Education article

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Anticoagulation in Pregnancy and Puerperium: *With a Focus on the Benefits and Risks of the Applications of Vitamin K Antagonists on the Prevention of MECHANICAL Heart Valves Thrombosis*

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SUMMARY

Introduction: The current number of women in the reproductive phase (from 15 to 45 years) in Europe is estimated at about 105 million, with about 5 million children annually born in average. About 1% of pregnancies among women in Europe are complicated by heart disease, the risk of cardiovascular disease in pregnant women being further increased by the fact that ever older women are giving birth.

Methods: Preparing this paper is based on a systematic PubMed search of existing professional databases and accessible medical journals and textbooks dealing with this subject matter.

Topic: Being certainly drugs with the best anticoagulant effect in situations of high risk for thrombosis, especially in patients with mechanical prosthetic heart valves during pregnancy, vitamin K antagonists (VKA) on the other hand also entail a well-known dose-related risk of embryo toxicity, genotoxicity, and hemorrhage in the fetus and in the mother. The choice of appropriate anticoagulant depends on the stage of pregnancy. In accordance with the North-American guidelines (American College of Chest Physicians - ACCP) for women already on oral vitamin K antagonists actively trying to conceive frequent pregnancy tests, and substitution of VKA with heparin drugs when pregnant are recommended rather than VKA replacement with low molecular weight heparin (Low Molecular Weight Heparin - LMWH) when planning a pregnancy. Heparin derivatives have no embryo toxic and fetotoxic characteristic effects of VKA but they are less effective at preventing valve thrombosis, due to which they have

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recently been superseded by improved techniques for monitoring effects of heparin, with a mentioned made that low molecular weight heparin used in high therapeutic doses requires obligatory (on a weekly basis) monitoring of anti-factor Xa coagulation activities.

Conclusion: Adequate anticoagulant therapy during pregnancy requires an analysis of risk factors for thrombosis, hemorrhage risk, consideration of comorbidities in pregnant women, especially renal function, especially taking into account the gestational age. Though it must be admitted that there is no absolutely safe anticoagulant therapy during pregnancy, a choice of the safest option regarding the stated risks for the mother and the child is of paramount importance.

Keywords: pregnancy, anticoagulant therapy, mechanical prosthetic valves

INTRODUCTION

The current number of women in the reproductive phase (from 15 to 45 years) in Europe is estimated at about 105 million, with about 5 million children annually born in average. About 1% of pregnancies among women in Europe are complicated by heart disease, the risk of cardiovascular disease in pregnant women being further increased by the fact that ever older women are giving birth [1].

Pregnancy is a condition of increased risk of thrombosis due to synergy of all the three components of the Virchow's triad [2]. Due to altered physiology in pregnant women and hormonal status procoagulant factors and the procoagulant state dominates. Levels of fibrinolysis inhibitor (PAI-1 or PAI-2) produced by the placenta are elevated, causing a decrease in fibrinolytic activity during pregnancy. On the other hand, additional thrombogenic effect is associated with changes in the levels of natural anticoagulants, namely, a reduction in protein S levels is recorded as early as the first trimester; the concentration of antithrombin (AT) decreases in case of a caesarean delivery. A series of homeostatic changes induced in pregnancy is associated with activated protein C resistance registered in a number of pregnant women [3-5]. Also, there is an increase in platelet-endothelial adhesion molecules as well as endothelial cell activation associated with a proinflammatory state, especially during labour or caesarean section when damage to blood vessels is incurred [2,6,7].

In addition, the gravid uterus compresses major blood vessels of the abdomen and pelvis, this resulting in venous dilatation and slowed venous flow, which poses a risk of deep venous thrombosis of the pelvis and legs. Consequently, in certain conditions during pregnancy there is a need for administering adequate anticoagulant therapy. Some diseases and conditions require the use of vitamin K antagonists (VKA), whose teratogenic potential presents a significant safety issue [2]. Though VKA administration represents the most effective anticoagulant therapy for the prevention of thrombosis in pregnant women with mechanical heart valves, at the same time it may lead to serious birth defects, embryopathy, even stillbirth [8]. Therapy with heparin drugs, especially with low molecular weight heparins (LMWH) has reduced adverse fetal outcomes, but, on the other hand was accompanied by a higher incidence of prosthetic valve thrombosis in patients with prosthetic heart valves. The risk of thrombosis in practice may be reduced by using higher doses of LMWH, more frequent testing and adjusting not only peak anti-Xa activity levels analyzed from a blood sample 4 h after subcutaneous injection of LMWH, but also trough anti-Xa activity levels, analyzed in the blood sample immediately prior to the administration of subcutaneous injections of LMWH. When administering LMWH in order to prevent thrombosis prosthetic valves, it is advised to maintain anti Xa activity values at a high therapeutic level [2].

METHODS

Preparing this paper is based on a systematic PubMed search of existing professional databases and accessible medical journals and textbooks dealing with this subject matter.

ORAL ANTICOAGULANTS DURING PREGNANCY

Anticoagulant therapy is indicated in pregnancy in women with mechanical prosthetic valves, with previous or current venous thrombosis and thromboembolism as well as in presence of a thrombus in the cardiac chambers, atrial fibrillation with a high thromboembolic risk, in pulmonary hypertension due to severe thrombophilia or if there is a history of recurrent miscarriage. Besides thrombophilia with recurrent miscarriage, anticoagulant therapy is also considered in cases of stillbirth, preeclampsia, post-thrombotic syndrome, ovarian hyperstimulation syndrome in the first trimester, known to be likely associated with a hypercoagulable state [2,9].

Oral anticoagulation with vitamin K antagonists provides better maternal protection against thrombosis than heparin preparations, though its administration may be associated with a potential risk of embryopathy, fetal malformation as well as loss, especially in the period of 6-12 weeks of gestation and prior to delivery [8,10]. It being considered by authors such as Dr. Celine Montovan that VKA administration, particularly between 6-12 weeks of pregnancy, may lead to embryotoxicity, this is a period when VKA replacement with heparin preparations is strongly suggested [9]. It is of special importance when VKAs are administered at higher doses or when the dose of warfarin is higher than 5 mg per day [9]. Warfarin in higher doses of 5 mg and more cause a higher percentage of fetal abnormalities, miscarriage and stillbirth [2].

Vitamin K antagonists (VKA) cross the placenta and may cause embriopathy in specific phases of the first trimester [10,11]. Also, VKA increase the risk of miscarriage, hemorrhaging and teratogenicity [10]. Administering VKA in absolute and relative sensitive period of fetal development (from 28 to 112 days) may cause fetal abnormalities, disturbances in fetal osteogenesis and chondrogenesis. In addition, there occur abnormalities of the CNS, such as microcephaly [12]. The most common fetal abnormalities associated with warfarin are: midfacial hypoplasia, stippled pineal gland (chondromalatia punctata), hypoplasia with nose, limb and finger deformities [9,10,13].

Rare anomalies such as the formation of the dorsal middle line dysplasia have been described as well as agenesis of the corpus callosum, Dandy-Walker malformation, mid line cerebellar atrophy, ventral middle line dysplasia which may lead to atrophy of the *nervus opticus*. Blindness, epilepsy, deafness, respiratory distress, kidney agenesis or hypofunction, anal dysplasia, cleft lip and soft palate may likewise occur [10,13]. The risk of developing embryopathy is estimated at 5-7%, this percentage being higher when broadened to include the less pronounced CNS disorders induced by warfarin [9].

Due to the transfer of VKA through the placenta, the fetus is at significantly increased risk of hemorrhage. The immaturity of the fetal liver is a major cause of slow warfarin metabolism and low clotting factor levels in the fetus itself, the anticoagulant effect thus being markedly greater than in the mother. Furthermore, there is a high risk of hemorrhage in newborns during childbirth, sometimes with a possible fatal outcome. Therefore, interruption of VKA therapy at 34-36 weeks of gestation is recommended or a cesarean section suggested reducing the possibility of hemorrhage in the child due to birth trauma [9]. Some authors specifically point out the development of retroplacental hematoma as a common cause of fetal loss [14]. The European guidelines state that VKA administration in the third trimester of pregnancy can cause fetal and neonatal hemorrhage and placental abruption as well as lead in any trimester to abnormalities in the central nervous system, such as optic atrophy, microcephaly, mental retardation, hypotonia and spasticity [9,10,11,15].

Along with hemorrhagic complications and damage to the central nervous system, VKA administration in the second and third trimester causes a number of minor malformations and other neural-developmental problems. Larger cohort studies do not enlist the occurrence of major neurological anomalies when VKAs are administered in the second and third trimesters. Children whose mothers received VKAs during pregnancy do not differ from other children related to the mean intelligence quotient scores while differences in reading and solving arithmetic problems are described. Contrary to the above assertion made in recommendations by the ACCP, Dr. Judit Wesseling has registered twice higher risk of minor neurological disorders and a higher incidence of reduced intelligence quotient (less than 80%) in children exposed to VKA during the second and third trimester

of pregnancy (OR 2. 1, CI 1. 2-3.8) [16-18].

Teratogenic effect of VKA is dose-dependent, being lower at acenocoumarol doses of less than 2 mg or warfarin doses of less than 5 mg than at doses above 5 mg (8 vs. 2.6%). However, in certain populations even this dose proved to be too large, for example in Japanese examinees [12,19]. W.C. Chan states the embryopathy incidence of 6.4%/ in mothers receiving warfarin doses less than 5 mg [9,20]. Some studies report 81% of fetal complications in pregnant women with warfarin administered in a dose higher than 5 mg [13].

With a warfarin dose exceeding 5 mg/day embryopathy is registered in 9% and fetal complications in 88% of the cases. At doses of warfarin less than 5 mg embryopathies are not registered while the risk of fetal complications is 15% [21,22]. The North American recommendations (ACCP) state that the use of vitamin K antagonists during the first 6 weeks carries no risk of embryopathy, as well as that warfarin should be replaced with heparin preparations in the period of 6-12 weeks [10]. In the study by Chan and associates none of the 125 women using warfarin only during the first 6 weeks of gestation gave birth to a child with birth defects [10,20].

Middeldorp S. reports that teratogenic effect only occurs when VKAs are administered in the 6-12 weeks of gestation period [16].

Schaeafer further states that none of the 235 newborn infants whose mothers received VKA only during the first 8 weeks of gestation had abnormalities [10].

Frequent pregnancy tests are advised to women already taking oral vitamin K antagonists trying to conceive. At the time of conception, substitution of vitamin K antagonists by heparin preparations is suggested not VKA replacement with LMWH while planning conception [10].

According to the North American recommendations, the use of VKA is not recommended three weeks before childbirth [10].

It should be specifically underlined that VKA should not be used from 6-12 weeks of pregnancy and 3 weeks before delivery and that during this period parenteral heparin preparation administration along with adequate monitoring of achieved anticoagulant

STAGE OF PREGNANCY	TERATOGENICITY AND FETAL TOXICITY
From fertilization till the 27th day	No effects at this stage, malformations do not occur, there is no implantation or abortion occurs
From 28th to 50th day	Absolutely sensitive stage, important for the formation of fetal organs, there is a high risk of teratogenicity
From 51th to 112th day	Relatively sensitive period, the formation of the genital area, soft palate is not yet completed, teratogenicity like palate cleft
From 113th to delivery	Potentially sensitive stage, the risk of teratogenicity is small, attention should be paid to the fetal toxicity

Table 1. General review of pregnancy stages, fetal toxicity and fetal teratogenicity in use of VKA [12]

Medicine	FDA category	Adverse effects	Teratogenicity	Use during lactation	Remark
Vitamin K antagonists (warfarin, aceno-coumarol)	X	Teratogenicity, fetal bleeding complications	Yes	Allowed; Small amounts of metabolites pass into breast milk, but without the side effects	-
Heparin (UFH)	C	Bone demineralization during extended use, osteoporosis, fractures in mother, risk of HIT, higher incidence of thrombosis than with warfarin	No	Allowed	-
Low molecular weight heparins (LMWH)	B	Lower risk of HIT and osteoporosis than with UFH	No	Allowed	
Danaparoid	B	-	No	Allowed	-

Table 2. The effects of antithrombotic drugs in pregnancy and puerperium [1,12]

effect is strongly advised in the course of this period.

PARENTERAL ANTICOAGULANTS IN PREGNANCY

Unfractionated heparin and low molecular weight heparins do not cross the placenta and therefore do not affect the formation and development of the fetus, but carry an increased risk of thrombotic complications in mothers with prosthetic heart valves, even with a properly adjusted dose and careful monitoring [14,21].

Heparin administration during pregnancy virtually eliminates the risk of embryopathy, has no adverse effect on development of the fetus, but does not provide protection from thrombotic complications equivalent to that of ensured by VKA administration [14,23].

Chan W.C. states that the use of heparin products in the period between 6 and 12 weeks does not lead to teratogenicity, but such a therapeutic approach entails a much higher risk of thromboembolic complications of 9.2% [9,20].

A combined approach of treatment with VKA and heparin drugs throughout the period of absolute risk for embriopathy, significantly, almost completely eliminates the risk of embryopathy but increases the risk of thromboembolism and thrombosis of prosthetic valves [14].

Tanaka H. and his colleagues indicate the complexity of the problem of VKA administration in pregnant women. Being much safer for the fetus, unfractionated heparin administered in appropriate doses is recommended for the prevention of thrombosis valve (2-3 times prolonged aPTT compared to controls) but does not prevent completely valve thrombosis formation [8]. On the other hand intracranial hemorrhage is recorded in patients treated with UFH along with considerable aPTT variation over 50% during the night [8]. Recent studies find warfarin the best suited anticoagulant medication for preventing valve thrombosis, noting that the valve thrombosis also register at VKA therapy, as confirmed by Chan who determined an overall incidence of valve thrombosis of 4% [8,20]. During administration of VKA individual cases of intracranial hemorrhage in the mother have also been recorded [8]. The risk of hemorrhage in mothers receiving anticoagulant therapy is estimated at around 2.5%, pointing out that about 80% hemorrhage is peripartal [21].

It should be emphasized that in pregnancy there is an increase in the glomerular filtration rate as well as in plasma volume, consequently resulting in decreased plasma drug concentrations. In addition, placental heparinase activity is elevated, necessitating higher doses of LMWH. This also requires weekly checks of plasma anti-Xa levels in order to attain a target level of 1.0-1.2 U/mL [21,24].

Quinn finds that a mean increase in the dose of LMWH of 54.4% is necessary during pregnancy to achieve the optimum anticoagulant effect [24]. More recent research suggests that along with peak anti-Xa activity there should also be monitored trough (lowest) levels of anti-Xa activity [24]. It is known that pregnant women receiving enoxaparin every 12h with peak anti-Xa levels of 0.7-1.2 U/mL are associated with sub-therapeutic trough levels, with a pre-dose level of less than 0.6 IU/mL in over 50% of cases [24-27].

We would like to lay particular stress on the fact that low molecular weight heparins (according to the summary of product characteristics) are not indicated for the prophylaxis of thrombosis in patients with prosthetic heart valves [21,28-30].

In his study, *Salazar E.* accentuated 2 cases of female patients who between 6-12 weeks of pregnancy developed fatal valve thrombosis upon replacement of acenocoumarol with heparin despite adequate anti-coagulation with aPTT ratio maintained between 55-95 seconds (control time of 30-35 seconds) concluding that subcutaneous heparin with a target aPTT 1, 5-2, 5 times the control heparin is not effective in preventing prosthetic valve thrombosis [21,31].

Thrombogenicity valve, clinical and laboratory parameters of patients should be kept in mind when choosing the most appropriate therapeutic regimen for pregnant women with mechanical valves. Factors known to increase the risk of prosthetic valve thrombosis are: older types of valves (*ball-cage valves, Starr-Edwards, Bjork-Shiley valve standard, Omniscience*) compared with newer types (St Jude Medical, Medtronic Hall), then the mitral valve position more than the aortic position, heart failure, an ejection fraction of less than 35%, atrial fibrillation, previous history of thromboembolism [2,10,21,32]. A VKA is the most reliable anticoagulant in pregnancy.

The decision on whether to administer a VKA depends on the risk of valve thrombosis. It should never be neglected that prosthetic heart valve thrombosis is a potentially fatal condition in all patients, particularly pregnant women [20,27].

RECOMMENDATIONS	ANTICOAGULANT REGIME
ACC/AHA guidelines 2014.	1. Continuation of VKA therapy during the first trimester if the **dose of warfarin is lower than 5 mg** with a target INR of 3.0 (2.5-3.5) or 2. LMWH in 2 doses achieving high therapeutic peak levels of anti-Xa activity of 0.8-1.2 U / mL (taken 4-6 h after drug administration); 3. If the **daily dose of warfarin is higher than 5mg** during the first trimester, **administration** of iv infusion of UFH with target aPTT 2 x longer than the control * Consider adding aspirin in low doses of 75-100mg
ESC guidelines 2011.	1. In patients with prosthetic mechanical valves in cases when **less than 5 mg of warfarin** is required to achieve adequate INR /for achieving adequate INR is required **less than 5 mg of warfarin** continue with the application of warfarin till the 36 weeks of pregnancy; 2. If the required warfarin dose is **greater than 5 mg**, then switch between 6-12 weeks from VKA to treatment with iv infusions UFH or LMWH **s.c.** with a one-week control of anti-Xa levels (a target value of 0.8-1.2 U/ml in the blood sample taken 4-6 hours after injection)

Table 3. The recommendations and the various modalities of administering parenteral anticoagulants and vitamin K antagonists during pregnancy in patients with mechanical heart valves compared with the warfarin dose needed to achieve a therapeutic INR [1,7,33]

PROSTHETIC VELVE THROMBOSIS PREVENTION IN PREGNANT WOMEN

American ACC/AHA (*American College of Cardiology and the American Heart Association*) guidelines, the ESC guidelines (*European Society of Cardiology*) and ACCP (*American College of Chest Physicians*) vary considerably among themselves in approaches to mechanical prosthetic heart valve thrombosis prevention [24]. **The ACC/AHA guidelines** permit the continuation of vitamin K antagonists therapy during the first trimester if the warfarin dose is lower than 5 mg or where low molecular weight heparins are administered in 2 doses to achieve high therapeutic peak levels of anti-Xa activity of 0.8-1.2 U/mL in a sample taken 4–6 hours after subcutaneous injection [24,33]. In case that the daily dose of warfarin is higher than 5 mg during the first trimester the same guidelines alternatively propose the use of intravenous infusion of heparin with the target aPTT twice longer than the control [24,33]. Administration of low-dose aspirin (75-100 mg daily) may be advised as an additional medication during the second and third trimester [24]. If warfarin is the drug of choice during pregnancy, its dosing aims to achieve a target INR of 3.0 (2.5-3.5).

The ACCP (*American College of Chest Physicians*) **guidelines** published in 2012 guidelines recommend continuation of warfarin therapy in high-risk patients with prosthetic valve thrombosis risk factors defined above [10,24]. In female patients with low risk for valve thrombosis subcutaneous administration of UFH is advised in order to achieve "mid-interval" aPTT at least 2 times higher than the control or anti-Xa level of 0.3-0.7 U/mL or alternatively low molecular weight heparin (LMWH) subcutaneously 6-12 weeks of gestation or throughout the entire pregnancy administered with 12h dosage regimen, it being recommended that target anti Xa levels planned for LMWH at the given dose regimen be achieved, monitored on a weekly basis [10,24]. In addition to low molecular weight heparin in high-risk female patients there may also be considered administering a once daily regimen of 75 or 100 mg low-dose aspirin [10,24]. In women with bileaflet aortic valve prosthesis with a lower risk of thrombosis achievement of slightly lower INR of 2.5 (2-3) using VKA therapy is advised instead of the target INR for patients with a high risk of 3.0 (2.5-3.5) [10].

The ESC guidelines 2011, in case of female patients with prosthetic mechanical valves when less than 5 mg of warfarin is needed to achieve an adequate INR also recommend continuation of warfarin up to 36 weeks of pregnancy with the risk of embryopathy less than 3%; and, if doses of warfarin greater than 5 mg between 6-12 weeks are necessary, switching to treatment with intravenous UFH infusions or LMWH (with monitoring to achieve an aPTT in the therapeutic range 2-2.5 higher than the control – A/N Author's Note) or LMWH with a one-week control of peak anti-Xa levels to attain a target value of 0.8-1.2

U/ml in the blood sample taken 4-6 hours after injection [23,34]. Trough levels of anti-Xa activity, so-called pre-dose levels are not yet sufficiently harmonized, especially with regard to the relationship between thromboembolism and hemorrhage, for any firm conclusions to be reached, but for the time being it is considered that they should be higher than 0,6 U/mL [1].

Heparin treatment is initiated with an **intravenous** bolus (starting dose) of 80 IU/kg (body weight bolus) followed by18 IU/kg/h infusion [35]. To achieve a therapeutic aPTT measured every 6h during the initial phase of treatment, it is recommended that UFH be administered by intravenous route at doses adjusted based on the Raschke's nomogram [35]. The standard dosage of **subcutaneous heparin** regimens in pregnancy is: 17,500 to 20000 IU every12 hours, or more precisely starting with the initial dose of 333 IU/ kg followed by the subsequent 2 x 250 IU/kg dose, it being advised that the mid-interval aPTT (measured 6h after the s. c. dose) be maintained to a ratio 2-3 times the control value [34-37].

When warfarin doses higher than 5

Table 4. The dosage of anticoagulant drugs [34,38-45]

UNFRACTIONATED HEPARIN (UFH) INTRAVENOUS	UNFRACTIONATED HEPARIN (UFH) SUBCUTANEOUS	ENOXAPARIN	NADROPARIN	DALTEPARIN	VITAMIN K ANTAGONISTS (VKA)
Dosing according to body weight: an initial bolus iv 5000-10000 IU or 80 IU/kg, then continue with 18 IU/kg/h iv Dose of heparin modify according to the aPTT, target aPTT 1.5-2 times higher than the control value (Rasche nomogram)	The initial dose of 333 IU/kg s.c., then continue 2 x 250 IU/kg s.c.	1mg/kg/12h s.c.	2x86 IU/kg s.c.	2 x 100 IU/kg (max to 18000 IU per day)	Dosing according to the INR; target INR 2-3 (3,5)

Table 5. Comparative review of current recommendations for anticoagulant therapy in patients with mechanical valves [45]

Recommendation	ACC / AHA	ACCP	ESC
Oral anticoagulants	Can be used throughout pregnancy, with substitution by dose adjusted UFH or LMWH *during weeks 6-12 of gestation* if preferred by the patient	Can be used throughout pregnancy **in high risk patients**, with substitution by dose adjusted LMWH or UFH close to term (time frame not specified but normally 48h before delivery)	**If warfarin dose is ≤ 5mg daily**, oral anticoagulants *throughout pregnancy* is the safest regimen (associated with <3% embryopathy)
Anticoagulation Target	INR 3 for all patients with mechanical prosthetic heart valves	INR 2-3 for patients with bileaflet aortic valves without high risk features	No INR target recommendation
Heparin Derivatives (UFH, LMWH)	Monitored UFH or LMWH might be options throughout gestation or during weeks 6-12 of gestation	Dose adjusted and monitored LMWH or UFH throughout pregnancy or during weeks 6-12 of gestation is acceptable	LMWH or UFH during weeks 6-12 of gestation should be considered if high dose warfarin is required to maintain therapeutic anticoagulation
LMWH	**LMWH** dose should be adjusted to give an anti-factor Xa activity 0.7-1.2U/ml 4-6h after administration	In **low risk patients**, **LMWH** should be given twice daily and the dose adjusted to achieve the manufacturer's peak inhibition of anti -factor Xa 4h after s.c. injection	**LMWH** dose should be adjusted to give an anti-factor Xa activity of 0.8-1.2 U/ml 4-6h after administration
Aspirin	Low dose aspirin in addition to anticoagulation during the second and third trimesters	Low dose aspirin in addition to anticoagulation in high risk patients	Aspirin in addition to anticoagulation is not recommended

HIGHER RISK Old generation MPHV in mitral position, MPHV in tricuspid position atrial fibrillation, history of TE on heparin	LOWER RISK New generation MPHV in mitral position and MPHV in aortic position
	LMWH SQ Q 12h (**through anti-Xa ≥ 0.6** IU/ml, **peak anti-Xa < 1.5** IU/ml), then **UFH iv (aPTT > 2.0)** to parturition
Warfarin (INR 2.5 - 3.5) for 35 to 36 weeks followed by **iv UFH (aPTT >2.5)** to parturition or **LMWH through (pre-dose) anti-Xa ≥ 0.7 + ASA*** 81 to 100mg /day	**UFH s.c. (mid-interval aPTT 2.0-3.0) or LMWH (through anti-Xa ≥ 0.6** IU/ml, for 12 weeks. followed by warfarin (INR 2.5-3.0) up to 35 weeks, then s.c. UFH (**mid-interval aPTT 2.0-3.0) or LMWH (through anti-Xa ≥ 0.6** IU/ml)
OR	OR
LMWH SQ Q 12h **through anti-Xa ≥ 0.7** IU/ml, **peak anti-Xa < 1.5** IU/ml or **UFH SQ** Q12h **or iv (mid interval aPTT 2.5-3.5**) for 12 weeks, followed by **warfarin (INR 2.5 to 3.5)** to 35 to 36 weeks, then **UFH** iv (aPTT > 2.5) or **LMWH through (pre-dose) anti-Xa ≥ 0.7** to parturition + **ASA*** 81 to 100mg /day	**LMWH SQ** Q 12h **through anti-Xa ≥ 0.6** IU/ml, **peak anti-Xa < 1.5** IU/ml or **UFH SQ** Q12h **or iv** (mid interval **aPTT 2.0-3.0**) for 12 weeks, followed by **warfarin (INR 2.5 to 3.0)** to 35 to 36 weeks, then **UFH iv (aPTT > 2.0)** to parturition UFH s.c. (mid interval aPTT 2.0-3.0) or LMWH (through anti-Xa ≥ 0.6 IU/ml)

Table 6. Recommendation for anticoagulant therapy for woman with MPHV during pregnancy in relation to thromboembolism risk [24,36]

* acetylsalicylic acid

mg are required to maintain the target INR, in the first trimester it is advised to switch from warfarin to LMWH therapy with precisely tailored dosing regimens along with monitoring of anti-Xa activity [24].

All of the above guidelines agree that it is harmful to administer LMWH without regularly monitoring the patient's anti-factor Xa levels [2,10,15,24,33,34].

PERIPARTUM USE OF ANTICOAGULANTS

According to the North American ACCP guidelines 2012, VKA administration is not recommended three weeks before anticipated delivery [10]. The ACC/AHA 2014 guidelines advise discontinuation of VKA in 36th week and initiation of therapy IV UFH (in recommended doses sufficient to achieve target therapeutic aPTT levels that should exceed approximately 2-2.5 times the control value - A/N) it being advised that UFH be stopped about 4 to 8 hours prior to expected delivery and restarted 4 to 6 hours after delivery in the absence of significant bleeding. Then, VKA therapy resuming is recommended 24 h after delivery [23,33].

The ESC guidelines advise stopping VKAs at 36 weeks of gestation and their replacement with IV UFH or LMWH until 36 hours before delivery, when LMWH is switched to IV UFH [24,34]. **The ACCP guidelines** advise that patients with very high risk of thromboembolism (older generation valves in the mitral position and previous thromboembolism) should continue with warfarin administration until close to delivery, generally 48 hours before the anticipated time of delivery, when VKA therapy is replaced with UFH or LMWH [10,24].

In the event of unexpected labour, prior to the scheduled date in the patient on oral anticoagulant therapy, a caesarean section is advised because of the risk of fetal intracranial hemorrhage in case of vaginal delivery or for other obstetric reasons [24]. *Panduranga* advises discontinuation of IV UFH infusion 4-6 hours before delivery and restarting it 4-6 h after delivery [24]. Montavon considers that UFH or LMWH should be introduced 12 hours following cesarean section or 6h after vaginal delivery in conjunction with a VKA on the following day to be overlapped with heparin preparations until therapeutic INR values are achieved [9].

Therapy with heparin preparations, especially low molecular weight heparins, has proven effective in reducing adverse effects on the fetus, but is associated with a high rate of valve thrombosis in female patients with prosthetic heart valves.

Administration of anticoagulant therapy in nursing mothers

Anticoagulant therapy may be continued soon after birth, depending on the type of delivery and whether adequate hemostasis is achieved, usually after 6-12h, that is, 12-24h after epidural catheter removal. Treatment is initiated with

unfractionated heparin or LMWH administered parenterally, overlapped with VKA on the following day, continued for two consecutive days until a therapeutic INR is achieved, when UFH or LMWH therapy is ceased [10]. Though VKA administration to lactating women is considered safe for the newborn, it is thought that the transfer of coumarin into maternal milk may, however, leave exclusively breastfed babies at risk for vitamin K deficiency [9,15].There is no evidence that vitamin K supplementation longer than the one commonly recommended in newborns can compensate for this defect, but it was determined that INR monitoring in the infant may detect those who developed vitamin K deficiency [9] Recommendations, on the other hand, advise that warfarin, acenocoumarol and heparin are safe to use during lactation [10]. It is also advisable for nursing mothers to continue therapy with LMWH, danaparoid or hirudin, but not with fondaparinux [10]. According to the North American recommendations, low doses of aspirin, if indicated, can likewise be safely administered to nursing mothers, although some authors advise caution pointing to potential problems, such as rare occurrences of Reye's syndrome in neonates and infants [1,10,12].

Concise practical recommendations

Based on the foretasted, the following recommendations can be set apart:

For women already on oral vitamin K antagonists (VKA) trying to conceive, according to the current ACCP guidelines frequent pregnancy tests are recommended as well as substitution of VKA with preparations of heparin when pregnant rather than an option of replacing VKA with low molecular weight heparins during the pre-conceptual period [2,10,15,33,34,46,47].

VKA administration, especially between 6-12 weeks of pregnancy, may lead to embryotoxicity, it therefore being a period when VKA replacement with heparin preparations is specifically advised, which is of crucial importance when VKA is given in higher doses, that is when the warfarin dose is greater than 5 mg daily and that of acenocoumarol higher than 2 mg as higher doses of VKA are associated with a higher rate of fetal abnormalities, stillbirth and miscarriage, while in some studies with VKA used at lower doses no embryopathy was recorded and the risk of fetal complications was several fold lower [2,8,20,21].

It is considered that the use of vitamin K antagonists during the first 6 weeks does not carry the risk of embryopathy as well as that from 6-12 weeks gestation warfarin should be replaced with heparin preparations [10]. The administration of heparin products between 6 and 12 weeks of pregnancy does not lead to teratogenicity, but such a therapeutic approach entails a much higher risk of thromboembolic complications of 9.2%, noting that the use of UFH in adequate doses recommended for valve thrombosis prophylaxis does not absolutely prevent valve thrombosis occurring as well as the fact that there is also a risk of considerable variation of aPTT levels along with a chance of bleeding, even intracranial hemorrhage [7,8,19].

The increasing use of LMWH (recommended by current guidelines but not yet officially indicated for the prevention of thrombosis of mechanical valves in the summaries of the drug characteristics) requires treatment with therapeutic doses, determined based on periodic monitoring of the anti-Xa activity (measurements of peak anti-Xa levels mandatory, it also being possible in specific cases to measure through anti Xa activity levels) [23-29].

Therefore, the guidelines allow for the possibility of considering VKA administration during the first trimester in case that the daily warfarin dose of less than 5 mg and the acenocoumarol one of less than 2 mg is sufficient to achieve therapeutic anticoagulation, especially in patients with valves of high thrombogenicity, reduced ejection fraction, atrial fibrillation, a previous episode of thromboembolism and other risk factors for thromboembolic complications [1,23]. A target INR of 2.5 is recommended in patients with newer generations of mechanical aortic valves (bileaflet or current generation tilting single disc), having no additional factors for thromboembolism, while a target INR of 3 is advised for patients with the foretasted aortic valves and risks for thromboembolism (atrial fibrillation, systolic heart failure, previous thromboembolism), older generation of aortic valves (ball in cage valves) or mitral valves [33]. Replacement of peroral VKA therapy between 6-12 weeks with therapeutic doses of UFH or LMWH is advisable in case that higher doses of VKA are required to achieve the target INR for a specific valve (warfarin over 5 mg daily, acenocoumarol over 2 mg daily) [1].

Therapeutic doses of heparin are determined based on aPTT values and the initial therapeutic dose of LMWH in a subcutaneous regime applied twice daily, in the further course to be optimized to the target based on the levels of anti Xa [1]. The ACCP guidelines also suggest the possibility of administering UFH via the subcutaneous route, it being advised that the dose should be adjusted to maintain the mean interval of aPTT value (at least 2, that is, more precisely 2-2.5 times higher than the control – A/N) or anti X target values from 0.35 to 0.75 U / mL [10].

Due to the VKA transfer to the fetus and immaturity of the fetal liver, the fetus is at greatly increased risk of hemorrhage, there is a possibility of retro placental hematoma, placenta abruption and fetal loss. Therefore, interruption of VKA therapy at 34-36 weeks of gestation is generally recommended or a cesarean section suggested reducing the possibility of hemorrhage in the child due to birth trauma, though in some cases entailing very high risk of valve thrombosis VKAs may be administered even 48 hours before birth [8,13]. VKA administration in the third trimester of pregnancy can cause fetal and neonatal hemorrhage as well as placental abruption while in any trimester it can lead to certain central nervous system anomalies [8-10,15].

It is advised that VKA be ceased in 36th week, and then followed by IV UFH or LMWH until 36 hours prior to delivery, when LMWH are replaced with IV UFH [23,34]. UFH is discontinued 4-6 hours before the expected time of delivery and restarted 4-6 h after delivery in the absence of significant bleeding (there are positions that UFH or LMWH are to be introduced 12 hours after cesarean section), with/while VKA therapy continuation may be recommended 24 hours after delivery [8,23,33]. Vitamin K antagonists, unfractionated heparin and LMWH may be safely used during lactation [10].

CONCLUSION

The appropriate use of anticoagulant therapy during pregnancy requires an assessment of potential benefits of the administered drug in the corresponding indication versus alternative medicines also taking into account possible complications caused by the specific drug administered that may affect the fetus (teratogenicity, fetotoxicity or fetal death). In addition, there is a need to assess the risk for thrombosis in the mother, with special attention paid to potential hemorrhagic complications. Personalization of therapy requires an assessment of risk factors for thrombosis, the risk for bleeding, consideration of comorbidities in the mother, especially renal function, particularly having regard to the stage of pregnancy. There is no absolutely safe anticoagulant treatment in pregnancy, but selecting the safest option in relation to the stated risks for the mother and the child is always an overriding concern.

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Primena antikoagulantne terapije u trudnoći i puerperijumu: *sa fokusom na korist i rizik od primene antagonista vitamina K na prevenciju tromboze mehaničkih srčanih zalistaka*

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KRATAK SADRŽAJ

Uvod: U Evropi živi oko 105 miliona žena u reproduktivnoj fazi (od 15 do 45 godina), a tokom godine se prosečno rodi oko 5 miliona dece. Oko 1% trudnoća kod žena u Evropi je komplikovano srčanim bolestima, a činjenica da sve starije žene rađaju, povećava rizik od kardiovaskularnih bolesti trudnica.

Metodologija: Priprema ovog rada bazirana je na sistematskom pretrazivanju PubMed: postojecih strucnih baza dostupnih medicinskih casopisa i udzbenika koji se bave ovom tematikom u periodu 1999. do 2015.

Tema: U stanjima visokog rizika za nastanak tromboze, naročito u bolesnica sa mehaničkim veštačkim zaliscima u trudnoći antagonisti vitamina K (VKA) predstavljaju lekove sa najboljim antikoagulantnim efektom, ali na drugoj strani i dobro poznatim dozno zavisnim rizikom od embriotoksičnosti, fetotoksičnosti, hemoragijom kod fetusa i kod majke. Izbor odgovarajućeg antikoagulansa zavisi od stadijuma trudnoće. Po savetu severno-američkih preporuka (*American College of Chest Physicians – ACCP*) za žene koje već koriste peroralne antagoniste vitamina K (VKA) i pokušavaju da ostanu trudne, savetuju se česti testovi trudnoće, supstitucija VKA preparatima heparina kada zatrudne, pre nego zamena VKA sa niskomolekularnim heparinima (*Low Molecular Weight Heparin – LMWH*) u periodu planiranja trudnoće. Heparinski derivati nemaju embriotoksično i fetotoksično dejstvo karakteristično za VKA, ali imaju slabiji efekat na sprečavanje tromboze valvule, što se u novije vreme pokušava nadomestiti savršenijim tehnikama praćenja dejstva heparina, uz napomenu da se niskomolekulski heparin koristi u visokim terapijskim dozama uz obavezno (sedmično) praćenje aktivnosti anti Xa faktora koagulacije.

Zaključak: Pravilna antikoagulantna terapija u trudnoći zahteva analizu faktora rizika za nastanak tromboze, rizika za krvarenje, sagledavanje komorbiditeta kod trudnice, naročito renalne funkcije, posebno imajući na umu gestacionu starost trudnoće (*gestation age*). Apsolutno sigurna antikoagulantna terapije u trudnoći ne postoji, ali se u odnosu na navedene rizike za majku i dete mora odabrati najbezbednija opcija.

Ključne reči: trudnoća, antikoagulantna terapija, mehaničke veštačke valvule

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