Anticoagulant Therapy in Pregnant Women with Mechanical Heart Valves: Italian Federation of Centers for Diagnosis and Surveillance of the Antithrombotic Therapies (FCSA) Position Paper

Elena Campello[1] Paolo Bucciarelli[2] Filippo Catalani[1] Nicoletta Erba[3] Alessandro Squizzato[4] Daniela Poli[5] Scientific Reviewer Committee*

[1] Department of Medicine, General Medicine and Thrombotic and Hemorrhagic Unit, University of Padova, Padova, Italy
[2] Fondazione IRCCS Ca' Granda – Ospedale Maggiore Policlinico, A. Bianchi Bonomi Hemophilia and Thrombosis Center, Milan, Italy
[3] Medical Division, Emergency, ONG Onlus, Milan, Italy
[4] Research Center on Thromboembolic Disorders and Antithrombotic Therapies, ASST Lariana, University of Insubria, Como, Italy
[5] Thrombosis Center, "Careggi" Hospital, Florence, Italy

Address for correspondence Paolo Bucciarelli, MD, A. Bianchi Bonomi Hemophilia and Thrombosis Center, Fondazione IRCCS Ca' Granda – Ospedale Maggiore Policlinico, Via Pace, 9, 20122 Milan, Italy (e-mail: paolo.bucciarelli@policlinico.mi.it).

Thromb Haemost 2024;124:695–708.

Abstract

The management of anticoagulant therapy in pregnant women with mechanical heart valves (MHVs) is difficult and often challenging even for clinicians experienced in the field. These pregnancies, indeed, are burdened with higher rates of complications for both the mother and the fetus, compared to those in women without MHVs. The maternal need for an optimal anticoagulation as provided by vitamin K antagonists is counterbalanced by their teratogen effect on the embryo and fetus. On the other hand, several concerns have been raised about the efficacy of heparins in pregnant women with MHVs, considering the high risk of thrombotic complications in these patients. Therefore, numerous clinical issues about the management of pregnant women with MHVs remain unanswered, such as the selection of the best anticoagulant agent, the optimal anticoagulation levels to be achieved and maintained, and the evaluation of long-term effects for both the mother and the fetus. Based on a comprehensive review of the current literature, the Italian Federation of the Centers for the Diagnosis and the Surveillance of the Antithrombotic Therapies (FCSA) proposes experience-based suggestions and expert opinions. Particularly, this consensus document aims at providing practical guidance for clinicians dealing with pregnant women with MHVs, to optimize maternal and fetal outcomes while guaranteeing adequate anticoagulation. Finally, FCSA highlights the need for the creation of multidisciplinary teams experienced in the management of pregnant women with MHVs during pregnancy,

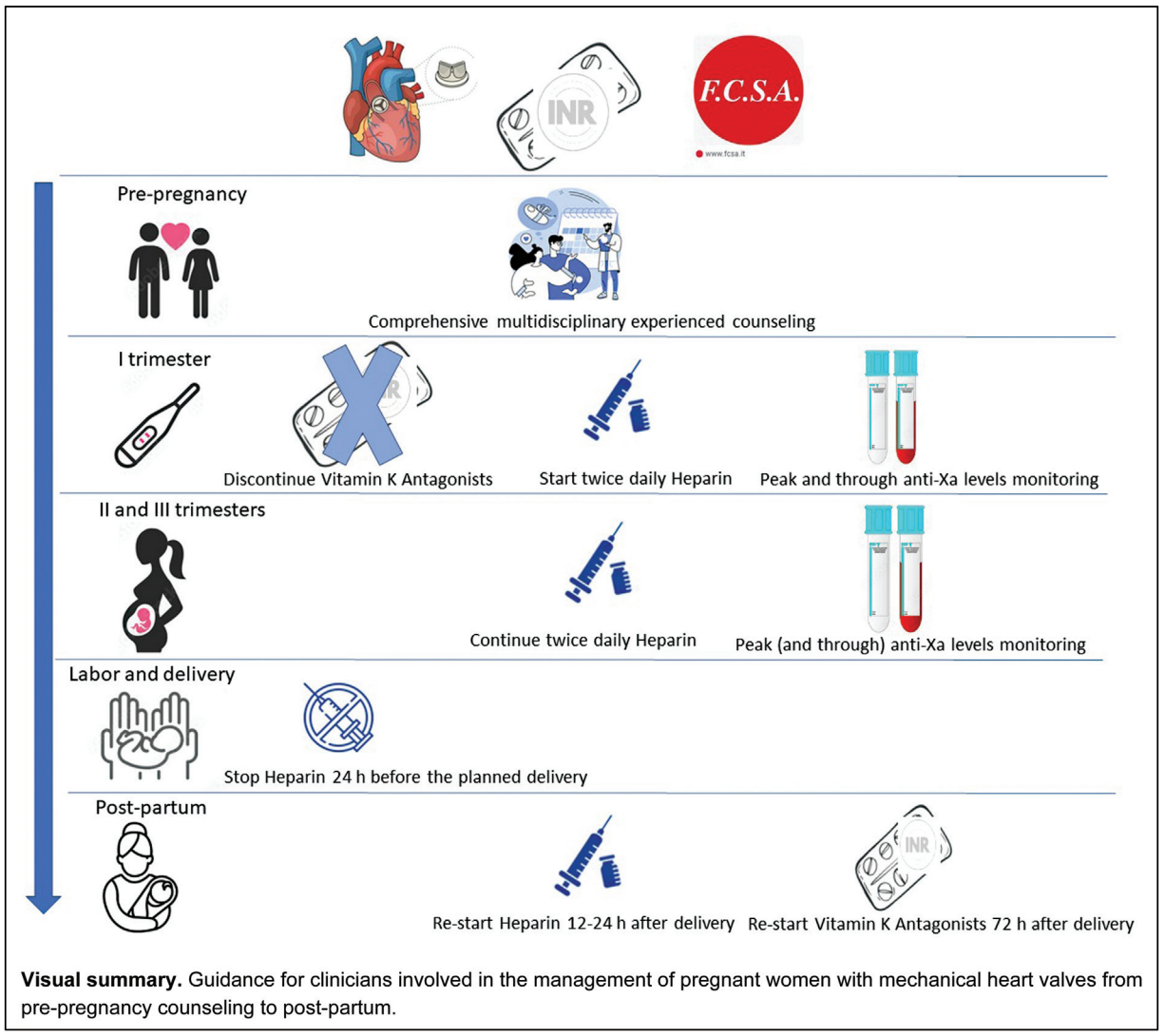
Keywords
- pregnancy
- prosthetic heart valves
- thromboembolism
- heparin
- vitamin K antagonists

* *Scientific Reviewer Committee Members: Gregory Y. H. Lip, Vanessa Roldan, Stefania Basili, Florian Langer, Jennifer Lewey.*

received
October 12, 2023
accepted after revision
February 18, 2024
accepted manuscript online
May 14, 2024
article published online
June 1, 2024

DOI https://doi.org/10.1055/a-2325-5658.
ISSN 0340-6245.

Georg Thieme Verlag KG, Rüdigerstraße 14, 70469 Stuttgart, Germany



Visual summary. Guidance for clinicians involved in the management of pregnant women with mechanical heart valves from pre-pregnancy counseling to post-partum.

delivery, and *postpartum*, in order to better deal with such complex clinical issues and provide a comprehensive counseling to these patients.

Introduction

Pregnancy poses unique challenges for women with mechanical heart valves (MHVs). Indeed, gestation in these patients is associated with a very high risk of complications, namely risk class III according to the Modified World Health Organization classification of maternal cardiovascular risk (risk classes I–IV),[1] with an estimated rate of an event-free pregnancy with a live birth of 58%, compared with 79% for women with bioprostheses, and 78% for those with heart disease but no prosthetic valves.[2] The delicate balance between maintaining maternal hemostasis and ensuring fetal well-being becomes a critical concern in managing these high-risk pregnancies, hence requiring a thoughtful and multidisciplinary approach.

MHVs are commonly implanted in patients with valvular heart disease, ensuring long-term durability and optimal valve function. However, the use of MHVs necessitates lifelong anticoagulation therapy due to the increased risk of valve thrombosis and embolic events.[3–5] All women with MHVs require uninterrupted therapeutic anticoagulation throughout pregnancy. Key considerations include selecting the most appropriate anticoagulant agent, maintaining therapeutic anticoagulation levels, monitoring fetal well-being, managing complications, and evaluating the long-term effects for both mother and child.

While vitamin K antagonists (VKAs) are highly effective in preventing thromboembolic complications,[6] they cross the placenta and their use is associated with miscarriage, spontaneous abortion, embryopathy and fetopathy or fetal intracranial

hemorrhage during the first and the second/third trimesters, respectively. Pregnant women with MHVs were historically mostly managed with unfractionated heparin (UFH) or low-molecular-weight heparin (LMWH), given their relative safety during pregnancy.[7] However, concerns have been raised, mostly about the efficacy of these agents. Indeed, the pharmacological properties of heparin can lead to suboptimal anticoagulant activity, increasing the risk of thromboembolic events. Particularly, optimal anti-Xa levels, evaluation of peak versus trough levels, and the time interval for anti-Xa monitoring are still matter of debate.[1] In addition, maternal bleeding has been associated with all anticoagulant regimens, but a lower incidence has been described with VKA than with UFH/LMWH.[1]

The aim of this Position Paper is to provide guidance for clinicians involved in the management of pregnant women with MHVs, in order to optimize maternal and fetal outcomes while ensuring adequate anticoagulant therapy. For each principal question (i.e. anticoagulation strategy in women with MHVs in the first, second, and third trimesters, at term and labor, in the postpartum and in resource-limited countries), a systematic search was performed in Pubmed (last updated July 2023) according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Available recommendations from major professional societies were summarized. General outlines were suggested by E.C., F.C, D.P. and revised by all the authors. The experience-based suggestions provided are the result of the subsequent consensus achieved by clinicians experienced in the field of the Italian Federation of the Centers for the Diagnosis and the Surveillance of the Antithrombotic Therapies (FCSA).

Available Evidence and Current Guidelines

The current evidence in terms of anticoagulant therapy in pregnant women with MHVs comes mostly from single-center retrospective studies, including small and heterogeneous cohorts. There is paucity of prospective cohort studies, and no randomized controlled trial has ever been published.

VKAs (warfarin—the most used in clinical practice—but also acenocoumarol and phenprocoumon), which represent the standard of care for nonpregnant patients with MHVs, cross the placenta and are associated with embryopathy (consisting of nasal bone hypoplasia, stippled epiphyses, and choanal atresia) when exposure occurs between 6 and 12 weeks of gestation.[8,9] Late exposures are associated with fetopathy, consisting of central nervous system abnormalities and intracranial hemorrhage. The most common fetal adverse events are miscarriage and stillbirth, potentially occurring at any gestational age[9] (►**Table 1**). It appears that warfarin has a dose-dependent effect on fetal outcomes, with the highest risk associated with >5 mg daily warfarin doses[10]; however, a lower risk with lower doses has not been demonstrated in all studies.[2] A meta-analysis published in 2017 concluded that the rate of livebirths among women taking ≤5 mg compared to those treated with >5 mg of warfarin per day was 83.6% (95% confidence interval [CI]: 75.8–91.4%) versus 43.9% (95% CI: 32.8–55.0%), respectively.[11] The rate of embryopathy/fetopathy was 2.3% (95% CI: 0.7–4.0%) with the lower dose (≤5 mg) and 12.4% (95% CI: 3.3–21.6%) with the higher dose (>5 mg) of warfarin.[11]

Table 1 Pros and cons of anticoagulant drugs in pregnant women with MHVs

	Pregnancy		Labor	Puerperium
	Pros	Cons		
VKA	• Oral administration • Stable anticoagulation effect with INR monitoring • Less maternal thrombotic complications	• Risk of embryopathy/fetopathy • Miscarriage, stillbirth	High risk for traumatic fetal hemorrhage, fetal death, maternal major bleeding	Little risk to the breastfed infant
LMWH	• No risk of embryopathy/fetopathy • No risk of miscarriage/stillbirth	• Twice SC administration • More maternal thrombotic complications • Need for specialized laboratory anti-Xa monitoring	• No risk for traumatic fetal hemorrhage and fetal death • Risk for maternal major bleeding in case of urgent delivery due to long half-life	Little risk to the breastfed infant • The twice SC administration could be uncomfortable
UFH	Possible use in patients with severe renal insufficiency	• IV administration • Need for frequent monitoring and dose adjustment • More maternal thrombotic complications	• No risk for traumatic fetal hemorrhage and fetal death • Less maternal major bleeding in case of urgent delivery • It requires IV administration and monitoring is difficult	Little risk to the breastfed infant • Not indicated unless severe renal insufficiency

Abbreviations: INR, international normalized ratio; IV, intravenous; LMWH, low-molecular-weight heparin; MHVs, mechanical heart valves; SC, subcutaneous; UFH, unfractionated heparin; VKA, vitamin K antagonist.

On the other hand, LMWH does not cross the placenta and it is therefore not associated with embryopathy or fetopathy. Nevertheless, maternal thromboembolic complications can occur throughout pregnancy and may be related to subtherapeutic LMWH levels.[9] Thus, dose adjustment is needed due to changes in maternal renal clearance and volume of distribution over the course of pregnancy[12] (►**Table 1**). However, in contemporary studies, dose-adjusted LMWH is still associated with thromboembolic complication in 4 to 17% of pregnancies.[11,13,14]

The majority of the available studies adopts a sequential anticoagulation regimen, namely switching from parenteral anticoagulation in the first trimester to VKA during the second and third trimesters. In a few studies, however, the same anticoagulant strategy has been used throughout the whole pregnancy: LMWH—in the majority of cases—or VKA (regularly replaced by parenteral anticoagulation between weeks 36 and 38).[8,9] In the above-mentioned 2017 meta-analysis including 46 studies (2,468 pregnancies in 1,874 women), maternal and fetal outcomes of women treated with (1) VKAs, (2) first-trimester heparin followed by VKAs (sequential treatment), (3) LMWH, and (4) UFH during pregnancy were evaluated.[11] The results are summarized in ►**Table 2**: with VKAs use, livebirths were fewer (64.5% [95% CI: 48.8–80.2%]) than those with sequential treatment (79.9% [95% CI: 74.3–85.6%]) and LMWH alone (92.0% [95% CI: 86.1–98.0%]), whereas embryopathy or fetopathy increased (2.0% [95% CI: 0.3–3.7%] with VKA, 1.4% [95% CI: 0.3–3.5%] with sequential treatment, and 0% with LMWH alone). On the other hand, with the use of LMWH, maternal mortality and thrombotic complications increased.[11] When UFH was adopted throughout pregnancy, 11.2% (95% CI: 2.8–19.6%) of women experienced thromboembolic complications. A second metanalysis published in 2017 considering 18 studies and a total of 800 pregnancies[14] showed that the composite outcome of fetal adverse event (i.e., spontaneous abortion, fetal death, and the presence of any congenital defect) was lower with the use of LMWH throughout pregnancy (13.9% [95% CI: 3.7–29.0%]) and with the use of LMWH and VKA in a sequential regimen (16.4% [95% CI: 1.5–41.2%]). Instead, the use of VKA throughout pregnancy or of UFH and VKA in a sequential regimen was associated with higher risk of fetal adverse events (39.2% [95% CI: 27.0–52.1%] and 33.6% [95% CI: 18.4–50.8%]), respectively. Moreover, no significant difference in terms of fetal complications was observed between women taking $\leq$5 mg warfarin daily and those on a LMWH regimen (ratio of averaged risk: 0.9 [95% CI: 0.3–2.1]). By contrast, the composite outcome of maternal adverse event (i.e. maternal death, prosthetic valve failure, and systemic thromboembolism) was lower with VKA (5% [95% CI: 2.5–8.5%]) than with LMWH (15.5% [95% CI: 7.6–25.4%), LMWH and VKA in a sequential regimen (15.9% [95% CI: 4.9–31.6%]), and UFH and VKA in a sequential regimen (15.8% [95% CI: 9.2–23.8%]) (►**Table 2**).

It is worth mentioning that the presence of MHVs is a major, well-established contraindication to the use of direct oral anticoagulants (DOACs) given the proven lack of efficacy.[1,15–19] Furthermore, DOACs are never recommended in pregnancy, as no adequate, well-designed studies on safety and efficacy in pregnant women are currently available.[15,17,20]

In the following paragraphs, the evidence from the literature and the recommendations from the current guidelines are summarized, according to the gestational age. Current available guidelines referenced are the 2018 European Society of Cardiology (ESC) Pregnancy and Heart Disease guidelines,[1] the 2020 American Heart Association and the American College of Cardiology (ACC/AHA) Valvular Heart Disease guidelines,[17] and the 2023 British Society of Hematology guidelines.[21]

Prepregnancy Management

Available Evidence

Pregnancy in women with MHVs is burdened with high rates of complications for both the mother and the embryo/fetus, as there is not one anticoagulation strategy optimally safe. All women with MHV must be made aware of this. In a small prospective observational study, including a final number of 17 patients who underwent MHV implantation and subsequently became pregnant, an informative presurgery and prepregnancy counseling was offered. The patients were suggested to refer to medical attention as soon as they missed a period and to test for pregnancy every 3 days until positive pregnancy test or menstruation occurred. Only one woman experienced a valve thrombosis at the end of the first trimester but finally all the patients delivered full-term healthy babies.[22] Thus, a multidisciplinary prepregnancy counseling to all the women with MHV who wish to embark on pregnancy appears to be mandatory.

In women with cardiac heart diseases, the first phases of the counseling should take over during teenage years, providing a global overview of all the possible issues, such as fertility and miscarriage rates, the long-term prognosis, and estimated maternal risk and outcomes.[23] Particularly, in the setting of women with MHVs, a careful and specific counselling concerning drug therapy during a possible future pregnancy, with particular focus on the anticoagulation strategy, should be offered.[2]

Recommendations from Current Guidelines

According to the available guidelines,[1] preconception counselling is strongly recommended (class of recommendation I) in all women with known or suspected cardiovascular disease. Specifically, in the setting of women of child-bearing age with MHVs, considering the high-risk profile of these pregnancies, the counseling should be performed under the supervision of clinicians with expertise in managing women with MHVs during pregnancy.

FCSA Suggestions

A comprehensive prepregnancy counseling carried out by a multidisciplinary team experienced in the management of pregnant women with MHV is mandatory. Patients must be advised to refer to medical attention in case of suspicion of gestation and regular pregnancy tests at least on weekly basis until gestation is ruled out should be performed. The choice of the anticoagulant regimen in case of pregnancy

Table 2 Fetal and maternal risk with different anticoagulation strategies in pregnant women with MHVs

	Composite fetal risk[a]	Livebirth rate[b]	Anticoagulant-related fetal/neonatal adverse events[b]	Fetal death[c]	Congenital fetal anomaly[c]	Composite maternal risk[a]	Maternal mortality[b]	Maternal thrombo-embolism[b]	Maternal major bleeding[b]	Maternal death[c]	Maternal thrombo-embolism[c]	Maternal antepartum major bleeding[c]
VKA only	39.2% (27–52.1)	64.5% (48.8–80.2)	2% (0.3–3.7)	32.5% (29.6–35.5)	2.1% (1.3–3.3)	5% (2.5–8.5)	0.9% (0.4–1.4)	2.7% (1.4–4.0)	1.3% (0.7–1.9)	0.89% (0.48–1.60)	2.8% (2.0–3.8)	0.49% (0.2–1.2)
VKA ≤5 mg daily only	4.8% (0–16.9)	83.6% (75.8–91.4)		19.2% (15.7–23.3)	0.68% (0.18–2.14)					0.31% (0.02–1.97)	1.14% (0.4–3.1)	0.68% (0.2–2.1)
LMWH and VKA	16.4% (1.5–41.2)	79.9% (74.3–85.6)	1.4% (0.3–3.5)	22.6% (18.4–27.5)	0.74% (0.19–2.33)	15.9% (4.9–31.6)	2.0% (0.8–3.1)	5.8% (3.8–7.7)	3.6% (1.5–5.6)	0.86% (0.22–2.7)	7.4% (4.9–10.9)	0.61% (0.1–2.4)
LMWH only	13.9% (3.7–29)	92.0% (86.1–98.0)	0% (NA)	12.2% (6.8–20.8)	0% (0–4.7%)	15.5% (7.6–25.4)	2.9% (0.2–5.7)	8.7% (3.9–13.4)	11.5% (5.4–17.5)	1.77% (0.31–6.8)	4.4% (1.6–10.5)	4.08% (1.3–10.7)
UFH alone		72.4% (63.6–81.2)	7.6% (0.1–15.0) (intraventricular hemorrhage)	53.6% (41.3–65.5)	0% (0–4.41)		3.4% (0.4–6.5)	11.2% (2.8–19.6)		0.88% (0.05–5.5)	29.8% (19.6–42.4)	5.3% (2.2–11.6)
UFH and VKA	33.6% (18.4–50.8)					15.8% (9.2–23.8)						

Abbreviations: LMWH, low-molecular-weight heparin; MHVs, mechanical heart valves; UFH, unfractionated heparin; VKA, vitamin K antagonist.
Note: Numbers in brackets indicate 95% confidence intervals.
[a]From Steinberg et al[14]: 18 studies, comprising 800 pregnancies between 1974 and 2014 evaluating 4 regimens: (1) VKA throughout pregnancy (high and low dose); (2) LMWH for the first trimester, followed by a VKA (sequential LMWH and VKA); (3) LMWH throughout pregnancy; or (4) unfractionated heparin for the first trimester, followed by a VKA (UFH and VKA). Composite fetal risk includes: spontaneous abortion, fetal death, and the presence of any congenital defect; composite maternal risk includes: maternal death, prosthetic valve failure, and systemic thromboembolism.
[b]From D'Souza et al:[11] 46 studies, comprising 2,468 pregnancies in 1,874 women until 2016 evaluating 4 regimens: (1) VKA throughout pregnancy (high and low dose); (2) LMWH for the first trimester, followed by a VKA (sequential LMWH and VKA); (3) LMWH throughout pregnancy; or (4) UFH throughout pregnancy.
[c]From Xu et al[5]: 51 studies comprising 2,113 pregnancies in 1,538 women until 2015 evaluating (1) VKA throughout pregnancy (high and low dose); (2) sequential UHF/LMWH and VKA; (3) LMWH throughout pregnancy; or (4) UFH throughout pregnancy.

occurrence should be specifically addressed in advance by providing comprehensive and candid information concerning maternal and fetal risks and benefits for each possible anticoagulation strategy. The importance of the compliance with the anticoagulant regimen should be strongly remarked and the final decision on anticoagulation strategy should be shared with the patient.

Anticoagulation Management throughout Pregnancy and Postpartum

First Trimester

Available Evidence

There are two possible anticoagulation strategies during the first trimester of pregnancy: continuing the VKA or replacing it with heparin. No anticoagulation strategy is optimally safe for both the mother and the fetus.[1,17] Importantly, there is no evidence to change anticoagulation while conceiving. As early effects of VKAs on fetal development start from 6 weeks of gestation, guidelines suggest continuing VKA until pregnancy is achieved.[24] Additionally, concerns about the change of anticoagulation treatment from oral to parenteral administration may be detrimental and increase the psychological burden of conceiving couples. However, it is important that women be carefully informed to perform a pregnancy test early when they think they may be pregnant.[21]

As for fetal risk, the Registry of Pregnancy and Cardiac (ROPAC) disease European study shows that VKA use during the first trimester is associated with an increased risk of miscarriage compared with LMWH or UFH (28.6 vs. 9.2%), and the live birth rate is lower.[2] Additionally, its use during the first trimester results in embryopathy in 0.6 to 10% of cases.[3–5] Three systematic reviews concluded that the risk of fetal loss is dose-related (fetal loss rate with low-dose VKA is 19.2% [95% CI: 15.7–23.3%], total fetal loss rate with VKA is 32.5% [95% CI: 29.6–35.5%]).[5,11,14] On the other hand, the fetal loss rate with a combined LMWH/VKA regimen is 22.6% [95% CI: 18.4–27.5%], and with LMWH throughout pregnancy is 12.2% [95% CI: 6.8–20.8%].[5] The embryopathy risk related to VKA use is also dose-dependent (0.45–0.9% with low-dose warfarin) (►**Table 2**).[5,11,14] The comparison between studies, though, is hampered by reporting differences, and conclusions concerning the safety of low-dose VKA are controversial.[1,2,5,11,14]

As for maternal risk, in the ROPAC registry, valve thrombosis occurred in 4.7% of 202 pregnancies, and it was associated with 20% mortality.[2] Maternal risk appears to be lower in women using VKA throughout pregnancy and three times higher in those treated with alternative strategies (►**Table 2**).[5,9,11,14] Thromboembolic complications occur throughout pregnancy and may be related to sub-therapeutic anticoagulant activity during the bridging between different agents, especially in the first trimester.[9] Fixed-dose LMWH is associated with significantly higher thromboembolic complications compared with dose-adjusted regimens.[25] Thus, in course of treatment with LMWH, anti-Xa levels should be monitored at least weekly and the dose adjusted accordingly. In a small study of 11 pregnant patients with a starting dose of 1 mg/kg twice daily (b.i.d.) enoxaparin and subsequent monitoring of LMWH to achieve a peak enoxaparin anti-Xa level of 1.0 to 1.2 IU/mL, a mean increase in LMWH dose of 54% was required.[12] In another retrospective study, an enoxaparin dose of 1.3 mg/kg b.i.d. was required to achieve a peak enoxaparin anti-Xa level of 1.0 to 1.2 IU/mL.[26] Furthermore, a study by Barbour et al has clearly demonstrated that anti-Xa peak levels around 1.0 U/mL were associated with subtherapeutic trough levels of $<$0.5 U/mL in the great majority of cases.[27] Thus, the measurement of peak anti-Xa levels may not sufficiently assure adequate anticoagulation. Additionally, among pregnant women with peak anti-Xa levels within the recommended range of 0.8 to 1.2 U/mL, 57% had sub-therapeutic trough levels ($<$0.6 U/mL), probably because of fast renal clearance.[28] Low trough levels were still observed among women with peak anti-Xa levels at the upper range of 1.0 to 1.2 U/mL. Several small series have confirmed favorable thromboembolic outcomes among women treated with close monitoring of both peak and trough anti-Xa levels, with peak levels targeted between 1.0 and 1.2 U/mL.[8] These data, in addition to documented risk of valve thrombosis with subtherapeutic pre-dose anti-Xa levels, suggest the importance of routine measurement and maintenance of trough levels at therapeutic range (0.6–0.7 U/mL) in the highly thrombogenic population of pregnant women with MHV.[29]

Regarding UFH, there are several disadvantages as compared with LMWH, namely a greater risk of heparin-induced thrombocytopenia, line-associated infections, and osteoporosis: reasons why its use should be limited to clinical settings where dose-adjusted LMWH is not feasible.[7] Subcutaneous injection of UFH is not an acceptable alternative in Western countries, because it is associated with prohibitive rates of valve thrombosis.[30] However, this treatment could be considered only if other therapeutic strategies are not available.

Recommendations from Current Guidelines

According to the available guidelines,[1,17] VKA administration during the first trimester is feasible (class of recommendation: IIa), only if a daily low dose (i.e., warfarin $\leq$5 mg/day, acenocoumarol $\leq$2 mg/day, or phenprocoumon $\leq$3 mg/day) is sufficient to maintain the interquartile range (INR) within the target range. On the contrary, if a higher dose is needed (i.e., warfarin $>$5 mg/day, acenocoumarol $>$2 mg/day, or phenprocoumon $>$3 mg/day), VKA administration is still an option according to the ESC guidelines[1] but with a lower level of evidence (class of recommendation: IIb) compared to LMWH and intravenous (IV) UFH (class of recommendation: IIa), whereas its use is not indicated according to the AHA/ACC guidelines.[17] The target INR should be identified according to the current guidelines using the same range as outside of pregnancy depending on valve model, position, and patient's global thrombotic risk, and the INR should be monitored at least twice a week or weekly (►**Table 3**).[1] When a LMWH strategy is considered, discontinuation of VKA between weeks 6 and 12 and its replacement with LMWH (e.g., 1 mg/kg body weight for enoxaparin and 100 IU/kg for dalteparin) twice daily subcutaneously with dose

Table 3 Current guidelines recommendations and FCSA suggestions on anticoagulation strategy in pregnant women with MHVs

	I trimester	II and III trimesters (until 2 weeks prior to delivery)
2018 ESC Guidelines[1]		
VKA low dose[a]	VKA (IIa) Dose-adjusted LMWH (IIb) Dose-adjusted UFH (IIb)	VKA (I)
VKA high dose[b]	VKA (IIb) Dose-adjusted LMWH (IIa) Dose-adjusted UFH (IIa)	VKA (IIa) Dose-adjusted LMWH (IIb)
Monitoring	• INR at least twice weekly • In-hospital daily anti-Xa until target, then weekly (I) • Target peak anti-Xa (4–6 hours post-dose): 1.0–1.2 U/mL (mitral and right-sided valves) or 0.8–1.2 U/mL (aortic valves) (I) • Target trough anti-Xa (pre-dose): ≥0.6 U/mL (IIb)	• INR weekly or every 2 weeks • Peak (and trough) anti-Xa weekly • Monthly clinical follow-up including echocardiography
2020 AHA/ACC Guidelines[17]		
VKA low dose[a]	VKA (IIa) Dose-adjusted LMWH (IIb) Dose-adjusted UFH (IIb)	VKA (IIa)
VKA high dose[b]	Dose-adjusted LMWH (IIa) Dose-adjusted UFH (IIa)	VKA (IIa) Dose-adjusted LMWH (IIb)
Monitoring	• Target peak anti-Xa (4–6 hours after dose): 0.8–1.2 U/mL. Trough levels may aid in maintaining therapeutic range. • Continuous UFH adjusted to aPTT two times that of a control group	
FCSA suggestions		
	Twice-daily dose-adjusted LMWH	Twice-daily dose-adjusted LMWH VKA[c]
Monitoring	Closely monitored switch from VKA[d] Initial daily peak and trough anti-Xa, then weekly monitoring[e]	Weekly peak anti-Xa Trough anti-Xa when dose modification is needed Weekly or every 2 weeks INR monitoring

Abbreviations: aPTT, activated partial thromboplastin time; INR, international normalized ratio; LMWH, low-molecular-weight heparin; MHVs, mechanical heart valves; UFH, unfractionated heparin; VKA, vitamin K antagonist.

[a]Low-dose VKA: warfarin ≤ 5 mg/day, acenocoumarol ≤2 mg/day or phenprocoumon ≤3 mg/day.

[b]High-dose VKA: warfarin > 5 mg/day, acenocoumarol >2 mg/day or phenprocoumon >3 mg/day.

[c]For women at very high risk for maternal thrombosis (i.e., first-generation prosthetic valves, history of valve thrombosis), or for those who do not accept 9-month parenteral administration, or if anti-Xa monitoring is not feasible.

[d]Switch from VKA to LMWH must be led by specialists experienced in anticoagulation management and monitoring. In complex situation and when anti-Xa analysis is not quickly available, in-hospital management may be considered.

[e]Target peak anti-Xa (4 hours after dose): 1.0–1.2 U/mL; target pre-dose anti-Xa: ≥0.6 U/mL. This anti-Xa activity levels pertain to the twice-daily administration. The anti-factor Xa level should be drawn as a peak, 3–5 hours after the third dose of LMWH.

adjustment according to peak anti-Xa levels should be performed.[1,17] Importantly, switch to LMWH is recommended with close monitoring as follows: daily peak and trough anti-Xa levels until target is reached, then weekly. The recommended anti-Xa targets by ESC are: 1.0 to 1.2 U/mL (mitral and right-sided valves) or 0.8 to 1.2 U/mL (aortic valves) 4 to 6 hours post-dose (grade I) and ≥0.6 U/mL pre-dose anti-Xa levels (grade IIb).[1] According to 2020 ACC/AHA guidelines, in regions where LMWH is unavailable or cost-prohibitive, or if anti-Xa levels cannot be monitored, in-hospital IV continuous infusion of UFH can be used as an alternative to LMWH during the first trimester for women who require a warfarin dose of >5 mg/day.[17] If UFH is used during the first trimester, the dose should be adjusted to maintain the activated partial thromboplastin time (aPTT) to a ratio from 2.0 to 2.5 calculated on the normal aPTT value defined by the laboratory.

Finally, the addition of low-dose aspirin on top of VKA or LMWH has no proven advantage in preventing valve thrombosis, whereas it is associated with significantly higher rates of maternal bleeding complications, including fatal events.[1] Thus, aspirin 75 to 100 mg daily may be considered, in addition to anticoagulation, only if it is indicated for other medical reasons (i.e., prevention of preeclampsia).[17] According to the British Society of Hematology guidelines, it is reasonable to add low-dose aspirin (75 mg daily) from early pregnancy onwards if there are no contraindications or bleeding concerns, especially in pregnant individuals with a higher risk MHV and this should be continued for the duration of pregnancy.[21]

FCSA Suggestions

Pregnant women with MHV should be monitored in a tertiary-care center with a dedicated team of cardiologists, gynecologists, and hematologist experts in the field of thrombosis. Considering the overall fetal risk associated with VKA (roughly 2% for embryopathy and 20% for fetal loss) and the relatively low risk of maternal thrombotic complications when LMWH is administered with a proper monitoring, the FCSA suggests women with MHVs who become pregnant to discontinue VKA as soon as pregnancy is confirmed and to replace it with subcutaneous LMWH twice daily, with dose adjustment according to daily peak and trough anti-Xa levels (target 1.0–1.2 U/mL after 4 hours for peak and ≥0.6 U/mL for trough levels) (►**Fig. 1**). The anti-factor Xa level should be drawn as a peak, 3 to 5 hours after the third dose of LMWH, which should reflect the steady state. As the half-life of LMWHs ranges from 3 to 6 hours after subcutaneous injection, the twice-daily administration is preferable over the once-daily administration in order to maintain a steady and more predictable anticoagulant level over 24 hours. Importantly, the anti-Xa activity levels indicated pertain to the twice-daily administration. It is also important to bear in mind that most pregnant women required dose escalation between 10 and 20 weeks of gestation,[31] thus higher than the standard therapeutic dose (e.g., total 2.0 mg/kg/day enoxaparin) should be considered during transition.[21]

Switch from VKA to LMWH must be led by specialists experienced in anticoagulation management and monitoring. We suggest outpatient daily trough and peak monitoring until the anti-Xa activity target is reached, then a weekly monitoring of peak (and trough) anti-Xa levels is warmly suggested for the whole trimester (►**Table 3**). If regular access to outpatient setting with timed blood sampling is not feasible, in-hospital management may be considered.

The main reason for FCSA suggestion to discontinue VKA—regardless of the dosage used—and replace it with monitored LMWH is to avoid all risks for the fetus and to indicate the safest anticoagulant strategy for the mother and the fetus.

Level of evidence: the level of evidence is moderate, based on retrospective and prospective observational studies, systematic reviews, and meta-analyses.

Second and Third Trimesters

Available Evidence

VKA use during the second and the third trimesters of gestation is frequently the preferred anticoagulation strategy since it is burdened with lower rates of teratogen sequelae during these later phases of pregnancy. In fact, women taking low-dose VKA throughout pregnancy had similar fetal outcomes compared with women taking LMWH or sequential LMWH plus VKA[9] (►**Table 2**). However, close monitoring of fetal well-being is still mandatory because there is 0.7 to 2% risk of fetopathy (i.e., ocular and central nervous system abnormalities, intracranial hemorrhage) with VKA in the second and third trimesters.[1,3,5] Compared to LMWH, an oral way of administration is more feasible and usually preferred by the patients themselves. Moreover, as already mentioned, VKA seems to be associated with a lower incidence of maternal thrombotic events than LMWH, especially if its anticoagulant activity does not achieve the target range, which also requires frequent medical contacts or hospital admissions in experienced centers.[5,11,14] A plausible

Gestation and delivery	FCSA suggestion	Laboratory monitoring
I trimester	**Discontinue VKAs as soon as possible** (between weeks 6 and 12) **and start LMWH SC twice daily**	LMWH dose adjustment according to daily peak and through anti-Xa Then weekly monitoring of peak (and through) anti-Xa
II and III trimesters	**Continue LMWH SC twice daily** (VKAs for women at very high risk of maternal thrombosis)	Weekly peak anti-Xa Check trough anti-Xa in case of dose adjustment (Weekly or every 2 weeks INR monitoring)
Term and labor	**Continue in-hospital LMWH SC twice daily** (discontinue VKAs at least 2-weeks before the planned delivery) (IV UFH 36 h before the delivery in women at higher risk of hemorrhagic and thrombotic complications)	In-hospital LMWH dose adjustment according to daily peak anti-Xa (aPTT 2-2.5 times the normal aPTT every 6 h)
Delivery	**Latest LMWH SC dose by and no later than 24 h before the planned delivery** (stop IV UFH 4-6 h the delivery)	
Post-partum	**Restart LMWH SC** (prophylaxis or intermediate dose) **12-24 h after delivery, and full-dose 72 h after delivery** (Restart IV UFH 4-6 hours after delivery if high thrombotic and hemorrhagic risk) **Restart VKAs 72 h after delivery**	(aPTT 2-2.5 times the normal aPTT (every 6 h)

Fig. 1 FCSA practical suggestions on anticoagulation management for prosthetic mechanical heart valves in women during pregnancy. aPTT, activated partial thromboplastin time; FCSA, Federation of the Centers for the Diagnosis and the Surveillance of the Antithrombotic Therapies; INR, international normalized ratio; IV, intravenous; LMWH, low-molecular-weight heparin; SC, subcutaneous; UFH, unfractionated heparin; VKA, vitamin K antagonist.

explanation of this apparently poorer maternal outcome reported with LMWH could lay in the inadequate monitoring of its anticoagulation level. Indeed, according to the available literature, LMWH anticoagulant activity was assessed mostly just on monthly basis,[32,33] and patients' noncompliance along with the missed achievement of therapeutic anticoagulation levels contributed to adverse maternal outcome.[32]

Maternal hemorrhagic complications can occur with all the anticoagulation regimens, but their incidence is lower with VKA throughout pregnancy compared to LMWH/UFH throughout pregnancy.[5,11] Yet, it is important to consider that women treated with LMWH throughout pregnancy present the higher proportion of livebirths[11] (►**Table 2**), thus some investigators advocate LMWH use throughout pregnancy with anti-Xa levels monitoring.[34] The rationale of this dose-adjusted strategy at this stage, compared to a fixed-dose one, is related to mothers' physiological changes in renal clearance and volume of distribution, with the subsequent need for titration of heparin dose, in order to achieve the optimal anticoagulant activity.[1,17] Finally, UFH is associated with very high rates of valve thrombosis, stroke, and death in pregnant women with MHVs during the second and third trimesters.[4,11,35] Additionally, fetopathy has been described with UFH but not with LMWH throughout pregnancy.[5,11]

Recommendations from Current Guidelines

According to the available guidelines,[1,17] the anticoagulant drug of choice during the second and third trimesters is VKA (class of recommendation: I). There is still a limited indication (class of recommendation: IIb) for LMWH in this gestational age, for those patients requiring daily high dose of VKA (i.e., warfarin >5 mg/day, acenocoumarol >2 mg/day, or phenprocoumon >3 mg/day) to maintain the INR within the target range[1,17] (►**Table 3**). The effectiveness of the anticoagulation regimen (i.e., INR for VKAs or anti-Xa for LMWH) should be monitored weekly or every 2 weeks, and clinical follow-up (including transthoracic echocardiogram) should be performed monthly.[1] Particularly, peak (or peak and trough) anti-Xa levels should be assessed at least weekly until the target is achieved or when there is a below target at any stage and then regularly monitored thereafter (e.g., every 2 to 4 weeks depending on stability).[21] Same as for the first trimester, low-dose aspirin may be considered, in addition to anticoagulation, only in case of other coexisting medical indications.[1,17]

FCSA Suggestions

Favorable clinical outcomes have been demonstrated in women with MHVs treated with LMWH throughout pregnancy, but high levels of medication adherence and patient engagement are needed. Since the assessment of the safety profile of low-dose warfarin is based on a small number of studies and the risk of fetal loss is present throughout pregnancy, the FCSA suggests in pregnant women with MHVs to continue subcutaneous LMWH twice daily with dose adjustment according to weekly peak anti-Xa levels during the II and III trimesters of gestation (►**Table 3**). Trough (pre-dose) anti-Xa levels should also be checked even if LMWH dose adjustment is based on peak levels, in order to better ascertain the therapeutic range. A VKA strategy may be exceptionally considered for women at very high risk of maternal thrombosis, namely those with first-generation valves or in presence of other coexisting high-risk prothrombotic conditions, such as recent thromboembolism, valve dysfunction/mismatch, severe left ventricular dysfunction.[8,21] VKA use may also be considered if an appropriate LMWH use or anti-Xa monitoring is not feasible or in case of patient's refusal to parenteral drug administration. Yet, close INR monitoring is mandatory.

The main reason for FCSA suggestion to maintain LMWH throughout pregnancy in contrast to current guidelines is the better safety profile for the fetus, as the risk of fetal loss with VKA is present throughout pregnancy; the better safety profile for the hemorrhagic maternal risk, and the better efficacy profile for the maternal thrombotic risk, when properly monitored, compared to VKA.

Level of evidence: the level of evidence is moderate, based on retrospective and prospective observational studies, systematic reviews, and meta-analyses.

Term and Labor

Available Evidence

The management of the last weeks of gestation in patients with MHVs is challenging and should be held by clinicians experienced in the field. Even though there are no formal contraindications to vaginal delivery, the percentage of pregnant patients with MHVs undergoing a cesarean section is consistent in the majority of the available studies.[36–39] Delivery of a woman with MHV in course of therapy with VKA must be planned in order to safely bridge to either LMWH or UFH, at least 2 weeks prior to delivery.[13] The timing of this pharmacological switch need to be individualized, since some women with prosthetic heart valves are at risk of preterm delivery.[13] A planned caesarean section may therefore be considered, especially in patients with a high risk of valve thrombosis, to shorten the anticoagulation-free time as much as possible.[1] The risk of prolonged interruption of LMWH during the labor induction process is a potential risk for valve thrombosis. It is possible that this risk is reduced by bridging with IV UFH, which is currently the anticoagulant of choice in this phase in the majority of the studies, particularly in the prospective ones[40–42]: indeed, thanks to its short half-life, it minimizes the risk of maternal hemorrhage at labor. Nevertheless, it is worth mentioning that the aPTT response to UFH may be diminished due to increased levels of factor VIII and fibrinogen in pregnant patients.[32] Thus, in this setting it is recommended to monitor UFH using also an appropriately calibrated anti-Xa assay.[21] Moreover, the management of UFH pump infusion in the setting where it is not routinely used (e.g., delivery room) may be cumbersome and cause potential complications.

However, there are no studies examining the competing risks of bleeding versus valve thrombosis to inform recommendations on the mode of delivery in individuals with

MHV.[21] Caesarian section should be performed if urgent labor onset occurs while the patient is still on VKA after appropriate reversal of anticoagulation, in order to minimize traumatic fetal intracranial hemorrhage.[1,9]

The risk of maternal hemorrhage is high if delivery occurs while the mother is on LMWH at therapeutic dose.[17] Therefore, it is recommended to hospitalize the patient before planned delivery.

Recommendations from Current Guidelines

According to the current guidelines, in-hospital VKA substitution in favor of parenteral anticoagulation (LMWH twice daily or UFH) is mandatory at least 1 week before delivery[17] or at week 36.[1] If LMWH is the ongoing anticoagulant, current guidelines recommend its replacement by IV UFH at least 36 hours before planned delivery[1,17] (►**Table 4**). Regardless the heparin administered at this stage, in-hospital monitoring with anti-Xa or aPTT is also crucial to avoid supratherapeutic doses, with the subsequent high risk of bleeding during the imminent delivery. The ACC/AHA guidelines recommend stopping UFH long enough before delivery to reduce the risk of maternal bleeding and to allow a safe placement of epidural anesthesia (typically at least 6 hours before).[17]

Since LMWH has been used even at this late stage in selected studies,[43,44] according to the British Society of Haematology guidelines,[21] in individuals receiving therapeutic LMWH, the last dose should be $\geq$24 hours prior to the surgical delivery or planned induction. The exact timing should be established in advance and an efficient coordination with the obstetrics and the anesthesia team for the caesarian section is needed.[17] Consideration can be given to further doses, including prophylactic and intermediate doses, and this should be discussed by the multidisciplinary team as it may impact choices for labor analgesia. Alternatively, a switch to therapeutic IV UFH at least 36 hours prior to scheduled induction can be considered, especially in individuals where induction may be prolonged. The UFH infusion needs to be discontinued 4 to 6 hours prior to delivery; practically, the infusion is stopped when the patient is in early labor.[21] In individuals taking aspirin, the indication is to stop the treatment at least 3 days prior to scheduled delivery to reduce the risk of postpartum hemorrhage.[21]

Neuraxial anesthesia requires a prolonged interruption of anticoagulant therapy, thus contraindicating its use in pregnant women with MHVs.[1] The use of IV UFH may allow safer epidural anesthesia, provided that it is stopped at least 4 hours before a neuraxial blockade attempt and after the confirmation of a normal aPTT/anti-Xa.[17,21]

FCSA Suggestions

Considering maternal thrombotic and hemorrhagic risk during the delivery period, the FCSA recommends planning the delivery and switching VKA to LWMH at least 2 weeks before the planned delivery. If the patient is already on therapeutic LMWH, it should be continued. In-hospital admission is suggested at least 72 hours before the planned delivery or as long as deemed necessary for overall cardiological, gynecological, and anticoagulation management. Peak anti-Xa activity must be monitored daily during hospitalization. Caesarean section should be considered for women at high risk for thrombotic or hemorrhagic complications. FCSA suggests maintaining LMWH until labor and interrupting it 24 hours before the planned delivery, meaning that the last dose should be administered by and no later than 24 hours before the planned delivery (►**Fig. 1**). The exact timing of delivery should be agreed together with the obstetrics and the anesthesia team for caesarean section. FCSA suggests avoiding neuraxial labor analgesia in favor of general anesthesia.

Table 4 Current guidelines (ESC and ACC/AHA)[1,17] recommendations on anticoagulation strategy in pregnant women with MHVs during term and labor

Ongoing anticoagulant	Term (36 weeks or at least 1 week before delivery)	Labor (36 hours before planned delivery)	Delivery	Postpartum
VKA	In-hospital change to LMWH twice daily (I) In-hospital change to UFH (I)	IV UFH (I)	Stop IV UFH 4–6 hours before planned delivery (I)	Restart IV UFH 4–6 hours after delivery (I)
LMWH	In-hospital continue LMWH twice daily (I) In-hospital change to UFH (I)			
Monitoring	Target peak anti-Xa (4–6 hours after dose): 0.8–1.2 U/mL UFH adjusted to aPTT two times that of a control group	UFH adjusted to aPTT two times that of a control group		UFH adjusted to aPTT two times that of a control group

Abbreviations: ACC/AHA, American College of Cardiology and the American Heart Association; aPTT, activated partial thromboplastin time; ESC, European Society of Cardiology; IV, intravenous; LMWH, low-molecular-weight heparin; MHV, mechanical heart valve; UFH, unfractionated heparin; VKA, vitamin K antagonist.

IV UFH at labor (36 hours before the delivery) may be considered only in selected cases (e.g., women at very high risk of thrombotic or hemorrhagic complications, or who choose induced vaginal delivery). IV UFH must be stopped 4 to 6 hours before the planned delivery with a subsequent check of both aPTT and anti-Xa.

If an emergent delivery is required in a woman on VKA, a caesarean section is indicated after reversal therapy. The INR must be measured and a four-factor prothrombin complex concentrate (PCC) at a dose of 25 to 50 IU/kg should be administered to the mother prior to caesarean delivery along with vitamin K 10 mg IV. The fetus may also require IV vitamin K (30 mcg/kg by slow IV infusion) and fresh frozen plasma or 20 to 30 IU/kg PCC[21] and this should be addressed by neonatology and hematology teams.[1,13] If emergent delivery is required in a woman on therapeutic LMWH or UFH, protamine administration can be considered, even though it reverses only partially the anticoagulant effect of LMWH.[13]

Level of evidence: the level of evidence is low, based on retrospective and prospective observational studies.

Postpartum

Available Evidence

There are only a few studies evaluating the optimal timing of anticoagulation restart after delivery.[13,32,45,46] UFH is the most frequently administered heparin at this stage, but LMWH is also feasible.[47] Anticoagulation restart must be supervised by experienced clinicians and a cautious evaluation of thrombotic and hemorrhagic profiles must be assessed. In particular, the degree of uterine bleeding and total blood loss during the delivery must be considered, in order to establish the best timing of anticoagulation restart. According to the available studies, anticoagulant therapy is resumed on average from 6–12 to 24 hours after delivery,[12,45] with meticulous monitoring of anticoagulant activity. The timing of the subsequent bridging with VKA is variable, based on a case-by-case evaluation, with a median time of 2 days after delivery, according to some studies.[45]

Nursing mothers may safely breastfeed their babies while taking LMWH or UFH, since none of them is found in breast milk in any significant amount. Concerning VKA use during lactation, acenocoumarol is transferable to breast milk, but no adverse effect has ever been reported. Phenprocoumon and warfarin are also fundable in maternal milk but in the form of inactive metabolites. This evidence supports the use of all these VKAs as safe for nursing mothers.[1,13]

Recommendations from Current Guidelines

ESC guidelines suggest restarting anticoagulation with IV UFH from 4 to 6 hours after delivery, if no bleeding complications occur.[1]

Nursing mothers may safely breastfeed their babies while taking VKA, LMWH, or UFH.[13]

FCSA Suggestions

Although pregnancy is associated with a pro-thrombotic state and significant risk of valve thrombosis, the risk of thrombosis after pausing anticoagulation over a brief period is likely to be low; on the other hand, the risk of bleeding is high in the peripartum period and is likely to be exacerbated using very early postpartum therapeutic anticoagulation.[21] In order to minimize the risk of maternal major bleeding during the postpartum period, the FCSA suggests restarting LMWH at a reduced dose (prophylaxis or intermediate dose) in the first 12 to 24 hours following delivery, if no bleeding is detected. It is advisable to gradually increase LMWH from prophylaxis to intermediate/subtherapeutic dosage (i.e., 4,000 U/mL twice) in the first 24 to 48 hours, based on patient's hemorrhagic profile. Optimal surgical hemostasis is recommended. Full therapeutic LMWH dose should be resumed in accordance with the treating gynecologist 72 hours after delivery, if no bleeding is detected. Bridging with VKAs should be considered from 72 hours following delivery in accordance with the treating gynecologist, overlapping with LMWH until therapeutic INR is achieved (►**Fig. 1**). It is advisable to start VKA bridging 72 hours after delivery as the bleeding risk has decreased and in order to timely gain the INR target. IV UFH in the postpartum should be considered only in selected cases (e.g., in women at higher risk of thrombotic complications when full-dose anticoagulation is required as soon as possible, or for those conditions at high risk for postpartum hemorrhage, when a short-acting drug is more advisable). If using UFH postpartum, a gradual increase in anticoagulant intensity is recommended for the first few days.

The main reason for FCSA suggestion to use LMWH at labor and in the postpartum period in contrast to current guidelines is the better handling of LMWH in clinical practice, especially in nonspecialist contexts, resulting in a better safety and efficacy profile for the mother.

Level of evidence: the level of evidence is low, based on retrospective and prospective observational studies.

Pregnancy Anticoagulation Management in Resource-Limited Countries

Available Evidence

Many health care systems in resource-limited countries encounter difficulties in correctly managing pregnancy in women who need anticoagulation. Cultural, social, political, medical, and economic barriers pose pregnant women at a very high risk of complications. Moreover, many women live far from where they can get drug prescription, drug supply, and blood tests. These unsolved problems greatly amplify the risk in pregnancies with anticoagulation compared to the same situation in high-income countries.[48] A study performed at the Salam Centre for Cardiac Surgery in Sudan from April 2017 to November 2021, including 307 pregnancies, showed a definite high maternal mortality ($n = 15$ maternal deaths, 4.9%), thrombotic events ($n = 24$, 7.8%), and major bleedings ($n = 22$, 7.2%). Regrettably, only 47.6% of pregnancies had good maternal and neonatal outcomes. Indeed, all pregnant women continued VKA through pregnancy, and 40% of them had therapeutic doses above 5 mg/day, due to unavailability of LMWH and anti-Xa activity

Table 5 Therapeutic dose management of subcutaneous unfractionated heparin (UFH)

	Dosage available	*Total daily dose*[a]	*Daily pattern b.i.d.*	*Daily pattern t.i.d.*
Heparin sodium s.c. injection Example for 60 kg	25.000 U/5 mL	500 U/kg[a]	250 U/kg BID s.c.	165 U/kg TID s.c.
		30.000 U[a]	15.000 U (3 mL) b.i.d.	10.000 U 2 mL t.i.d.
Heparin calcium s.c. injection (if available)	12.500 U/0.5 mL	500 U/kg[a]	250 U/kg BID s.c.	–

Abbreviations: b.i.d., twice a day; s.c., subcutaneous; t.i.d., three times a day.
[a]The dose must be adjusted according to aPTT ratio (target >2 on the normal aPTT), 4–6 after the subcutaneous injection.

monitoring. In addition, a lower compliance was reported once the women became aware of their pregnancy. A small observational study performed at a tertiary center in South India from January 2011 to August 2020, including 138 pregnancies, of whom 32 received VKA and 106 were on sequential anticoagulation, showed the same unacceptable high risk of complications, and confirmed that pregnant women are often managed by personnel with limited training.[49] In this study, women choosing sequential anticoagulation were hospitalized, platelet count was assessed and subcutaneous UFH started (15,000–20,000 U per day in 3–4 divided doses), with the aim of achieving a target aPTT 2 to 2.5 times the control value (i.e., the normal value defined by the laboratory). Indeed, UFH has a partially predictable bioavailability, due to varying absorption following subcutaneous administration and its destruction by the placental heparinase enzyme, especially in the third trimester.

Management of anticoagulation in pregnant women with MHVs may improve only if health care systems of resource-limited countries will move towards a women-centered reorganization.[39] Local health authorities should establish anticoagulation centers with a sufficient trained staff to manage all pregnant women with MHVs in each tertiary care center and should offer the possibility to use at best also LMWH in their countries. Additional tasks of each center should include educational activities, aiming at sharing with women clinical risks, practical commitments, and daily burden associated with the therapeutic decision adopted, and training activities, to definitely improve the staff expertise in thrombosis and hemostasis.

FCSA Suggestions

Taking into account the actual difficulties of facing the management of pregnancy for women with MHVs living in countries with limited health system support, the following recommendations should be anyway applied to all pregnant women: (1) avoid first-trimester VKA; (2) ensure therapeutic levels of heparin; (3) stop heparin at the beginning of the labor; (4) since the use of low-dose aspirin (100 mg/day) can reduce the incidence of obstetric complications, consideration should be given to administering low-dose aspirin to all women with MHVs, along with anticoagulation, to reduce the risk of maternal complications.[49] As the use of UFH might be the only option—if LMWH is not available—practical suggestions for managing UFH is reported in ►**Table 5**.

Level of evidence: The level of evidence is low, based on observational studies.

Conclusion

Pregnancy in a woman with a MHV is associated with serious complications and consistent risk of poor fetal outcomes. A multidisciplinary team experienced in the management of prosthetic heart valves in pregnancy is essential to select the appropriate anticoagulation strategy, balancing the risk for the mother and the fetus during the whole pregnancy, the delivery and the postpartum, and to provide a comprehensive counseling. The management of anticoagulation in these patients requires specialized professionals, with appropriate skills also in laboratory test interpretation and anticoagulant drug management, as well as frequent in-hospital and ambulatory monitoring. Recognizing the limitations of the current evidence and acknowledging the need for individualized care, this Position Paper serves as a practical guide to inform the clinicians on the management of anticoagulation during pregnancy and postpartum and it is also intended to be a base for informed discussions and shared decision-making between professionals and pregnant women with MHVs.

Conflict of Interest
A.S. received honoraria for lectures, manuscript writing, and/or participation on advisory board from Daiichi Sankyo, Bayer, Pfizer, Bristol-Myers Squibb, Novartis, Viatris, Sanofi, Werfen, Boehringer-Ingelheim, Alexion, and Roche. All other authors have nothing to declare.

References

1 Regitz-Zagrosek V, Roos-Hesselink JW, Bauersachs J, et al; ESC Scientific Document Group. 2018 ESC Guidelines for the management of cardiovascular diseases during pregnancy. Eur Heart J 2018;39(34):3165–3241
2 van Hagen IM, Roos-Hesselink JW, Ruys TPE, et al; ROPAC Investigators and the EURObservational Research Programme (EORP) Team. Pregnancy in women with a mechanical heart valve: data of the European Society of Cardiology Registry of Pregnancy and Cardiac Disease ROBAC. Circulation 2015;132(02):132–142
3 Sillesen M, Hjortdal V, Vejlstrup N, Sørensen K. Pregnancy with prosthetic heart valves - 30 years' nationwide experience in Denmark. Eur J Cardiothorac Surg 2011;40(02):448–454
4 Chan WS, Anand S, Ginsberg JS. Anticoagulation of pregnant women with mechanical heart valves: a systematic review of the literature. Arch Intern Med 2000;160(02):191–196
5 Xu Z, Fan J, Luo X, et al. Anticoagulation regimens during pregnancy in patients with mechanical heart valves: a systematic review and meta-analysis. Can J Cardiol 2016;32(10):1248.e1–1248.e9

6 Hassouna A, Allam H. Limited dose warfarin throughout pregnancy in patients with mechanical heart valve prosthesis: a meta-analysis. Interact Cardiovasc Thorac Surg 2014;18(06):797–806
7 Abildgaard U, Sandset PM, Hammerstrøm J, Gjestvang FT, Tveit A. Management of pregnant women with mechanical heart valve prosthesis: thromboprophylaxis with low molecular weight heparin. Thromb Res 2009;124(03):262–267
8 Alshawabkeh L, Economy KE, Valente AM. Anticoagulation during pregnancy: evolving strategies with a focus on mechanical valves. J Am Coll Cardiol 2016;68(16):1804–1813
9 Lewey J, Andrade L, Levine LD. Valvular heart disease in pregnancy. Cardiol Clin 2021;39(01):151–161
10 Vitale N, De Feo M, De Santo LS, Pollice A, Tedesco N, Cotrufo M. Dose-dependent fetal complications of warfarin in pregnant women with mechanical heart valves. J Am Coll Cardiol 1999; 33(06):1637–1641
11 D'Souza R, Ostro J, Shah PS, et al. Anticoagulation for pregnant women with mechanical heart valves: a systematic review and meta-analysis. Eur Heart J 2017;38(19):1509–1516
12 Quinn J, Von Klemperer K, Brooks R, Peebles D, Walker F, Cohen H. Use of high intensity adjusted dose low molecular weight heparin in women with mechanical heart valves during pregnancy: a single-center experience. Haematologica 2009;94(11): 1608–1612
13 Bhagra CJ, D'Souza R, Silversides CK. Valvular heart disease and pregnancy part II: management of prosthetic valves. Heart 2017; 103(03):244–252
14 Steinberg ZL, Dominguez-Islas CP, Otto CM, Stout KK, Krieger EV. Maternal and fetal outcomes of anticoagulation in pregnant women with mechanical heart valves. J Am Coll Cardiol 2017; 69(22):2681–2691
15 Steffel J, Collins R, Antz M, et al; External reviewers. 2021 European Heart Rhythm Association practical guide on the use of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation. Europace 2021;23(10):1612–1676
16 Kleindorfer DO, Towfighi A, Chaturvedi S, et al. 2021 Guideline for the prevention of stroke in patients with stroke and transient ischemic attack: a Guideline from the American Heart Association/American Stroke Association. Stroke 2021;52(07): e364–e467
17 Otto CM, Nishimura RA, Bonow RO, et al. 2020 ACC/AHA Guideline for the Management of Patients With Valvular Heart Disease: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Circulation 2021;143(05):e72–e227
18 Eikelboom JW, Connolly SJ, Brueckmann M, et al; RE-ALIGN Investigators. Dabigatran versus warfarin in patients with mechanical heart valves. N Engl J Med 2013;369(13):1206–1214
19 Duraes AR, de Souza Lima Bitar Y, Schonhofen IS, et al. Rivaroxaban versus warfarin in patients with mechanical heart valves: open-label, proof-of-concept trial - The RIWA study. Am J Cardiovasc Drugs 2021;21(03):363–371
20 Lameijer H, Aalberts JJJ, van Veldhuisen DJ, Meijer K, Pieper PG. Efficacy and safety of direct oral anticoagulants during pregnancy; a systematic literature review. Thromb Res 2018; 169:123–127
21 Lester W, Walker N, Bhatia K, et al. British Society for Haematology guideline for anticoagulant management of pregnant individuals with mechanical heart valves. Br J Haematol 2023;202 (03):465–478
22 De Santo LS, Romano G, Della Corte A, et al. Mechanical aortic valve replacement in young women planning on pregnancy: maternal and fetal outcomes under low oral anticoagulation, a pilot observational study on a comprehensive pre-operative counseling protocol. J Am Coll Cardiol 2012;59(12):1110–1115
23 Roos-Hesselink JW, Budts W, Walker F, et al. Organisation of care for pregnancy in patients with congenital heart disease. Heart 2017;103(23):1854–1859
24 Vahanian A, Baumgartner H, Bax J, et al; Task Force on the Management of Valvular Hearth Disease of the European Society of Cardiology ESC Committee for Practice Guidelines. Guidelines on the management of valvular heart disease: the task force on the management of valvular heart disease of the European Society of Cardiology. Eur Heart J 2007;28(02):230–268
25 Oran B, Lee-Parritz A, Ansell J. Low molecular weight heparin for the prophylaxis of thromboembolism in women with prosthetic mechanical heart valves during pregnancy. Thromb Haemost 2004;92(04):747–751
26 Berresheim M, Wilkie J, Nerenberg KA, Ibrahim Q, Bungard TJ. A case series of LMWH use in pregnancy: should trough anti-Xa levels guide dosing? Thromb Res 2014;134(06):1234–1240
27 Barbour LA, Oja JL, Schultz LK. A prospective trial that demonstrates that dalteparin requirements increase in pregnancy to maintain therapeutic levels of anticoagulation. Am J Obstet Gynecol 2004;191(03):1024–1029
28 Goland S, Schwartzenberg S, Fan J, Kozak N, Khatri N, Elkayam U. Monitoring of anti-Xa in pregnant patients with mechanical prosthetic valves receiving low-molecular-weight heparin: peak or trough levels? J Cardiovasc Pharmacol Ther 2014;19(05):451–456
29 Elkayam U, Bitar F. Valvular heart disease and pregnancy: part II: prosthetic valves. J Am Coll Cardiol 2005;46(03):403–410
30 Salazar E, Izaguirre R, Verdejo J, Mutchinick O. Failure of adjusted doses of subcutaneous heparin to prevent thromboembolic phenomena in pregnant patients with mechanical cardiac valve prostheses. J Am Coll Cardiol 1996;27(07):1698–1703
31 Vause S, Clarke B, Tower CL, Hay C, Knight M(on behalf of UKOSS) Pregnancy outcomes in women with mechanical prosthetic heart valves: a prospective descriptive population based study using the United Kingdom Obstetric Surveillance System (UKOSS) data collection system. BJOG 2017;124(09):1411–1419
32 Khader KAAM, Saad AS, Abdelshafy M. Pregnancy outcome in women with mechanical prosthetic heart valves treated with unfractionated heparin (UFH) or enoxaparin. J Obstet Gynecol India 2016;66(05):321–326
33 Snape E, Thachil J, Clarke B, Vause S. Anti-Xa based dose changes during low molecular weight heparin anticoagulation for mechanical prosthetic heart valves during pregnancy. J Obstet Gynaecol 2018;38(05):721–722
34 Elkayam U. Anticoagulation therapy for pregnant women with mechanical prosthetic heart valves: how to improve safety? J Am Coll Cardiol 2017;69(22):2692–2695
35 Sbarouni E, Oakley CM. Outcome of pregnancy in women with valve prostheses. Br Heart J 1994;71(02):196–201
36 Khamoushi AJ, Kashfi F, Hosseini S, Alizadeh Ghavidel AR, Samiei N, Haddadzadeh M. Anti-coagulation during pregnancy in women with mechanical heart valves: a prospective study. Int J Fertil Steril 2011;5(01):47–51
37 Cousin B, Guglielminotti J, Iung B, Montravers P. Retrospective study of anaesthetic management of pregnancy patients with mechanical heart valve prosthesis and anticoagulants. Anaesth Crit Care Pain Med 2018;37(03):225–231
38 Samiei N, Kashfi F, Khamoushi A, et al. Pregnancy outcome after mechanical mitral valve replacement: a prospective study. J Tehran Heart Cent 2012;7(03):117–120
39 Meschengieser SS, Fondevila CG, Santarelli MT, Lazzari MA. Anticoagulation in pregnant women with mechanical heart valve prostheses. Heart 1999;82(01):23–26
40 Bian C, Qi X, Li L, Zhao J, Liu X. Anticoagulant management of pregnant women with mechanical heart valve replacement during perioperative period. Arch Gynecol Obstet 2016;293(01):69–74

41 Akhtar RP, Abid AR, Zafar H, Cheema MA, Khan JS. Anticoagulation in pregnancy with mechanical heart valves: 10-year experience. Asian Cardiovasc Thorac Ann 2007;15(06):497–501
42 Kariv S, Azibani F, Baard J, et al. Haemorrhage and other complications in pregnant women on anticoagulation for mechanical heart valves: a prospective observational cohort study. Cardiovasc J S Afr 2018;29(05):289–295
43 Lee JH, Park NH, Keum DY, Choi SY, Kwon KY, Cho CH. Low molecular weight heparin treatment in pregnant women with a mechanical heart valve prosthesis. J Korean Med Sci 2007;22(02): 258–261
44 Basude S, Hein C, Curtis SL, Clark A, Trinder J. Low-molecular-weight heparin or warfarin for anticoagulation in pregnant women with mechanical heart valves: what are the risks? A retrospective observational study. BJOG 2012;119(08):1008-–1013, discussion 1012–1013
45 Bhutta SZ, Aziz S, Korejo R. Pregnancy following cardiac surgery. J Pak Med Assoc 2003;53(09):407–413
46 Suri V, Keepanasseril A, Aggarwal N, et al. Mechanical valve prosthesis and anticoagulation regimens in pregnancy: a tertiary centre experience. Eur J Obstet Gynecol Reprod Biol 2011;159(02):320–323
47 Heuvelman HJ, Arabkhani B, Cornette JMJ, et al. Pregnancy outcomes in women with aortic valve substitutes. Am J Cardiol 2013; 111(03):382–387
48 Erba N, Gatti S, Hassan SAA, et al. Pregnancy outcomes in women with mechanical valve prostheses using vitamin K antagonist therapy: the experience of the Salam Centre for Cardiac Surgery in Sudan. Front Pediatr 2022;10(10):918547
49 Keepanasseril A, Pillai AA, Baghel J, et al. Alternatives to low molecular weight heparin for anticoagulation in pregnant women with mechanical heart valves in middle-income countries: a cohort study. Glob Heart 2021;16(01):68