently used than UFH and VKAs among respondents. A systematic review of 2468 pregnancies in 1874 women evaluating maternal, fetal, and neonatal outcomes among women with MHVs described 44 studies of pregnant patients with MHV of which 68% were in the mitral position [4]. Data on the use of sequential therapy and LMWH were available for 530 pregnancies (20 studies) and 132 pregnancies (10 studies) respectively; these strategies were associated with 5.8% and 8.7% maternal TECs, respectively [4]. Importantly, anticoagulation-related fetal/neonatal adverse events associated with LMWH throughout pregnancy did not occur in any of 103 infants included, and the live birth rate was 92% [4]. As such, the strategy of LMWH throughout pregnancy is currently being used and may be an option from a fetal/neonatal standpoint, so long as maternal safety can be optimized. A summary of associated risks for each anticoagulation strategy and current recommendations has been provided in Tables S4 and S5 of the Supplementary Appendix, respectively.

Most respondents reported using anti-Xa levels for dose adjustment of LMWH. The monitoring of trough and peak anti-Xa levels has been recommended by the European Society of Cardiology (level IC) (Table S5) [5]. However, whether anti-Xa level monitoring improves clinical outcomes among women with MHVs remains unclear. Indeed, adverse outcomes have been described among in women within the recommended therapeutic target anti-Xa level peak range of 1.0 to 1.2 IU/mL [12]. Moreover, how to adjust dosing as a function of anti-Xa levels is uncertain because achieving target peak anti-Xa levels did not always ensure maintenance of minimum trough levels among pregnant participants with MHVs [13]. In a national registry from the United Kingdom, monitoring practices using anti-Xa levels were highly variable [14]. The frequency at which anti-Xa levels were measured ranged from none to weekly and the target range for peak and trough levels were heterogeneous, highlighting a lack of standardized approach [15]. Observational studies have not demonstrated any clear clinical benefit in monitoring of anti-Xa levels for women using LMWH for the treatment of venous thromboembolism (VTE) in pregnancy [15–18]. In addition, considering the lack of calibration curves for the anti-Xa assay in pregnancy and the costs associated with anti-Xa monitoring, the American Society of Hematology has recommended against the use of anti-Xa levels in the management VTE in pregnancy [19]. Given differences in thrombotic risks between VTEs and MHVs, recommendations regarding anticoagulation for one condition may not be generalizable to the other. Thus, the use of anti-Xa levels specifically for MHVs in pregnancy needs to be clarified; in particular, whether peak and/or trough levels should be used, optimal anti-Xa levels, and best time intervals for anti-Xa monitoring require further research [5].

Low-dose aspirin, usually defined as ranging from 75 to 100 mg daily, was selected as an adjunct antithrombotic therapy for women taking LMWH. In the European Society of Cardiology's Registry of Pregnancy and Cardiac Disease, none of the 13 patients with aspirin in addition to anticoagulation had

TECs, whereas 2.5% of patients without aspirin developed mitral valve thrombosis [1]. In the nonpregnant setting, a Cochrane review highlighted that antiplatelet agents given in addition to anticoagulation decreased the risk of systemic embolism or death among patients with MHV, although the risk of bleeding events was slightly increased [20]. Further guidance on the addition of aspirin as part of the antithrombotic regimen is currently needed.

A minority of respondents used UFH in contemporary practice, in contrast to the use of UFH reported in systematic reviews [4]. In addition, VKAs were selected less frequently than LMWH-based strategies, contrasting with findings from prior studies most commonly describing the use of VKAs throughout pregnancy [4]. Therefore, we report a potential shift in clinical practice, whereby LMWHs appears to be increasingly selected either in conjunction with measurement of anti-Xa levels, at least in high-resource settings. This may reflect that UFH is the preferred heparin in middle- and low-resource settings, where LMWH use and monitoring is often cost prohibitive. As such, among respondents, the selection of UFH in high-income settings may have declined.

This international survey captured the anticoagulation regimens practiced by a variety of specialists, from diverse geographical settings. The data highlight important knowledge gaps in regard to the optimal dose adjustment and drug monitoring strategies for LMWH, which will serve to plan for future studies. This study has some limitations. First, the total number and baseline characteristics of all potential respondents is not known. Furthermore, results reflected the practice of the respondents only; practices of nonrespondents could not be assessed. A major limitation is that cardiologists were underrepresented because the survey was not sent to cardiology societies. Furthermore, most respondents had access to anti-Xa level monitoring. Thus, results may not be generalizable to areas of low- and middle-income. Lastly, case scenarios may not reflect actual physician practice [21,22]. To minimize this limitation, we developed scenarios that closely simulated real patients. In addition, we pilot tested the survey for face and content validity.

In summary, in an international survey of physicians, mostly from tertiary referral centers in high-resource settings, we described an important shift in clinical practice regarding the use and monitoring of LMWH and the addition of low-dose aspirin in those using LMWH among respondents. Most physicians reported using peak anti-Xa levels to adjust LMWH dose during pregnancy, with an increasing number reporting the additional use of trough anti-Xa levels. In light of these changes in clinical practice, and given the paucity of high-quality evidence to inform clinical decision making, international multicenter trials are required to determine the optimal anticoagulant strategy.

Acknowledgments

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Conflict of interest

Dr. Casais has received travel support from Sanofi. Dr. D'Souza has received a Canadian Institutes of Health Research Early Career Award, as well as speaking honoraria and grant funding from Ferring Inc. for topics unrelated to the current publication. Dr. Shehata has received honoraria and an educational grant from Sanofi. Drs. Malhame, Othman, Wald, Silversides, and Sermer have no conflicts of interest to declare.

Author contributions

Isabelle Malhame contributed to the design, analysis, interpretation of data, and writing of the initial draft; Maha Othman, Patricia Casais, Rohan D'Souza, Rachel M. Wald, Candice K. Silversides, and Mathew Sermer contributed to the design, interpretation of data, and critical revisions of the manuscript; Nadine Shehata supervised the design, analysis, interpretation of data, and critically revised the manuscript. All authors approved of the final version of the manuscript.

Supplementary Appendix

Table S1

Anticoagulation choices for mechanical mitral valve according to respondents' characteristics[1]

	VKA until delivery despite the dose of the VKA	VKA until delivery if dose is equivalent to 5 mg for warfarin	VKA until 6 weeks gestation, therapeutic LMWH until 12–14 weeks followed by VKA until delivery*	VKA until 6 weeks gestation, therapeutic UFH subcutaneously until 12–14 weeks followed by VKA until delivery*	VKA until 6 weeks gestation, therapeutic UFH intravenously until 12–14 weeks followed by VKA until delivery*	Therapeutic LMWH until delivery*	Therapeutic UFH subcutaneously until delivery	Other
Years of practice n=83**								
<5, n (%)	1 (9)	1 (9)	3 (27)	1 (9)	1 (9)	4 (36)	0	0
5–10, n (%)	1 (6)	2 (12)	7 (41)	0	0	7 (35)	0	1 (6)
11–20, n (%)	0	1 (5)	9 (43)	2 (10)	1 (5)	6 (33)	0	1 (5)
>20, n (%)	0	4 (12)	9 (26)	0	0	10 (29)	1 (3)	10 (29)
Specialty n=81**								
Cardiology, n (%)	0	2 (25)	4 (50)	0	0	2 (25)	0	0
Hematology/ Thrombosis, n (%)	1 (2)	1 (2)	17 (35)	0	2 (4)	18 (37)	1 (2)	9 (18)
Maternal-Fetal Medicine, n (%)	0	0	0	0	0	2 (67)	0	1 (33)
Obstetric Medicine, n (%)	1 (7)	3 (21)	6 (43)	2 (14)	0	2 (14)	0	0
Other, n (%)	0	2 (33)	1 (17)†	1 (0)	0	2 (33)	0	1 (17)
Continent of practice n=84**								
Africa, n (%)	1 (33)	1 (33)	1 (33)	0	0	0	0	0
Asia, n (%)	0	2 (25)	0	1 (13)	1 (13)	3 (38)	0	1 (13)
Australia and New Zealand, n (%)	0	0	0	0	0	2 (100)	0	0
Europe, n (%)	1 (3)	5 (14)	8 (23)	1 (3)	0	13 (37)	1 (3)	6 (17)
North America, n (%)	0	1 (3)	15 (48)	1 (3)	1 (3)	9 (29)	0	4 (13)
South America, n (%)	0	0	4 (33)	0	0	0	0	1 (20)

Notes: [1]All percentages represent row percent. *± Unfractionated Heparin near delivery. †Respondent with missing information on specialty. ** p =0.1, p=0.2 and p= 0.05 for differences in anticoagulation choices according to years of practice, specialty and continent of practice of respondents, respectively.

Table S2

Anticoagulation choices for mechanical aortic valve according to respondents' characteristics[1]

	VKA until delivery despite the dose of the VKA	VKA until delivery if dose is equivalent to ≤5 mg for warfarin	VKA until 6 weeks gestation, therapeutic LMWH until 12–14 weeks followed by VKA until delivery*	VKA until 6 weeks gestation, therapeutic UFH subcutaneously until 12–14 weeks followed by VKA until delivery*	VKA until 6 weeks gestation, therapeutic UFH intravenously until 12–14 weeks followed by VKA until delivery*	Therapeutic LMWH until delivery*	Other
Years of practice n=83**							
<5, n (%)	1 (9)	1 (9)	1 (9)	0	1 (9)	7 (64)	0
5–10, n (%)	1 (6)	2 (12)	5 (29)	0	0	8 (47)	1 (6)
11–20, n (%)	0	1 (5)	7 (33)	1 (5)	0	12 (57)	0
>20, n (%)	0	2 (6)	8 (24)	1 (3)	0	20 (59)	3 (9)
Specialty n=81**							
Cardiology, n (%)	0	2 (25)	4 (50)	0	0	2 (25)	0
Hematology/ Thrombosis, n (%)	1 (2)	0	11 (22)	1 (2)	1 (2)	33 (67)	2 (4)
Maternal-Fetal Medicine, n (%)	0	0	0	0	0	2 (67)	1 (33)
Obstetric Medicine, n (%)	1 (7)	2 (14)	4 (29)	1 (7)	0	6 (43)	0
Other, n (%)	0 (33)	2 (33)	2 (33) †	0	0	3 (50)	0
Continent of practice n=84**							
Africa, n (%)	1 (33)	1 (33)	0	1 (33)	0	0	0
Asia, n (%)	0	2 (25)	2 (25)	1 (13)	0	3 (38)	0
Australia and New Zealand, n (%)	0	0	0	0	0	2 (100)	0
Europe, n (%)	1 (3)	3 (9)	4 (11)	0	0	27 (77)	0
North America, n (%)	0	1 (3)	11 (35)	0	1 (3)	15 (48)	3 (10)
South America, n (%)	0	0	4 (80)	0	0	0	1 (20)

Notes: [1]All percentages represent row percent. *± Unfractionated Heparin near delivery. †Respondent with missing information on specialty. ** p =0.6, p=0.04 and p= <0.001 for differences in anticoagulation choices according to years of practice, specialty and continent of practice of respondents, respectively.

Table S3

Parameters used to guide low molecular weight heparin dosing adjustment1

	No adjustment	Peak anti-Xa	Trough anti-Xa	Peak and trough anti-Xa	Pregnancy weight	Pregnancy weight, peak and trough anti-Xa	No answer
Years into practice n=81**							
<5, n (%)	0	1 (10)	0	3 (30)	4 (40)	1 (10)	1 (10)
5–10, n (%)	0	6 (38)	0	7 (44)	2 (13)	1 (6)	0
11–20, n (%)	1 (5)	4 (19)	0	2 (10)	2 (10)	10 (48)	2 (10)
>20, n (%)	2 (6)	9 (26)	1 (3)	8 (24)	3 (9)	10 (29)	1 (3)
Specialty n=80**							
Cardiology, n (%)	0	2 (25)	0	3 (38)	1 (13)	2 (25)	0
Hematology/ Thrombosis, n (%)	2 (4)	15 (31)	1 (2)	10 (21)	8 (17)	11 (23)	1 (2)
Maternal-Fetal Medicine, n (%)	0	1 (33)	0	2 (67)	0	0	0
Obstetric Medicine, n (%)	0	1 (7)	0	4 (29)	1 (7)	6 (43)	2 (14)
Other, n (%)	1 (14)	1 (14)	0	1 (14)	1 (14)*	2 (29)	1 (14)
Continent of practice n=81**							
Africa, n (%)	2 (67)	0	0	0	0	1 (33)	0
Asia, n (%)	0	1 (13)	0	2 (25)	1 (13)	1 (13)	3 (38)
Australia and New Zealand, n (%)	0	0	0	1 (50)	0	1 (50)	0
Europe, n (%)	0	10 (31)	0	10 (31)	4 (13)	8 (25)	1 (3)
North America, n (%)	1 (3)	5 (16)	1 (3)	7 (22)	6 (19)	11 (34)	0
South America, n (%)	0	4 (100)	0	0	0	0	0

Notes: [1]All percentages represent row percent. *Respondent with missing information on specialty. **p =0.08, p=0.51 and p= n/a for differences in parameters used to guide low molecular weight heparin dosing adjustements according to years of practice, specialty and continent of practice of respondents, respectively.

Table S4

Anticoagulation strategies and their associated maternal, fetal, and neonatal risks [23]

Anticoagulation Strategy	Maternal thromboembolic events	Maternal deaths	Anticoagulation-related fetal/neonatal adverse events	Live births
VKAs throughout pregnancy	2.7% 95% CI (1.4, 4.0)	0.9% 95% CI (0.1, 1.6)	2% 95% CI (0.3, 3.7)	64.5% 95% CI (48.8, 80.2)
LMWH throughout pregnancy	8.7% 95% CI (3.9, 13.4)	2.9% 95% CI (0.2, 5.7)	N/A	92% 95% CI (86.1, 98.0)
Sequential therapy	5.8% 95% CI (3.8, 7.7)	2.0% 95% CI (0.8, 3.1)	1.4% 95% CI (0.3, 2.5)	79.9% 95% CI (74.3, 85.6)

Notes: LMWH = Low-molecular-weight heparin, VKA = Vitamin K antagonists.

Table S5

Current guidelines' recommendations for the antithrombotic management of women with mechanical heart valves in pregnancy [3]

	First trimester	Second and third trimesters	Aspirin use	Monitoring with anti-Xa levels
European Society of Cardiology 2018	**Warfarin dose <5 mg/day** Consider continuation of VKA **Warfarin dose >5 mg/day** Should consider discontinuation of VKAs between weeks 6 and 12 and replacement with adjusted-dose IV UFH (aPTT>2 x control) or adjusted-dose LMWH twice daily	**Warfarin dose <5 mg/day** Recommended continuation of VKA **Warfarin dose >5 mg/day** Should consider VKAs to be continued May consider LMWH with anti-Xa level monitoring and dose adjustment	«Addition of low-dose aspirin or heparins has no proven advantage in preventing valve thrombosis but is associated with significantly more maternal bleeding-complications, including fatal events»	LMWH is not recommended when weekly anti-Xa level monitoring and dose-adjustment is not available
American Heart Association 2014	**Warfarin dose ≤5 mg/day** Reasonable to continue warfarin after discussion with the patient of risks and benefits May be reasonable to switch to dose-adjusted LMWH ≥2 times daily or dose-adjusted continuous infusion UFH (aPTT ≥ 2 x control) **Warfarin dose >5 mg/day** Reasonable to switch to dose-adjusted LMWH ≥ 2 times daily or dose-adjusted continuous infusion UFH (aPTT ≥ 2 x control)	**Any warfarin dose** Recommend warfarin to goal INR	Recommend low-dose aspirin (75–100 mg once per day) in the second and third trimester	LMWH should not be administered unless anti-Xa levels are monitored 4–6 h after administration Target anti-Xa level 0.8–1.2 U/mL
American College of Chest Physicians 2012	Recommend all the following anticoagulant regiments in preference to no anticoagulation Dose-adjusted LMWH twice daily throughout pregnancy. or Dose-adjusted UFH s/c twice daily throughout pregnancy (mid-interval aPTT ≥ 2 x control or anti-Xa heparin level 0.35–0.70 IU/mL) or UFH or LMWH (as above) until 13th week then with substitution by VKA until close to delivery when UFH or LMWH is resumed In women judged to be at very high risk of TEC in whom concerns exist about the efficacy and safety of UFH or LMWH as dosed above, suggest VKA throughout pregnancy		For women at high risk of TECs, suggest low-dose aspirin (75–100 mg daily)	Suggest that doses be adjusted to achieve the manufacturer's peak anti-Xa level 4h post s/c injection

Notes: aPTT = activated partial thromboplastin time, INR = International normalized ratio, LMWH = Low-molecular-weight heparin; s/c = subcutaneous; TEC-thromboembolic complications, UFH = Unfractionated heparin, VKA = Vitamin K antagonists.

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Правила подачі та оформлення статей

Авторська стаття направляється до редакції електронною поштою у форматі MS Word. Стаття супроводжується офіційним направленням від установи, в якій була виконана робота, з візою керівництва (наукового керівника), завіреним круглою печаткою установи, експертним висновком про можливість відкритої публікації, висновком етичного комітету установи або національної комісії з біоетики. На останній сторінці статті мають бути власноручні підписи всіх авторів та інформація про відсотковий внесок у роботу кожного з авторів.

Приймаються оригінали супровідних документів з примірником рукопису, підписаного автором(ами), надіслані поштою, або скановані копії вищезазначених документів і першої (титульної) сторінки статті з візою керівництва, печаткою установи і підписами всіх авторів у форматі Adobe Acrobat (*.pdf), надіслані на електронну адресу редакції.

Статті приймаються українською, російською або англійською мовами.

Структура матеріалу: вступ (стан проблеми за даними літератури не більше ніж 5–7-річної давності); мета, завдання, матеріали та методи; результати дослідження та їх обговорення (висвітлення статистично опрацьованих результатів дослідження); висновки; перспективи подальших досліджень у даному напрямку; список літератури (два варіанти); реферати українською, російською та англійською мовами.

Реферат є незалежним від статті джерелом інформації, коротким і послідовним викладенням матеріалу публікації за основними розділами і має бути зрозумілим без самої публікації. Його обсяг не повинен бути менше 300–350 слів. Обов'язково подаються ключові слова (від 3 до 8 слів) у порядку значущості, що сприятиме індексуванню статті в інформаційно-пошукових системах. Реферат до оригінальної статті повинен мати структуру, що повторює структуру статті: мета дослідження; матеріали і методи; результати; висновки; ключові слова. Усі розділи у рефераті мають бути виділені в тексті жирним шрифтом. Для інших статей (огляд, лекція, клінічний випадок тощо) реферат повинен включати короткий виклад основної концепції статті та ключові слова.

Оформлення статті. На першій сторінці зазначаються: індекс УДК ліворуч, ініціали та прізвища авторів, назва статті, назва установ, де працюють автори та виконувалось дослідження, місто, країна. За умови проведення досліджень із залученням будь-яких матеріалів людського походження, в розділі «Матеріали і методи» автори повинні зазначати, що дослідження проводилися відповідно до стандартів біоетики, були схвалені етичним комітетом установи або національною комісією з біоетики. Те саме стосується і досліджень за участю лабораторних тварин.

Наприклад: *«Дослідження виконані відповідно до принципів Гельсінської Декларації. Протокол дослідження ухвалений Локальним етичним комітетом (ЛЕК) всіх зазначених у роботі установ. На проведення досліджень було отримано поінформовану згоду батьків дітей (або їхніх опікунів)».*

«Під час проведення експериментів із лабораторними тваринами всі біоетичні норми та рекомендації були дотримані».

Кількість ілюстрацій (рисунки, схеми, діаграми, фото) має бути мінімальною. Діаграми, графіки, схеми будуються у програмах Word або Excel; фотографії повинні мати один із наступних форматів: PDF, TIFF, PSD, EPS, AI, CDR, QXD, INDD, JPG (150–600 dpi).

Таблиці та рисунки розташовують у тексті статті відразу після першого згадування. У підпису до рисунку наводять його назву, розшифровують усі умовні позначки (цифри, літери, криві тощо). Таблиці мають бути оформлені відповідно до вимог ДАК, бути компактними, пронумерованими, мати назву. Номери таблиць, їхні заголовки і цифрові дані, оброблені статистично, повинні точно відповідати наведеним у тексті статті.

Посилання на літературні джерела у тексті позначаються цифрами у квадратних дужках та відповідають нумерації у списку літератури. **Статті зі списком літературних джерел у вигляді посилань на кожній сторінці або кінцевих посилань не приймаються.**

Необхідно подавати два варіанти списку літератури.

Перший (основний) варіант наводиться одразу після тексту статті, джерела розташовуються за алфавітом. Список літератури наводиться латиницею. Джерела на українській та російській мовах наводяться у тому написанні, як вони зазначені та реєструються на англійських сторінках сайтів журналів. Якщо джерело не має назви англійською мовою — воно наводиться у транслітерації. Таке оформлення списку літератури необхідно для аналізу статті та посилань на авторів у міжнародних наукометричних базах даних, підвищення індексу цитування авторів.

Другий варіант повторює перший, але джерела на українській та російській мовах подаються в оригінальній формі. Цей варіант необхідний для оформлення електронних версій журналу на російській та українській сторінках, цитованості у кирилічних наукометричних базах.

Згідно з Наказом МОН України №40 від 12.01.2017 р. «Про затвердження вимог до оформлення дисертацій» оформлення списку літератури здійснюється відповідно стилю APA (American Psychological Association style), що може використовуватися у дисертаційних роботах.

Приклади оформлення літературних джерел:

Author AA, Author BB, Author CC. (2005). Title of the article. Title of Journal. 10(2);3:49–53.

Author AA, Author BB, Author CC. (2006). Titile of the book. Sity: Publisher: 256.

У тексті статті допускаються загальноприйняті скорочення, а також авторські скорочення, які обов'язково розшифровуються у тексті при першому згадуванні та залишається незмінними по всьому тексту. У кінці статті автори мають заявити про наявність будь-яких конкуруючих фінансових інтересів щодо написання статті. Зазначення конфлікту інтересів або його відсутності у статті є обов'язковим.

Приклад: *«Автори заявляють про відсутність конфлікту інтересів» або «Матеріал підготовлений за підтримки компанії...»*

Стаття закінчується відомостями про усіх авторів. Зазначаються прізвище, ім'я, по батькові (повністю), вчений ступінь, вчене звання, посада в установі/установах, робоча адреса з поштовим індексом, робочий телефон і адреса електронної пошти; ідентифікатор ORCID (https://orcid.org/register). Автор, відповідальний за зв'язок із редакцією, надає свій мобільний/контактний номер телефона.

Відповідальність за достовірність та оригінальність наданих матеріалів (фактів, цитат, прізвищ, імен, результатів досліджень тощо) несуть автори.

Редакція забезпечує рецензування статей, виконує спеціальне та літературне редагування, залишає за собою право скорочувати обсяг статей. Відмова авторам у публікації статті може здійснюватися без пояснення причин и не вважається негативним висновком щодо наукової та практичної значущості роботи.

Статті, оформлені без дотримання правил, не розглядаються і не повертаються авторам.

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ЗАПРОШУЄМО АВТОРІВ НАУКОВИХ СТАТЕЙ ДО СПІВПРАЦІ

ПУБЛІКАЦІЯ БЕЗКОШТОВНА

Видавництво ТОВ «Група компаній МедЕксперт» випускає журнали для лікарів різних спеціальностей. Ми створюємо видання європейського зразка з інноваційним для України підходом до формування наповнення кожного випуску і висвітлення профільної тематики. Нашими експертами є не лише визнані українські вчені, але й провідні фахівці країн Балтії, Польщі, Великої Британії, Молдови, Франції, Італії, Туреччини, Ізраїлю, Китаю та інших. Усі наші журнали видаються великими накладами, доступні для читачів і мають авторитет у фаховому середовищі. Кожен з них надійно закріпив за собою позиції кращого у спеціалізованих рейтингах.

«Сучасна педіатрія. Україна»

Журнал публікує результати наукових досліджень щодо методів діагностики та лікування дитячих хвороб з метою підвищення якості надання допомоги дітям в Україні.

«Український журнал Перинатологія і педіатрія»

Єдине в Україні видання, яке публікує результати сучасних досліджень з проблем акушерства та розвитку дитини від зачаття до підліткового віку.

«Хірургія дитячого віку. Україна»

На сторінках видання публікуються результати оригінальних досліджень, унікальні та складні клінічні випадки, висвітлюються нові підходи до діагностики та лікування різних хірургічних захворювань.

Всі журнали включені у категорію «Б» Переліку наукових фахових видань України, у яких можуть публікуватися результати дисертаційних робіт на здобуття наукових ступенів доктора і кандидата наук.

Визнанням авторитетності наших журналів є те, що всі вони входять у міжнародні наукометричні бази. Статтям присвоюється цифровий ідентифікатор об'єкта DOI.

IV МІЖНАРОДНИЙ КОНГРЕС

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Antibiotic resistance STOP!

Стійкість до антибіотиків зростає до загрозливо високих рівнів у всьому світі. Нові механізми стійкості з'являються і поширюються всюди, створюючи перешкоди для лікування розповсюджених інфекційних захворювань

- World Health Organization

ANTIBIOTIC RESISTANCE

Розвиток нових антибіотиків має надзвичайне значення, оскільки еволюція мікробів продовжуватиметься безперервно, а резистентність до лікарських засобів зростає.

Проблема антибіотикорезистентності стала глобальним викликом сьогодення. Головною його причиною вважають нераціональне застосування антибактеріальної терапії.

Тож під час Всесвітнього тижня поінформованості про антибіотики, в Україні традиційно буде проведено

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