

Pregnancy and challenges of anticoagulation

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- Pregnancy is a prothrombotic state.
- 5-fold increase in the risk of venous thromboembolism (VTE) during pregnancy.
- This risk remains elevated until 12 weeks post-partum .
- 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 .

Current status

- Approximately 80% of thromboembolic events in pregnancy are venous , with a prevalence of 0.5–2.0 per 1,000 pregnant women.

Venous thromboembolism (VTE) is one of the leading causes of maternal mortality in the United States, accounting for 9.3% of all maternal deaths .

James AH, Jamison MG, Brancazio LR, et al Am J Obstet Gynecol 2006;194:1311–5

Creanga AA, Syverson C, Seed K, Callaghan WM. Pregnancy-related mortality in the United States, 2011–2013. Obstet Gynecol 2017;130:366–73.

Current status

- PE is the most common cause of direct maternal death in the UK, with an incidence of 1.26 deaths per 100 000 pregnancies, and it is the fifth most common cause of maternal death overall. The case fatality rate is 3.5%

Conditions where anticoagulation used in Pregnancy

- 1. The treatment of VTE
- 2. Patients with mechanical heart valve
- 3. Valvular heart disease
- 4. To prevent complications in women with antithrombin deficiency, antiphospholipid antibody (APLA) syndrome or other thrombophilias who have had a prior VTE .

Anticoagulants in pregnancy

- Heparin Compounds
 - Low molecular weight heparins (LMWHs)- Preferred agent
 - Unfractionated heparin (UFH)
- Warferin – in mechanical heart valve (<5mg)
- Newer agent- Fondaparinux

Maternal changes influencing anticoagulant therapy

- 40–50% increase in maternal blood volume;
- an increase in glomerular filtration, which results in increased renal excretion of heparin compounds;
- an increase in protein binding of heparin.
- During pregnancy, unfractionated heparin and low-molecular-weight heparin have shorter half-lives and lower peak plasma concentrations, usually necessitating higher doses and more frequent administration in order to maintain effective concentration

Heparin Compounds

Neither unfractionated heparin nor low-molecular-weight heparin crosses the placenta and both are considered safe in pregnancy .

Heparin Compounds (cont.)

- The recommended therapeutic dose is calculated on early pregnancy body weight (e.g. enoxaparin 1 mg/kg body weight twice daily, dalteparin 100 IU/kg body weight twice daily, or tinzaparin 175 IU/kg), aiming for 4–6 h peak anti-Xa values of 0.6–1.2 IU/mL.

Heparin Compounds (cont.)

- The efficacy and safety of several LMWH preparations was shown in a review of 2777 pregnant women treated for DVT or PE. The risk of recurrent VTE with therapeutic doses of LMWH was 1.15%. The observed rate of major bleeding was 1.98%. Heparin-induced thrombocytopenia is markedly lower with LMWH than with UFH, as is heparin-induced osteoporosis (0.04%)

Heparin Compounds (cont.)

- Because of its greater reliability and ease of administration, low-molecular-weight heparin is recommended rather than unfractionated heparin for prevention and treatment of VTE within and outside of pregnancy.
- Relative disadvantages of low-molecular-weight heparin surrounding the time of delivery include its longer half-life, the inability to rapidly assess current effect with standard laboratory studies (eg, aPTT), and the inability to pharmacologically reverse its effect, which are important considerations for neuraxial anesthesia and peripartum bleeding risk .

Warfarin

- Warfarin, a vitamin K antagonist(VKA) commonly used for long-term anticoagulation therapy outside of pregnancy, has been associated with potentially harmful fetal effects, especially with first-trimester exposure Warfarin embryopathy has been linked with exposure at weeks of gestation, highlighting the importance of pre pregnancy and early pregnancy care in patients using warfarin .

Warfarin (cont.)

- VKAs cross the placenta and their use in the first trimester can result in embryopathy (limb defects and nasal hypoplasia) in 0.6–10% of cases. Substitution of a VKA with UFH or LMWH in weeks 6–12 almost eliminates the risk of embryopathy.

Warfarin (cont.)

- There is evidence that the embryopathy risk with VKA is also dose dependent. The risk was 0.45–0.9% in pregnancies with low-dose warfarin according to two recent systematic reviews. In addition to the risk of embryopathy that is limited to the first trimester, there is a 0.7–2% risk of foetopathy (e.g. ocular and central nervous system abnormalities and intracranial haemorrhage) when VKAs are used in the second and third trimesters.

Hassouna A, Allam H. Limited dose warfarin throughout pregnancy in patients with mechanical heart valve prosthesis: A meta-analysis. *Interact Cardiovasc Thorac Surg* 2014;18:797–806.

Warfarin (cont.)

- Pregnancy with a mechanical heart valve constitutes the WHO risk class III (significantly increased risk of maternal mortality or severe morbidity)
- Although rarely prescribed in pregnancy, vitamin K antagonists such as warfarin are still considered for women with mechanical heart valves because of the high risk of thrombosis even with heparin or low molecular-weight heparin anticoagulation therapy

Pregnancy with a mechanical heart valve

There is no ideal anticoagulation regimen.

- Anticoagulation options are :
 - (1) use of VKA (warfarin) throughout pregnancy with switch to UFH at 36 weeks;
 - (2) use of UFH/LMWH restricted to the first 6-12 weeks, by warfarin up to 36 weeks with a switch to heparin
 - (3) use of UFH/LMWH throughout pregnancy.
- The last regimen is usually not favored, as continuous use of UFH/LMWH throughout pregnancy markedly increases the risk of prosthetic heart valve thrombosis (PHVT)

Nishimura RA, Otto CM, Bonow RO, et al. 2014 AHA/ACC guideline for the management of patients with valvular heart disease: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol.* 2014;63:2438-2488

Regitz-Zagrosek V, Blomstrom Lundqvist C, Borghi C, et al. ESC Guidelines on the management of cardiovascular diseases during pregnancy: The Task Force on the Management of Cardiovascular Diseases during Pregnancy of the European Society of Cardiology (ESC). *Eur Heart J.* 2011;32:3147-3197.

Comparision between three regimen

- In a systematic review comprising 24 studies of over 900 pregnant women with mechanical PHVs, Chan and colleagues evaluated maternal and fetal outcomes according to the type of antithrombotic regimen used during pregnancy

Chan WS, Anand S, Ginsberg JS. Anticoagulation of pregnant women with mechanical heart valves: A systematic review of the literature. *Arch Intern Med.* 2000;160:191-196

TABLE 53–3. Frequency of Fetal and Maternal Complications by Anticoagulation Regimen During Pregnancy

Anticoagulation Regimen	Congenital Fetal Anomalies	Thromboembolic Complications
Regimen 1 (oral anticoagulants alone) ^a	35/549 (6.4%)	31/788 (3.9%)
Regimen 2 (heparin during first trimester/ oral anticoagulants) ^a	6/174 (3.4%)	21/229 (9.2%)
Regimen 3 (heparin alone) ^a	0/17 (0.0%)	7/21 (33.3%)
Regimen 4 (no anticoagulation) ^a	3/92 (3.3%)	26/107 (24.3%)
LMWH throughout pregnancy ⁶⁶	0/92	9/92 (9.8%)

Rate of spontaneous abortions among regimen

- When OA was used throughout pregnancy (regimen 1), spontaneous abortions resulted in 24.7% (196/792) of pregnancies. When heparin was substituted for OA in the first trimester (regimen 2), spontaneous abortions resulted in 24.8% (57/230) of pregnancies. Regimen 3 (use of heparin throughout) was associated with spontaneous abortions in 23.8% (5/21) of pregnancies, and regimen 4 (no anticoagulation or antiplatelet agent use alone) resulted in spontaneous abortions in 9.8% .

Congenital fetal anomalies

- The prevalence of congenital fetal anomalies in the livebirths associated with regimen 1 was 6.4% (35/549). The prevalence was 3.4% (6/174) if heparin was substituted in the first trimester; however, if warfarin was replaced by heparin at or prior to 6 weeks, there were no (0/108) fetal anomalies, compared with 11.1% (4/36) if heparin was replaced after 6 weeks. No congenital anomalies (0/17) were reported with regimen 3.

Maternal complications

- Thromboembolic complications were reported in 3.9% (31/788) of pregnancies in women treated with regimen 1. When regimen 2 was used, TEC occurred in 9.2% (21/229) of pregnancies. When heparin alone was used, in low or adjusted doses (regimen 3), the frequency of TEC was 7 (33.3%) of 21 pregnancies, whereas when no anticoagulation therapy was used, the frequency was 26 (24.3%) of 107.

Maternal mortality

- The overall maternal mortality was 2.9% (25/854). Maternal deaths were reported in 1.8% (10/561) and 4.2% (7/167) of women receiving regimens 1 and 2, respectively. The maternal mortality rate was 15.0% (3/20) with regimen 3 and 4.7% (5/106) with regimen 4.

MONITORING

- Monitoring is essential in patients treated with LMWH with mechanical valves but the evidence is less clear in patients with VTE.
- Given the need for dose increase as pregnancy progresses to maintain a certain therapeutic anti-Xa level (peak: 0.7–1.2 IU/ml, it seems reasonable to also determine anti-Xa peak levels during pregnancy in patients with VTE.
- This appears particularly justified in view of the fact that PE occurred in women receiving prophylactic doses of LMWH. As with the use of LMWH in women with mechanical valves, using trough levels and adjusting the dosage frequency may be necessary to achieve adequate anticoagulation.

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;191:1024–1029

Friedrich E, Hameed AB. Fluctuations in anti-factor Xa levels with therapeutic enoxaparin anticoagulation in pregnancy. *J Perinatol* 2010;30:253–257.

Monitoring and target

Warferin	INR	A therapeutic INR of 2-3 (INR of 2.5–3.5 for mitral valves) for all patients prescribed a VKA .
Unfractionated Heparin	aPTT	activated partial thromboplastin time (aPTT) two times greater than the control.
LMWH	anti-Xa	peak anti-Xa levels be measured 4 to 6 hours after administration with target anti-Xa level of 1.0 IU/ml to 1.2 IU/ml. Trough anti-Xa levels of 0.6–0.7 IU/ml are recommended

Recent recommendations

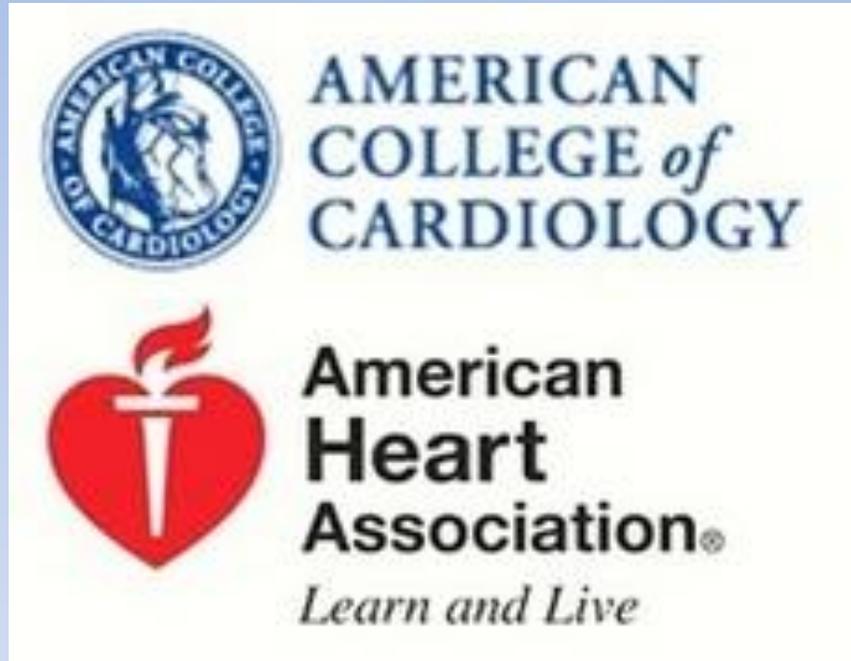


FIGURE 1 Management Strategy for Women of Childbearing Age With Prosthetic Heart Valves

	Pre-pregnancy Planning	1 st Trimester	2 nd & 3 rd Trimesters	Peripartum
<p>➤ Discuss the risks and benefits and consider bioprosthetic valve implantation if desiring pregnancy</p> <p>➤ Define risk profile for TEC and eliminate modifiable risk factors:</p> <ul style="list-style-type: none"> • Atrial arrhythmia • Smoking • Start aspirin 				
ACC/AHA		Warfarin if dose \leq 5 mg/d (IIa) or Dose-adjusted LMWH* (IIb) or Dose-adjusted IV UFH [†] (IIb)	Warfarin + daily Aspirin (I)	Dose-adjusted IV UFH (I)
ESC		Warfarin if dose < 5 mg/d (IIa) or > 5 mg/d (IIb) Dose-adjusted LMWH (IIb) or Dose-adjusted IV UFH (IIb)	Warfarin (I)	Dose-adjusted LMWH or IV UFH (I)

*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.

Factor Xa and thrombin inhibitors

- Fondaparinux indirectly inhibits factor Xa activity via ATIII binding. There are a few observational studies on the use of fondaparinux in pregnancy, with the largest reporting good outcomes for 65 pregnancies managed with fondaparinux.
- Its use can be considered if there is an allergy or adverse response to LMWH .
- One study showed minor transplacental passage of fondaparinux, and more work is required to assess the risk of congenital malformations .

. De Carolis S, di Pasquo E, Rossi E, Del Sordo G, Buonomo A, Schiavino D, Lanzone A, De Stefano V. Fondaparinux in pregnancy: Could it be a safe option? A review of the literature. *Thromb Res* 2015;135:1049–1051

[2018 ESC Guidelines for the management of cardiovascular diseases during pregnancy](#) *European Heart Journal* (2018) 39, 3165–3241

Factor Xa and thrombin inhibitors

- Rivaroxaban, a direct factor Xa inhibitor, crosses the placental barrier and therefore is not recommended in pregnancy .
- However, its long half-life poses challenges for regional anesthesia in the peripartum period .

Mode of delivery

- Planned delivery is recommended in all patients unless obstetric indications call for caesarean section
- Cesarean delivery associated with greater risks of hemorrhage, thrombosis, and infection during delivery and the post-partum period
- Strategies to increase vaginal delivery, with the exception of women taking VKAs requiring emergent delivery, will likely help decrease complication rates around delivery
- Vaginal delivery while the mother is on VKAs is contraindicated because of the risk of foetal intracranial bleeding.

Liu S, Liston RM, Joseph K, et al., for the Maternal Health Study Group of the Canadian Perinatal Surveillance System. Maternal mortality and severe morbidity associated with low-risk planned cesarean delivery versus planned vaginal delivery at term. *CMAJ* 2007;176:455–60.

van Driel D, Wesseling J, Sauer PJ, Touwen BC, van der Veer E, Heymans HS. Teratogen update: Fetal effects after in utero exposure to coumarins overview of cases, follow-up findings, and pathogenesis. *Teratology* 2002;66:127–140

Management of Delivery

- It is recommended that all women on VKA switch to LMWH or UFH at week 34–36 with induction or caesarean at around 38 weeks.
- LMWH should be switched to i.v. UFH at least 36 h before the induction of labour or caesarean delivery is planned. UFH should be discontinued 4–6 h before anticipated delivery and restarted 6 h after delivery if there are no bleeding complication

Breast feeding

- UFH and LMWHs are not secreted into breast milk, and 2 reports have shown that maternal administration of warfarin does not induce an anticoagulant effect in the breastfed infant. Thus, women using these agents can safely breastfeed.

Take home messages

- Currently, there is no ideal anticoagulant agent available for pregnant women. Each medication has specific factors that must be taken into account.
- Heparin products are the mainstay of treating VTE in pregnancy, chiefly because they do not cross the placenta
- Altered metabolism rates of anticoagulants in pregnant women often necessitate closer monitoring than is required outside of pregnancy in order to ensure efficacy and safety.

- In women with mechanical heart valves, the ideal anticoagulation regimen remains controversial as heparin use has shown inferior outcomes for preventing thromboembolic complications compared to warfarin, but warfarin carries risk for fetal embryopathy
- Other populations where a heparin alternative is necessary include women with a history of heparin induced thrombocytopenia (HIT) or other heparin intolerance

- Further challenging the management of anticoagulation in pregnancy is the dearth of randomized clinical trials. The evidence governing treatment recommendations is largely based on expert guidelines, observational studies, or extrapolation from non-pregnant cohorts.
- Attractive features for emerging therapies include a medication that does not cross the placenta, is easily administered, and does not need intensive monitoring

- A careful critique of a woman's history, as well as the available data, is essential for optimal management of anticoagulation in pregnancy. Such decisions should involve a multidisciplinary team involving obstetrics, hematology, cardiology, and anesthesia.



Thank You All