ACC Latin America Conference 2017

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Solutions for Every Day Problems: Management of Anticoagulation and Valvular Heart Disease in Pregnancy

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CLINICA MODELO DE MORON

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no disclosure

Preconception evaluation in women with valvular heart disease planning a pregnancy

- Careful history, family history, and physical examination, including screening for connective tissue disorders
- 12-lead electrocardiogram
- Echocardiogram including assessment of left- and right-ventricular and valve function
- Exercise test to be considered for objective assessment of functional classification
- Careful counselling including maternal risks for complications and mortality, information on choices of therapy (heparin vs. Vitamin K), risk of miscarriage, risk of early delivery, and small for gestational age and, when applicable, risk of foetal congenital defect (inheritance risk)

European Heart Journal (2015) 36, 1078–1089

Pregnancy in women with native valve disease

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Risk stratification according to type of valvular lesion and severity

Lesion	Aetiology[a]	Risk to mother	Risk to foetus	Possible intervention[b]	Preferred mode of delivery
Mitral regurgitation	Rheumatic, congenital	Moderate-to-severe MR with good LV function: low risk with good care Severe MR with LV dysfunction: high risk of heart failure or arrhythmia	No increased risk of foetal complications has been reported	Non-pregnant: patients with severe regurgitation and symptoms or impaired LV function or dilatation should be referred for pre-pregnancy surgery Pregnant: Symptoms of fluid overload can be managed with diuretics. Surgery in women with intractable HF.	Vaginal delivery is preferable. Epidural anaesthesia and shortened second stage is advisable
Aortic regurgitation	Rheumatic, congenital, degenerative	Moderate-to-severe AR with good LV function: low risk with good care Severe AR with LV dysfunction: high risk of heart failure or arrhythmia	No increased risk of foetal complications has been reported	Non-pregnant: patients with severe regurgitation and symptoms or impaired LV function or severe dilatation should be referred for pre-pregnancy surgery Pregnant: Symptoms of fluid overload can be managed with diuretics and bedrest. Surgery in women with intractable HF, preferably after delivery.	Vaginal delivery is preferable. Epidural anaesthesia and shortened second stage is advisable
Tricuspid regurgitation	Functional, Ebstein's anomaly, endocarditis	Moderate-to-severe TR with good RV function: arrythmias Moderate-to-severe TR with impaired RV function: heart failure	No increased risk of foetal complications has been reported	Non-pregnant: patients with severe regurgitation and symptoms or impaired LV and/or RV function or dilatation should be referred for pre-pregnancy TV repair Pregnant: severe TR can usually be managed medically with diuretics	Vaginal delivery is preferable.

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Pregnancy in women with native valve disease

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Risk stratification according to type of valvular lesion and severity

Lesion	Aetiology[a]	Risk to mother	Risk to foetus	Possible intervention[b]	Preferred mode of delivery
Mitral stenosis	Rheumatic	Mild MS (area >1.5 cm^2/ asymptomatic: low risk Moderate-to-severe MS (area <1.5 cm^2, in AF): may develop heart failure; mortality up to 3%.	Prematurity 20–30%, intrauterine growth retardation 5–20%, still birth 1–3%. Offspring risk higher in women in NYHA class >II.	Non-pregnant: Moderate–severe MS should be counselled before pregnancy and may need intervention. In pregnancy: beta-blockers and duretics; in AF digoxin Percutaneous mitral commissurotomy in NYHA FC III/IV or PAP >50 mmHg on medical therapy	Vaginal delivery in mild MS; Caesarean in moderate–severe MS in FC III/IV or having pulmonary HT on medical therapy.
Aortic stenosis	Congenital bicuspid	Severe AS-Asymptomatic on exercise test: Low risk Severe AS symptoms or drop in BP on exercise test: heart failure in 10% and arrhythmias in 3–25%.	Foetal complications increased in moderate and severe AS as pre-term birth, intrauterine growth retardation, low birth weight in up to 25%.	Non-pregnant: symptomatic severe AS or asymptomatic AS with LV dysfunction or aortic dilatation >45 mm should be counselled against pregnancy or have an intervention first. In pregnancy: restrict activities and in AF beta-blocker or a non-dihydropyrine for rate control. Percutaneous valvuloplasty in severely symptomatic patient despite bedrest and medical therapy.	Non-severe AS vaginal delivery, in selected cases of severe AS Caesarean delivery can be considered.

European Heart Journal (2015) 36, 1078–1089

Aortic and pulmonic valve disease

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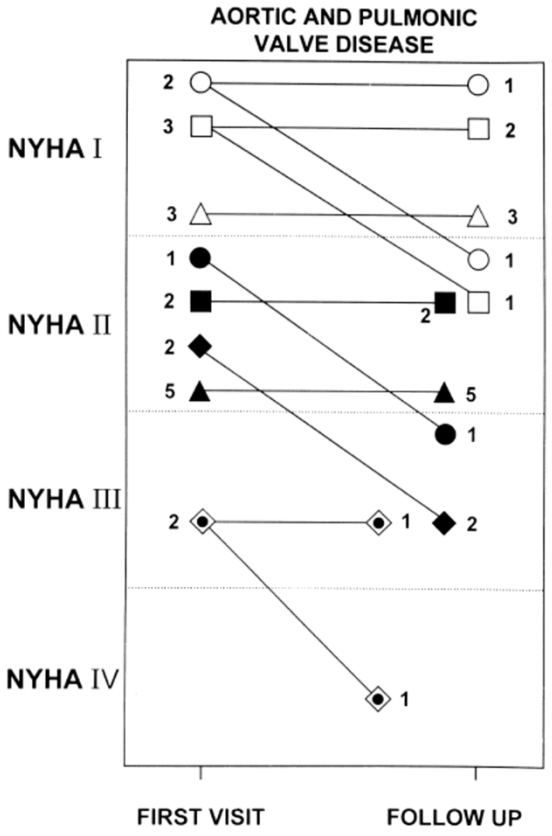
Change in New York Heart Association (NYHA) functional class between first visit and follow-up during pregnancy in patients with predominant aortic and pulmonic valve disease.

- ● mild aortic stenosis
- ■ moderate aortic stenosis
- ◆ severe aortic stenosis
- ▲ pulmonic stenosis

Open symbols: NYHA functional class I on presentation

Closed symbols: NYHA class II on presentation

Dotted diamonds: NYHA functional class III on presentation



Hameed A; J Am Coll Cardiol 2001;37:893–9

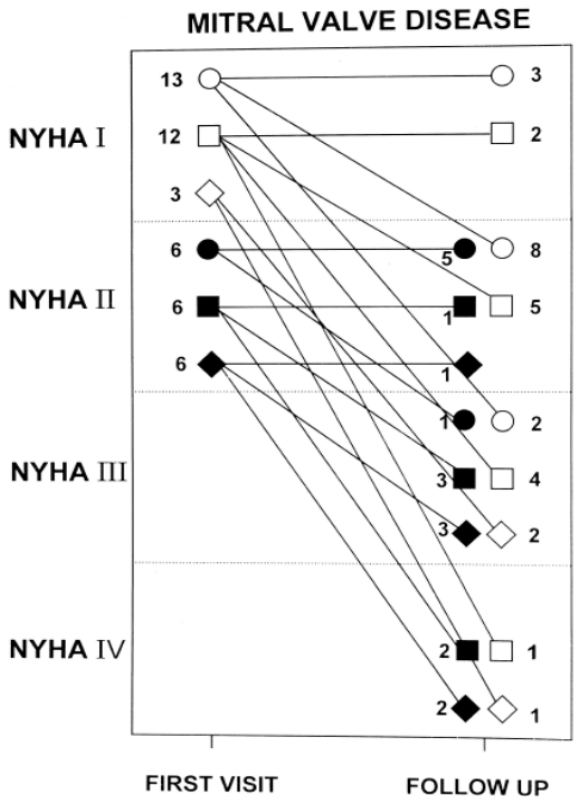
Mitral valve disease

Change in New York Heart Association (NYHA) functional class between first visit and follow-up during pregnancy in patients with predominant mitral valve disease.

- ● mild mitral stenosis
- ■ moderate mitral stenosis
- ◆ severe mitral stenosis.

Open symbols: NYHA functional class I on presentation

closed symbols: NYHA functional class II on presentation.



Hameed A; J Am Coll Cardiol 2001;37:893–9

Pregnancy in women with prosthetic heart valves

- The two major groups of artificial heart valves, bioprosthesis tissue valves (TV) and mechanical valvular prosthesis, have different risk/benefit profiles with regard to
  - Need for anticoagulation
  - Valve haemodynamics
  - Incidence of thrombotic events
  - Durability
  - Impact on foetal outcome

- MVs can be surgically repaired or opened by mitral balloon valvotomy

European Heart Journal (2015) 36, 1078–1089

Pregnancy in women with prosthetic heart valves

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- There are three key issues related to the need for heart valve replacement in the context of the desire for a future pregnancy:

1. Selection of prosthetic heart valves
2. Management during pregnancy
3. Maternal and foetal risks

European Heart Journal (2015) 36, 1078–1089

Tissue valves

- Use of a TV in women of childbearing age avoids the use of anticoagulation and its complications, as well as the risk of thromboembolism
- High risk of valve deterioration and need for reoperation
  - Calcification
  - Degradation leading to tears
  - Pannus overgrowth

Mechanical valves

- Mechanical prosthesis have:
  - Excellent durability
  - Good haemodynamic profile
- Problems in pregnancy:
  - Risk of thromboembolism
  - Risk associated to higher level of anticoagulation needed, which might lead to maternal bleeding
- Valve thrombosis often occurs during the first trimester 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,
  - Unidentified homeostatic factors germane to patients with mechanical valves

Risk factors for thromboembolism in women with prosthetic valves

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Reported Risk Factors	Probable Risk Factors
• Prosthetic mitral valve • Prosthetic tricuspid valve • Atrial arrhythmia • Not on aspirin • First-generation prosthetic valves • Prosthetic valve in a patient with thrombophilia	• History of valve thrombosis • History of thromboembolism • Systolic heart failure • Medication nonadherence • Active smoking

J Am Coll Cardiol 2016;68:1804–13

Anticoagulation

- Hypercoagulability during pregnancy due to increasing levels of thrombogenic factors VII, VIII, and X; von Willebrand factor; and fibrinogen, and decreases in protein S, increase risks of mechanical valve thrombosis
- Coumarin derivates reduces the risk of mechanical valve thrombosis
- Coumarin derivates are linked to an increased risk of miscarriage, foetal embryopathy, and late foetal loss (it has been suggested a dose-dependent relation)
- LMWHs during pregnancy have proved to be effective in many conditions, but in patients with an PHV, several cases of valve thrombosis have been reported suggesting that the use of LMWH may be associated with a higher risk of valve thrombosis.

Select Anticoagulant Agents and Implications in Pregnancy

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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)

J Am Coll Cardiol 2016;68:1804–13

Recommendations for the management of mechanical valves in pregnancy

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Recommendations	Class[a]	Level[b]
Mechanical valves		
OACs are recommended during the second and third trimesters until the 36th week.	I	C
Change of anticoagulation regimen during pregnancy should be implemented in hospital.	I	C
If delivery starts while on OACs, caesarean delivery is indicated.	I	C
OAC should be discontinued and dose-adjusted UFH (a PTT ≥2× control) or adjusted-dose LMWH (target anti-Xa level 4–6 h post-dose 0.8–1.2 U/mL) started at the 36th week of gestation.	I	C
In pregnant women managed with LMWH, the post-dose anti-Xa level should be assessed weekly.	I	C
LMWH should be replaced by intravenous UFH at least 36 h before planned delivery. UFH should be continued until 4–6 h before planned delivery and restarted 4–6 h after delivery if there are no bleeding complications.	I	C
Immediate echocardiography is indicated in women with mechanical valves presenting with dyspnoea and/or an embolic event.	I	C
Continuation of OACs should be considered during the first trimester if the warfarin dose required for therapeutic anticoagulation is <5 mg/day (or phenprocoumon <3 mg/day or acenocoumarol <2 mg/day), after patient information and consent.	IIa	C
Discontinuation of OAC between Weeks 6 and 12 and replacement by adjusted-dose UFH (a PTT ≥2× control; in high-risk patients applied as intravenous infusion) or LMWH twice daily (with dose adjustment according to weight and target anti-Xa level 4–6 h post-dose 0.8–1.2 U/mL) should be considered in patients with a warfarin dose required of >5 mg/day (or phenprocoumon >3 mg/day or acenocoumarol >2 mg/day).	IIa	C
Discontinuation of OACs between Weeks 6 and 12 and replacement by UFH or LMWH under strict dose control (as described earlier) may be considered on an individual basis in patients with warfarin dose required for therapeutic anticoagulation <5 mg/day (or phenprocoumon <3 mg/day or acenocoumarol <2 mg/day).	IIb	C
Continuation of OACs may be considered between Weeks 6 and 12 in patients with a warfarin dose required for therapeutic anticoagulation >5 mg/day (or phenprocoumon >3 mg/day or acenocoumarol >2 mg/day).	IIb	C
LMWH should be avoided, unless anti-Xa levels are monitored.	III	C

Adapted from ESC guidelines on the management of cardiovascular disease in pregnancy

Anticoagulation strategies

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	Risk to mother (% average risk)	Risk to baby (% average risk)	Risk of either maternal or fetal event (% averaged risk)
Vitamin K antagonist (VKA)	0 5 10 15 20 25 30 35 40+ (5%; 95% CI 2% to 9%)	0 5 10 15 20 25 30 35 40+ (39%; 95% CI 27% to 52%)	0 5 10 15 20 25 30 35 40+ (44%)
Low-dose warfarin	0 5 10 15 20 25 30 35 40+ (5%; 95% CI 0% to 16%)	0 5 10 15 20 25 30 35 40+ (15%; 95% CI 7% to 27%)	0 5 10 15 20 25 30 35 40+ (20%)
Low-molecular-weight heparin (LMWH)	0 5 10 15 20 25 30 35 40+ (15%; 95% CI 8% to 25%)	0 5 10 15 20 25 30 35 40+ (14%; 95% CI 4% to 29%)	0 5 10 15 20 25 30 35 40+ (29%)
LMWH + VKA	0 5 10 15 20 25 30 35 40+ (16%; 95% CI 5% to 32%)	0 5 10 15 20 25 30 35 40+ (16%; 95% CI 1% to 41%)	0 5 10 15 20 25 30 35 40+ (32%)
Unfractionated heparin + VKA	0 5 10 15 20 25 30 35 40+ (16%; 95% CI 9% to 24%)	0 5 10 15 20 25 30 35 40+ (34%; 95% CI 18% to 51%)	0 5 10 15 20 25 30 35 40+ (50%)

Steinberg Z et al; JACC 2017, 69 2681

Management Strategy for Women of Childbearing Age With Prosthetic Heart Valves

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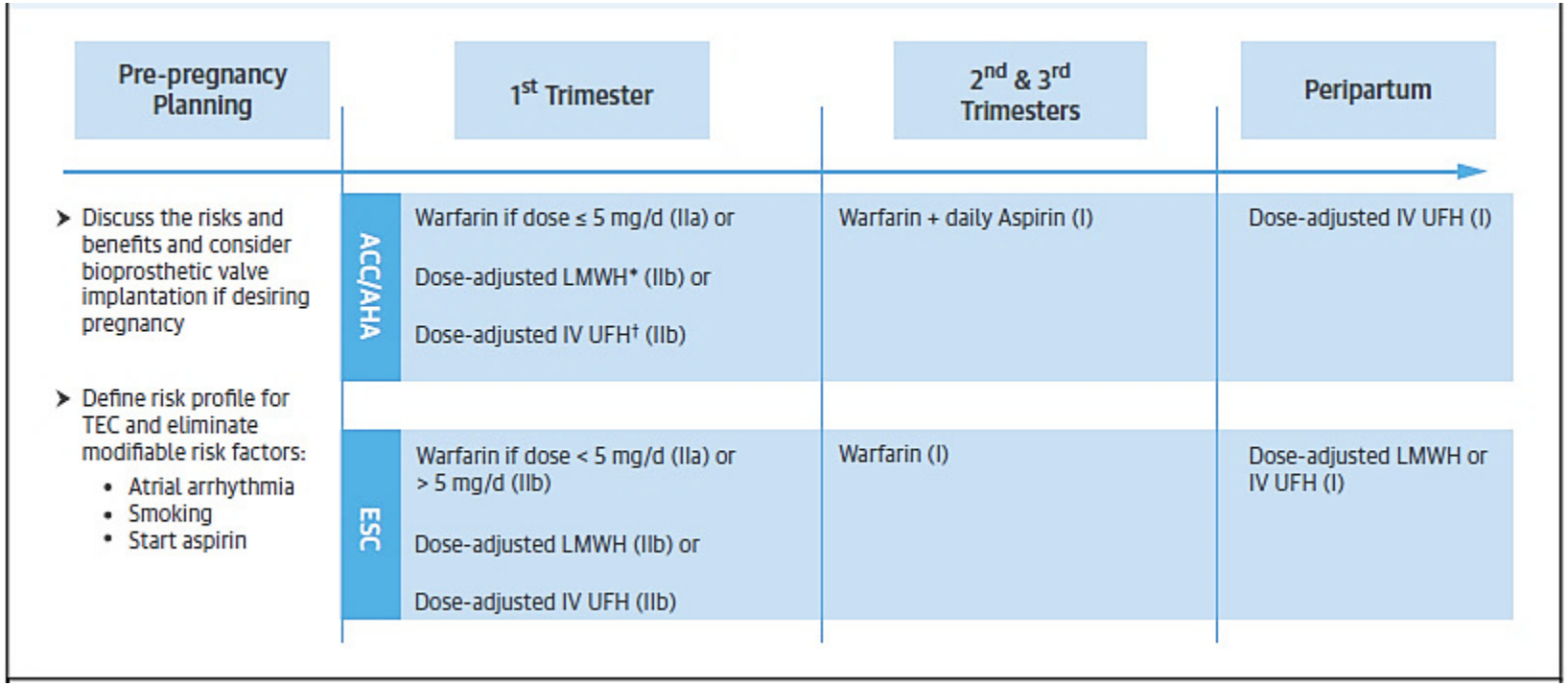

J Am Coll Cardiol 2016;68:1804–13


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Muchas gracias