JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY
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PUBLISHED BY ELSEVIER

VOL. 68, NO. 16, 2016
ISSN 0735-1097/$36.00
http://dx.doi.org/10.1016/j.jacc.2016.06.076

REVIEW TOPIC OF THE WEEK

Anticoagulation During Pregnancy

Evolving Strategies With a Focus on Mechanical Valves

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ABSTRACT

Pregnancy is associated with a hypercoagulable state. Women requiring anticoagulation need careful attention throughout pregnancy and the post-partum period. The choice of anticoagulant therapy, the degree of monitoring, and the therapeutic target should be modulated by balancing the risks and the benefits to the mother and fetus. Many of the available anticoagulant agents may be used safely in pregnancy, but they are disadvantaged by competing efficacy and risks to the mother and fetus. For example, vitamin K antagonists are the most efficacious for preventing mechanical valve thrombosis, but they pose risks to the fetus. Collaborative research that collects patient-level data will help clinicians navigate the intricate process of anticoagulation in pregnancy. Development of anticoagulant agents that are homogeneous, efficacious, safe to the fetus, and not affected by physiological perturbations of pregnancy will have tremendous effect on the outcomes of pregnancy in women who require anticoagulation. (J Am Coll Cardiol 2016;68:1804–13) © 2016 by the American College of Cardiology Foundation.

Pregnancy is a prothrombotic state. The coalescence of venous stasis and hypercoagulability results in nearly a 5-fold increase in the risk of venous thromboembolism (VTE) during pregnancy. This risk remains elevated until 12 weeks post-partum (1). The goal of anticoagulation during pregnancy is to safely balance the maternal risk of thromboembolism and hemorrhage with the fetal risk of exposure to oral vitamin K antagonists (VKAs). The continuously changing pharmacokinetics of low molecular weight heparins (LMWH) during the various stages of pregnancy adds an additional challenge. The risks of various anticoagulation strategies must be acknowledged, and the choice of anticoagulant agent must be individualized on the basis of maternal and fetal factors (**Central Illustration**). Factors to consider include cumulative risks of the underlying disease process that warrants anticoagulation, medication side effects, compliance with medical therapy, and physician/patient choices for mode of delivery.

This review will examine strategies for anticoagulation during and after pregnancy, with a focus on women with mechanical heart valves. Development of more standardized monitoring protocols and the use of novel anticoagulant agents will be discussed.

RELEVANT PHYSIOLOGY IN PREGNANCY

RISK OF THROMBOSIS. As pregnancy progresses, the risk of hypercoagulability increases, due to increasing levels of thrombogenic factors VII, VIII, and X; von Willebrand factor; and fibrinogen, and decreases in protein S (2). The risk is highest in the immediate post-partum period and slowly decreases back to pre-pregnancy levels by 8 to 12 weeks post-partum (3). In accordance with these observations, one might expect most thrombotic complications to occur in the post-partum period. However, in women with mechanical heart valves, valve thrombosis often occurs during the first trimester (4). In contrast, VTE in

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Manuscript received April 24, 2016; revised manuscript received May 24, 2016, accepted June 6, 2016.

pregnancy occurs in a more predictable fashion, with the highest risk in the puerperium (5). Valve thrombosis may occur earlier in pregnancy due to subtherapeutic anticoagulation during transition from VKAs to heparins in the early stages of pregnancy, continuously changing anticoagulant agent pharmacokinetics (particularly LMWH) in pregnancy that lead to underdosing, or other, unidentified homeostatic factors germane to patients with mechanical valves (6–8). In addition, some women may discontinue VKAs once a diagnosis of pregnancy is made due to concerns about the teratogenic effects of these agents. This may occur prior to the initiation of another anticoagulant agent, leading to lapses in anticoagulation.

RISK OF BLEEDING. Delivery poses the greatest risk for bleeding. Women must be transitioned off long-acting anticoagulant agents to receive regional anesthesia or undergo Cesarean delivery (4). The American Society of Regional Anesthesia and Pain Medicine recommends that women have an international normalized ratio (INR) ≤1.5 or that LMWH is discontinued for at least 12 to 24 h before undergoing lumbar instrumentation (9). Additionally, VKAs cross the placenta, increasing the risk of fetal bleeding during delivery. Therefore, a delicate balance must be achieved to minimize these risks while protecting the gravida against thrombosis.

DRUG PHARMACODYNAMICS AND PHARMACOKINETICS. The most significant increases in glomerular filtration rate occur during the second trimester and continue through the post-partum period (10). Medications that are cleared by the kidney typically require proactive dose-adjustment throughout pregnancy. These adjustments for maternal physiological changes are imperative in the case of mechanical valves. **Table 1** summarizes select anticoagulant agents and their implications in pregnancy, with Food and Drug Administration (FDA) pregnancy category classifications. Several decades ago, the FDA established 5 categories to indicate the potential of a drug to cause birth defects if used during pregnancy (Online Table 1). The categories are determined by the reliability of documentation and the risk to benefit ratio. They do not take into account any risks from pharmaceutical agents or their metabolites in breast milk. Most currently available anticoagulant agents are category B; VKAs are classified as category X for their first-trimester effects, except in the presence of mechanical heart valves, where they are considered category D (11,12). However, in December 2014, the FDA published the Pregnancy and Lactation Labeling Rule, which requires the removal of these categories from all human prescription drugs and biological products, and replaces them with subsections that provide details about the use of the drug in pregnancy and lactation in women and men of reproductive potential (13). The pregnancy section will include potential risks to the developing fetus, known dosing alterations in pregnancy, effects of timing and duration of exposure during pregnancy, maternal adverse reactions, effects of the drug on labor and delivery, and information on a pregnancy exposure registry for the drug, if one exists. These changes went into effect on June 30, 2015. Most available medications will not have been relabeled by the time this document is published, and their current labels still carry the prior category classification.

ABBREVIATIONS AND ACRONYMS

INR = international normalized ratio

LMWH = low molecular weight heparin

TEC = thromboembolic complications

UFH = unfractionated heparin

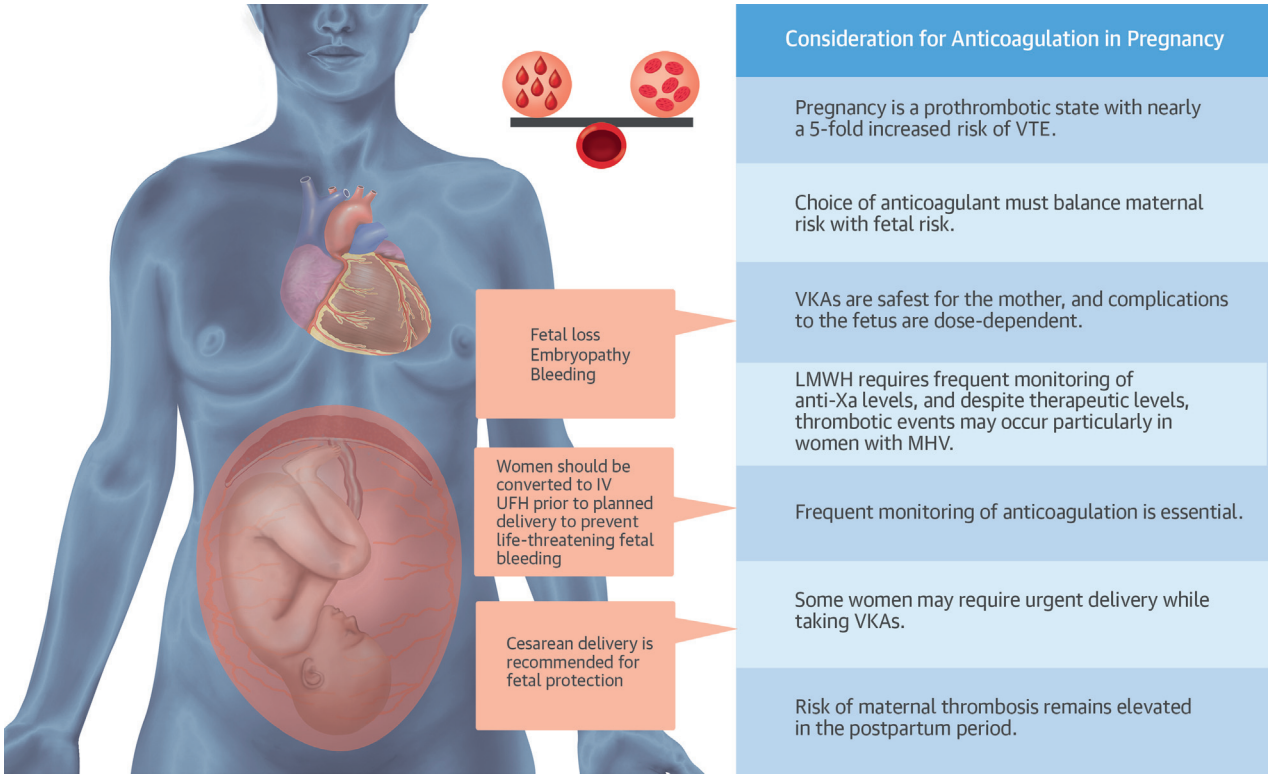
VKA = vitamin K antagonist

VTE = venous thromboembolism

FETAL CONSIDERATIONS. VKAs cross the placenta and have a dose-dependent relationship with increased adverse outcomes, such as miscarriage, stillbirth, and embryopathy, occurring predominantly at doses >5 mg daily (14). The rate of miscarriage (<24 weeks gestation) in a large series of pregnant patients with mechanical valves was 28.6% in women receiving VKAs in the first trimester compared with 9.2% in women receiving any form of heparin ($p < 0.001$) (4). The risk of late fetal mortality (>24 weeks gestation) was also significantly higher in women who received VKAs in the first trimester ($p = 0.016$). In a meta-analysis of studies of anticoagulant agents in pregnancy, the rate of fetal wastage, defined as spontaneous abortion, therapeutic abortion, stillbirth, and neonatal death, was 19.2% in the low-dose (≤5 mg) warfarin group versus 63.9% in the high-dose group. Importantly, a heparin strategy in the first trimester followed by VKAs in the remainder of pregnancy did not eliminate the risk of fetal wastage (22.7%), in contrast to a strategy of LMWH throughout pregnancy which was associated with a 12.2% rate of fetal wastage (15).

Vitamin K antagonism suppresses carboxylation of gamma-carboxyglutamic acid, a component of osteocalcin and other bone proteins, which may result in fetal embryopathy (occurrence 4% to 7%), characterized by nasal cartilage hypoplasia (16–18). During vaginal delivery, use of VKAs is associated with a higher risk of fetal hemorrhage, most dangerously intracranial bleeding (15). Careful planning of the timing and mode of delivery is critical. Some investigators advocate a planned Cesarean delivery for mothers who take any VKAs (19). However, the mode of delivery should be guided by obstetric indications with the caveat that women who present in labor fully anticoagulated with VKAs should undergo Cesarean

CENTRAL ILLUSTRATION **Balancing the Risks of Anticoagulation in Pregnancy**



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Maternal and fetal factors should be taken into consideration when initiating or maintaining anticoagulation. Anticoagulation needs will change across trimesters and shorter acting agents should be used to decrease risk of bleeding at delivery. While vitamin K antagonists may be the safest choice for preventing thromboembolism, they carry risk of fetal loss, embryopathy, and hemorrhage. IV = intravenous; LMWH = low molecular-weight heparin; MHV = mechanical heart valve; UFH = unfractionated heparin; VKAs = vitamin K antagonists; VTE = venous thromboembolism.

delivery for fetal protection. In this setting, massive transfusion protocols may be needed to support the mother through delivery. Heparin preparations do not cross the placenta, and thus do not exert direct effects on the fetus.

ADDITIVE RISKS. Table 2 lists the previously identified and probable additive risk factors for thrombosis. For example, patients with mitral or tricuspid mechanical valves are at particularly high risk of thromboembolic complications (TEC) in pregnancy, irrespective of the anticoagulant agent used (4,20,21).

CLINICAL PRACTICE AND EVOLVING STRATEGIES

MECHANICAL HEART VALVES. Women who have mechanical heart valves and become pregnant are at high risk of TEC (11,22). The hypercoagulability of pregnancy is compounded by the imperfect choices of anticoagulant agents during this critical time. Mechanical valve thrombosis is the most feared complication, and carries a 20% risk of mortality (4). Current guidelines advocate 2 anticoagulation strategies.

Warfarin continued throughout pregnancy offers the best thromboembolic protection to the mother (11), but carries a higher risk of fetal loss and complications. Nevertheless, due to suboptimal alternatives, current American College of Cardiology/American Heart Association (ACC/AHA) valvular heart disease guidelines support use of warfarin at doses ≤5 mg/day throughout pregnancy. At these doses, the risk of fetal toxicity is much lower than at higher doses, a finding further supported by a recent meta-analysis (15). When the dose to achieve the target INR exceeds 5 mg, substitution with LMWH or

continuous unfractionated heparin (UFH) during the first trimester, the critical phase of organogenesis, is recommended (**Figure 1**, Online Table 2). There are several points worth highlighting with this approach. Although this strategy minimizes both embryopathy and fetal wastage, the anticoagulant effect of warfarin in the fetus remains high, and it is unclear how long before a planned vaginal delivery warfarin needs to be withheld to eliminate the risk of traumatic intracranial hemorrhage in the fetus (22). For example, if labor ensues prematurely, a Cesarean delivery might be safer for the fetus but carries a higher risk of bleeding for the mother, in addition to the usual postoperative risks. Although giving vitamin K to reverse warfarin's effect in the mother may seem appropriate, it is unclear whether it would reverse warfarin's effect in the fetus to the same magnitude, and importantly, it could precipitate TEC in the setting of a mechanical valve. Additionally, the risk of fetal loss remains a concern with the use of VKAs throughout pregnancy, irrespective of the dose (15,16).

An alternative anticoagulant strategy is weight-based LMWH. It has superior bioavailability compared with subcutaneous UFH, is dosed twice daily, and does not cross the placenta. LMWH is cleared entirely by the kidneys; thus, fixed, weight-based dosing tends to underperform as the pregnancy advances, due to the increase in glomerular filtration rate (and clearance of LMWH) throughout pregnancy (23). Thus, as per the current guidelines, when LMWH is used, peak anti-Xa level should be checked 4 to 6 h post-dose, and LMWH carries a low risk of TEC when the levels are kept between 1.0 to 1.2 U/ml (23–25). However, concerningly, thrombotic events still occur in patients who achieve therapeutic peak anti-Xa levels (4). One potential explanation is that peak anti-Xa levels might not be adequate to ascertain therapeutic anticoagulation. In a study of 30 pregnant women receiving LMWH, peak anti-Xa was in an "optimal" therapeutic range of 0.8 to 1.2 U/ml in 115 of 187 of the measurements, and subsequent trough levels were subtherapeutic (<0.6 U/ml) in 66 (57%) of these measurements (26). This study advocates a strategy of monitoring trough levels in pregnant women with mechanical valves, particularly women who are at high risk of TEC.

Two observations are worth discussing. First, LMWH successfully treats and prevents thromboembolism in pregnant women (27). The additive risk of thrombosis in the setting of mechanical valve is, perhaps, unique and may not be eliminated by close monitoring of LMWH. Warfarin may be more efficacious than LMWH in preventing thrombosis of mechanical heart valves because warfarin targets factor

TABLE 1 Select Anticoagulant Agents and Implications in Pregnancy

Drug	Mechanism	Therapeutic Dose	Monitoring	Metabolism/Clearance	Pregnancy Category	Present in Breast Milk	Crosses the Placenta
Warfarin	Vitamin K antagonism	Variable	INR	Hepatic	D	No	Yes
Unfractionated heparin	Antithrombin by potentiating antithrombin III	Variable (IV or SC)	aPTT	Hepatic	C	No	No
Enoxaparin	Inhibits factor Xa and potentiates antithrombin III	1 mg/kg dose every 12 h	Peak anti-Xa level 4–6 h after dose	Hepatic metabolism and renal clearance	B	No	No
Dalteparin	Inhibits factor Xa and thrombin	100 U/kg dose every 12 h	Peak anti-Xa level 4–6 h after dose	Renal	B	No	No
Fondaparinux	Inhibits factor Xa and potentiates antithrombin III	5–10 mg once daily	Peak anti-Xa level 4–6 h after dose	Renal	B	Unknown	No
Dabigatran	Direct thrombin inhibitor	110–150 mg twice daily	NA	Mainly renal excretion	C	Unknown	Likely (57)
Apixaban	Selective Xa inhibitor	2.5–10.0 mg twice daily	NA	Hepatic metabolism and excreted in urine and feces	B	Unknown	Yes (58)
Rivaroxaban	Selective Xa inhibitor	15–20 mg once daily	NA	Hepatic metabolism and excreted in urine and feces	C	Unknown	Likely (59)
Edoxaban	Selective Xa inhibitor	30–60 mg once daily	NA	Hydrolysis and excreted primarily in the urine	C	Unknown	Likely (60)

aPTT = activated partial thromboplastin time; INR = international normalized ratio; IV = intravenous; NA = not applicable; SC = subcutaneous.

TABLE 2 Risk Factors for Thromboembolism in Women With Prosthetic Valves

Reported Risk Factors
Prosthetic mitral valve (4,21)
Prosthetic tricuspid valve (20)
Atrial arrhythmia* (61,62)
Not on aspirin* (63)
First-generation prosthetic valves† (64)
Prosthetic valve in a patient with thrombophilia (30)
Probable Risk Factors
History of valve thrombosis
History of thromboembolism
Systolic heart failure
Medication nonadherence
Active smoking

*Demonstrated in nonpregnant patients. †Starr-Edwards or Bjork-Shiley prosthetic valves.

IX (involved in the contact-activation pathway), which leads to generation of thrombin after contact of blood with the foreign surface of the valve structure, and targets factor VII of the extrinsic tissue-factor pathway, which is known to be activated in pregnancy (28). Also, warfarin inhibits factor X in the common pathway. The finding that dabigatran, an oral direct thrombin inhibitor, was associated with a higher rate of valve thrombosis in patients shortly after placement of mechanical valves compared with warfarin further supports this hypothesis (29). LMWH might be advantageous in patients with thromboembolic disease, but not for a mechanical heart valve in the setting of a parous hypercoagulable state. Alternative therapeutic approaches, pharmacological preparations, or monitoring strategies of LMWH might achieve better thromboembolic protection.

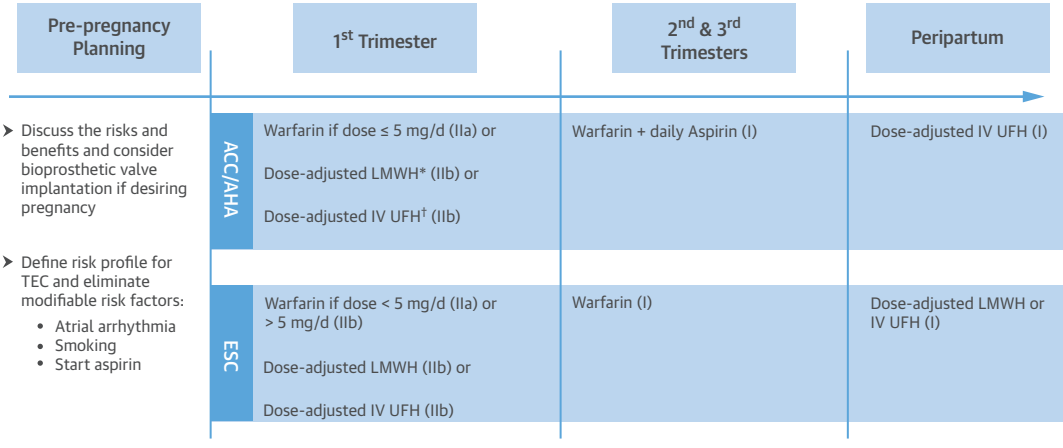
Second, in the Registry of Pregnancy and Cardiac Disease analysis of 212 women with mechanical heart valves, 10 women experienced a mechanical valve thrombosis, of which 5 occurred in the first trimester, after switching from VKAs to heparin (4). This may have been a consequence of subtherapeutic anti-Xa levels during the transition between anticoagulant agents. In 1 study, a mean 54.4% increase in the dose of LMWH was required throughout pregnancy to maintain therapeutic peak anti-Xa; thus, weight-based initiation should be followed by close monitoring and, perhaps, by trough dosing in the setting of prosthetic valves (30).

Subcutaneous UFH at therapeutic doses was 1 of the first agents used as an alternative to VKAs. It carries a high risk of TEC and its use has largely been abandoned, except in developing countries (4). Intravenous UFH, however, is indicated in women around the time of delivery, due to its rapid onset and clearance.

Dabigatran and the oral direct factor Xa inhibitors are contraindicated for mechanical heart valves. Their use in pregnancy may be limited, as they also cross the placenta (11).

THROMBOPHILIA AND VTE. Women with thrombophilia or a history of VTE who take anticoagulant agents before pregnancy should continue anticoagulation during pregnancy. Table 3 summarizes

FIGURE 1 Management Strategy for Women of Childbearing Age With Prosthetic Heart Valves



*Start 1 mg/kg twice daily, guided by weekly anti-Xa levels to achieve a peak 0.1 to 1.2 U/ml and trough >0.6 U/ml. †Activated partial thromboplastin time at least 2× control. ACC/AHA = American College of Cardiology/American Heart Association; ESC = European Society of Cardiology; IV = intravenous; LMWH = low molecular weight heparin; TEC = thromboembolic complications; UFH = unfractionated heparin.

the American Congress of Obstetrics and Gynecology recommendations requiring anticoagulation in at-risk pregnant women, which were synthesized, in part, with the American College of Chest Physicians (31).

LMWH offers advantages over UFH, including a longer half-life, efficacy with once-daily dosing, and weight-based dosing. Importantly, there are no documented fetal or neonatal risks to maternal use of LMWH during pregnancy. In a pooled analysis of 174 pregnant women on a therapeutic dose of LMWH, 2 experienced deep venous thrombosis and none experienced arterial embolism, supporting the efficacy of LMWH for prophylaxis of VTE (27). Low-risk pregnant women who need anticoagulation for the prevention of VTE probably do not need special monitoring.

LMWH preparations with longer half-lives might offer more stable anticoagulation coverage. The American Congress of Obstetrics and Gynecology recommends fondaparinux, an indirect factor Xa inhibitor, for anticoagulation in the setting of heparin-induced thrombocytopenia or other heparin allergy. Fondaparinux is an attractive alternative, as its long half-life (15 to 17 h) allows once-daily subcutaneous dosing. However, this also raises concerns for prolonged anticoagulant agent activity up to 48 h after the last dose (32,33). Due to its long half-life, fondaparinux should be discontinued in the late third trimester due to concerns for regional anesthesia and bleeding around delivery (9).

The newer oral anticoagulant agents are increasingly used in women prior to pregnancy. However, there is a scant evidence to guide therapy in these women during pregnancy, as oral direct thrombin inhibitor and direct factor Xa inhibitors have not been systematically examined in pregnancy. In a study of 37 pregnancies in women who were taking rivaroxaban and were exposed to it during the first trimester, there were 6 spontaneous abortions, 8 elective terminations of pregnancy, and 23 live births (34). Because these medications cross the placenta, their safety in pregnancy cannot be substantiated with this level of evidence (4,20,21).

LIMITATIONS IN CURRENT RESEARCH

The current evidence is limited by inherent biases of single-center case series, small sample sizes, and lack of control arms. The majority of studies enroll patients after they present in the first trimester of pregnancy; thus, there is variable capture of exposure time to whatever therapy they were taking prior to pregnancy. This results in inaccurate ascertainment of risk attributable to the anticoagulant agents that are subsequently chosen in the later stages of pregnancy.

Second, the contribution of the underlying heart disease and functional status to maternal and fetal risks in women with mechanical valves has not been explored. In the European Registry on Pregnancy and Heart disease of over 1,300 pregnant women with structural heart disease, pre-pregnancy functional status was found to be the most predictive factor for maternal and fetal complications (35). In the absence of control arms, it is not possible to untangle the additive (or deductive) risk of the underlying cardiac pathology (e.g., rheumatic, congenital, or acquired etiologies). Last, the ACC/AHA guidelines suggest a VKA approach when feasible to minimize maternal complications. Although the rate of maternal TEC is lower with VKAs, and embryopathy is decreased with lower doses of VKAs, the rate of fetal loss remains high. Until a better anticoagulant agent becomes available, clinicians must use the evidence at hand to guide therapeutic decisions (**Central Illustration**).

TABLE 3 The American College of Obstetricians and Gynecologists Guidelines for Prevention of Thromboembolism in Pregnancy*

Clinical Scenario	Antepartum	Post-Partum
High risk†		
No history of VTE	Prophylactic dose	Therapeutic dose
History of VTE	Intermediate or therapeutic dose	Therapeutic dose
Low risk‡		
No history of VTE	Surveillance	Surveillance or prophylactic dose if additional risk factors§
History of VTE	Surveillance or prophylactic dose	Intermediate or therapeutic dose
History of single VTE		
Related to pregnancy, estrogen, or idiopathic	Prophylactic dose	Therapeutic dose
Unrelated to pregnancy or estrogen	Surveillance	Therapeutic dose
History of ≥2 VTE		
Taking anticoagulation	Therapeutic dose	Therapeutic dose
Not taking anticoagulation	Prophylactic or therapeutic dose	Therapeutic dose

*Adapted with permission from Yarrington et al. (31). †Antithrombin deficiency; double heterozygous for prothrombin G20210A mutation and factor V Leiden; factor V Leiden homozygous or prothrombin G20210A mutation homozygous. ‡Factor V Leiden heterozygous; prothrombin G20210A heterozygous; protein C or protein S deficiency. §First-degree relative with a history of a thrombotic episode before 50 years of age, or other major thrombotic risk factors (obesity or prolonged immobility).

VTE = venous thromboembolism.

FUTURE DIRECTIONS AND POTENTIAL STRATEGIES

DECISIONS PRIOR TO PREGNANCY. Finding the delicate balance between adequate anticoagulation

of the mother and fetal safety poses a challenging dilemma for clinicians caring for women who require anticoagulation during pregnancy. It is imperative to identify these women pre-pregnancy and provide appropriate pre-conceptual counseling. This is particularly important for women with mechanical heart valves, who must accept that despite meticulous anticoagulation and strict adherence to guidelines, the risk for valve thrombosis and for maternal and fetal adverse outcomes is still high.

Several investigators have suggested innovative approaches to managing women with mechanical heart valves. De Santo et al. (19) "challenged" 22 young women referred for valve replacement with VKAs prior to undergoing valve replacement surgery. The goal was to determine the dose required to achieve a therapeutic INR as a guide to the decision of whether to place a mechanical or a bioprosthetic valve at the time of cardiac surgery. Women who were able to achieve therapeutic INR using <5 mg warfarin were encouraged to undergo a mechanical valve replacement, and all were in the aortic position. Conversely, women requiring ≥5 mg warfarin were advised to undergo bioprosthetic valve placement. Only 2 women had mitral valve disease and subsequently received bioprosthetic valves. Newer-generation mechanical aortic valves were used in most patients with a target INR of 1.5 to 2.5.

Although this study was performed in a single center with a small number of participants, it highlights the feasibility of a tactful approach for a select group of women with aortic valve disease. Newer-generation mechanical valves in the aortic position may permit a lower INR threshold in pregnancy. An argument could also be made to substitute VKAs for LMWH in women who are at low risk of TEC, due to the risk of fetal loss when any dose of VKAs is used. Furthermore, contrary to earlier reports that indicated possible early deterioration of bioprosthetic valves after pregnancy, later studies using newer valve designs did not show such findings, which corroborate the strategy of offering such valves to women of childbearing age (36-38).

A total of 50% of valve thrombosis events reported in the European Society of Cardiology Registry of Pregnancy and Cardiac Disease occurred in the first trimester, not in late pregnancy (4). It is difficult to draw conclusions from registry data, as it is unclear whether these women were off anticoagulation for a period of time or had inefficient bridging. Nevertheless, this observation is at odds with first principles: more events should occur later in pregnancy because of the increasingly hypercoagulable state as the pregnancy progresses. We hypothesize that the switch, in most instances, from VKAs to LMWH in the first trimester (usually by starting weight-based LMWH for the first few doses), in the setting of higher renal clearance during early stages of pregnancy, explains the observed higher risk of TEC in the first trimester. It also highlights the vulnerability of these women to medication changes and resultant fluctuation in anticoagulation in the setting of the hypercoagulable state of pregnancy. In the general population, high variability of anticoagulation is a strong predictor of reduced survival in patients with mechanical heart valves (39).

Until better therapy is available, active surveillance and early institution of an appropriate dose of LMWH for women who are at high risk of TEC is important. Ideally, the medication would be switched once pregnancy is diagnosed and titrated aggressively according to anti-Xa levels (with consideration of using peak and trough dosing). It is crucial to educate women preconceptually on the risks of suboptimal anticoagulation and to formulate a personalized plan as soon as they desire pregnancy.

MONITORING STRATEGIES. Trough anti-Xa levels have been proposed as complementary to peak anti-Xa levels (40,41). In an elegant study, Patel et al. evaluated the pharmacokinetics of enoxaparin in various stages of pregnancy (42). For a given dose of enoxaparin, anti-Xa trough levels are affected by volume of distribution, whereas peak anti-Xa levels are mainly determined by creatinine clearance. During early stages of pregnancy, there is a greater increase in creatinine clearance compared with the increase in the volume of distribution (43). As pregnancy progresses, the maternal volume of distribution increases and reaches a point where it equals the increase in creatinine clearance compared to pre-pregnancy values (42). Thus, one might conclude that monitoring trough levels might be important during the first trimester, particularly in patients who achieve therapeutic peak anti-Xa levels, to ensure that trough levels >0.6 U/ml have been reached (44). Some investigators even advocate dividing the daily dose of enoxaparin into 3, instead of 2 doses to achieve a more stable steady state (45).

In certain circumstances of heightened coagulability, discrepancies exist between different laboratory tests designed to measure levels of anticoagulation. For example, in patients who experience thrombosis of ventricular prosthetic circulatory support devices and who are on continuous intravenous heparin infusion, divergent values of anti-Xa and activated partial thromboplastin time

have been observed (46). Thus, in addition to drug effects, underlying pathophysiology affects measures of "functional" clotting (i.e., activated partial thromboplastin time) to a greater degree than the "drug level" measure (i.e., anti-Xa). Conversely, in practice, there is no functional test for monitoring the anticoagulant effect of LMWH. Thromboelastography, a point-of-care test for general viscoelastic parameters of blood clot formation, might prove to be a functional test for LMWH that transcends the perturbations of thrombosis in pregnancy (47).

THERAPEUTIC STRATEGIES. Antiplatelet agents also have a role in prevention of TEC in pregnancy. Current ACC/AHA valvular heart disease guidelines recommend all women with bioprosthetic heart valves to be maintained on low-dose aspirin in the second and third trimesters of pregnancy (11). There is a paucity of data on the use of other antiplatelet agents during pregnancy. The published reports did not specifically address the safety and efficacy of adding aspirin in addition to anticoagulant agents for women with mechanical valves, and there is inconsistent use of aspirin in this population. Some studies documented the use of aspirin in all participants, whereas others did not (4,24,25,30,33,48). Although it is not possible to draw definite conclusions, aspirin use in women who are at high risk of TEC appears justified. Clopidogrel inhibits platelet aggregation and activation by preventing the binding of fibrinogen to the adenosine diphosphate receptor, and there is a risk of excessive bleeding, although none has been documented. In our practice, we hold clopidogrel 7 days before a scheduled delivery to minimize the risk of post-partum hemorrhage (49,50).

The role of oral direct thrombin and direct Xa inhibitors in the treatment and prevention of VTE in pregnancy has not been explored. These medications are of low molecular weight and are known to cross the placenta. Their effects on the fetus are unknown, and their use in pregnancy is not recommended. Recently, Beyer-Westendorf et al. (51) presented an abstract reporting the outcomes of 169 pregnancies with known exposure to rivaroxaban, dabigatran, or apixaban. Although the report is the largest to date, there are substantial gaps in reporting of the outcomes and circumstances of events. Meaningful trends regarding teratogenicity and pregnancy outcomes cannot yet be ascertained from such heterogeneous data. However, as more women of childbearing age are being prescribed these anticoagulant agents, efforts should be made to further explore their efficacy and safety during pregnancy (34).

Another consideration for improvement in the outcomes for women on anticoagulation during pregnancy is attention to mode of delivery, which has direct effects on maternal outcomes, with Cesarean delivery associated with greater risks of hemorrhage, thrombosis, and infection during delivery and the post-partum period (52). Strategies to increase vaginal delivery, with the exception of women taking VKAs requiring emergent delivery, will likely help decrease complication rates around delivery.

Currently, there is no ideal anticoagulant agent available for pregnant women. Each medication has specific factors that must be taken into account. Attractive features for emerging therapies include a medication that does not cross the placenta, is easily administered, and does not need intensive monitoring. Of the currently available medications, the long-acting LMWH fondaparinux might hold promise (33,53,54). However, its long half-life poses challenges for regional anesthesia in the peripartum period. Close monitoring of any LMWH administered during pregnancy is crucial (33).

Currently available LMWHs are depolymerized from heparin, are isolated from porcine intestine, and demonstrate measurable heterogeneity in their molecular weight and activity (55). Promising new research may, importantly, allow precise chemical synthesis of hepatically-cleared heparins with lower side-effect profiles and greater homogeneity than the currently available preparations (56).

CONCLUSIONS

Women requiring anticoagulation need careful attention throughout pregnancy and the post-partum period. Risks and benefits to the mother and fetus should be balanced in the choice of anticoagulant therapy, degree of monitoring, and therapeutic target. Future research should investigate different approaches and combinations of anticoagulant agents in pregnancy, in addition to furthering our understanding of the distinctive factors that lead to thromboembolism in pregnancy. Development of anticoagulant agents that are homogeneous, efficacious, safe to the fetus, and not affected by physiological perturbations of pregnancy will have a tremendous effect on the outcomes of pregnancy in women who require anticoagulation.

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KEY WORDS factor Xa inhibitors, heart disease, heart valves, heparin, thrombosis, venous thromboembolism

APPENDIX For supplemental tables, please see the online version of this document.