ESC European Society of Cardiology

European Heart Journal (2018) **39**, 3165–3241
doi:10.1093/eurheartj/ehy340

ESC GUIDELINES

2018 ESC Guidelines for the management of cardiovascular diseases during pregnancy

The Task Force for the Management of Cardiovascular Diseases during Pregnancy of the European Society of Cardiology (ESC)

Endorsed by: the International Society of Gender Medicine (IGM), the German Institute of Gender in Medicine (DGesGM), the European Society of Anaesthesiology (ESA), and the European Society of Gynecology (ESG)

Authors/Task Force Members: Vera Regitz-Zagrosek* (Chairperson) (Germany), Jolien W. Roos-Hesselink* (Co-Chairperson) (The Netherlands), Johann Bauersachs (Germany), Carina Blomström-Lundqvist (Sweden), Renata Cífková (Czech Republic), Michele De Bonis (Italy), Bernard Iung (France), Mark Richard Johnson (UK), Ulrich Kintscher (Germany), Peter Kranke[1] (Germany), Irene Marthe Lang (Austria), Joao Morais (Portugal), Petronella G. Pieper (The Netherlands), Patrizia Presbitero (Italy), Susanna Price (UK), Giuseppe M. C. Rosano (UK/Italy), Ute Seeland (Germany), Tommaso Simoncini[2] (Italy), Lorna Swan (UK), Carole A. Warnes (USA)

* Corresponding authors. Vera Regitz-Zagrosek, Charité Universitaetsmedizin Berlin, Institute for Gender in Medicine, CCR, DZHK, partner site Berlin, Hessische Str 3-4, 10115 Berlin, Germany, Tel: +49 30 450 525 288, Fax: +49 30 450 7 525 288, E-mail: vera.regitz-zagrosek@charite.de. Jolien W. Roos-Hesselink, Department of Cardiology, Erasmus Medical Center Rotterdam, Dr Molewaterplein 40, 3015CGD, Rotterdam, Netherlands, Tel: +31 10 7032432, E-mail: j.roos@erasmusmc.nl

ESC Committee for Practice Guidelines (CPG) and National Cardiac Societies document reviewers: listed in the Appendix.

[1]Representing the European Society of Anaesthesiology (ESA)

[2]Representing the European Society of Gynecology (ESG)

ESC entities having participated in the development of this document:

Associations: Acute Cardiovascular Care Association (ACCA), European Association of Cardiovascular Imaging (EACVI), European Association of Percutaneous Cardiovascular Interventions (EAPCI), European Heart Rhythm Association (EHRA), Heart Failure Association (HFA).

Councils: Council on Cardiovascular Nursing and Allied Professions, Council on Cardiovascular Primary Care, Council on Hypertension, Council on Valvular Heart Disease.

Working Groups: Aorta and Peripheral Vascular Diseases, Cardiovascular Pharmacotherapy, Cardiovascular Surgery, Grown-up Congenital Heart Disease, Myocardial and Pericardial Diseases, Pulmonary Circulation and Right Ventricular Function, Thrombosis.

The content of these European Society of Cardiology (ESC) Guidelines has been published for personal and educational use only. No commercial use is authorized. No part of the ESC Guidelines may be translated or reproduced in any form without written permission from the ESC. Permission can be obtained upon submission of a written request to Oxford University Press, the publisher of the European Heart Journal and the party authorized to handle such permissions on behalf of the ESC (journals.permissions@oxfordjournals.org).

Disclaimer. The ESC Guidelines represent the views of the ESC and were produced after careful consideration of the scientific and medical knowledge and the evidence available at the time of their dating. The ESC is not responsible in the event of any contradiction, discrepancy and/or ambiguity between the ESC Guidelines and any other official recommendations or guidelines issued by the relevant public health authorities, in particular in relation to good use of health care or therapeutic strategies. Health professionals are encouraged to take the ESC Guidelines fully into account when exercising their clinical judgment as well as in the determination and the implementation of preventive, diagnostic or therapeutic medical strategies. However, the ESC Guidelines do not override in any way whatsoever the individual responsibility of health professionals to make appropriate and accurate decisions in consideration of each patient's health condition and in consultation with that patient and the patient's caregiver where appropriate and/or necessary. Nor do the ESC Guidelines exempt health professionals from taking careful and full consideration of the relevant official updated recommendations or guidelines issued by the competent public health authorities in order to manage each patient's case in light of the scientifically accepted data pursuant to their respective ethical and professional obligations. It is also the health professional's responsibility to verify the applicable rules and regulations relating to drugs and medical devices at the time of prescription.

© The European Society of Cardiology and The European Society of Hypertension 2018. All rights reserved. For permissions please email: journals.permissions@oup.com.

Downloaded from https://academic.oup.com/eurheartj/article-abstract/39/34/3165/5078465 by guest on 13 September 2018

Document Reviewers: Christi Deaton (CPG Review Coordinator) (UK), Iain A. Simpson (CPG Review Coordinator) (UK), Victor Aboyans (France), Stefan Agewall (Norway), Emanuele Barbato (Italy), Pavel Calda[2] (Czech Republic), Antonio Coca (Spain), Ioan Mircea Coman (Romania), Julie De Backer (Belgium), Victoria Delgado (The Netherlands), Giovanni Di Salvo (UK), Samantha Fitzsimmons (UK), Donna Fitzsimons (UK), Madalina Garbi (UK), Sofie Gevaert (Belgium), Gerhard Hindricks (Germany), Guillaume Jondeau (France), Jolanda Kluin (The Netherlands), Christos Lionis (Greece), Theresa A. McDonagh (UK), Pascal Meier (UK/Switzerland), Philip Moons (Belgium), Antonis Pantazis (UK), Massimo Francesco Piepoli (Italy), Bianca Rocca (Italy), Marco Roffi (Switzerland), Stephan Rosenkranz (Germany), Andrea Sarkozy (Belgium), Evgeny Shlyakhto (Russia), Candice K. Silversides (Canada), Karen Sliwa (South Africa), Miguel Sousa-Uva (Portugal), Juan Tamargo (Spain), Sara Thorne (UK), Marc Van de Velde[1] (Belgium), Bryan Williams (UK), Jose Luis Zamorano (Spain)

The disclosure forms of all experts involved in the development of these Guidelines are available on the ESC website www.escardio.org/guidelines

Online publish-ahead-of-print 25 August 2018

Keywords Guidelines • Pregnancy • Cardiovascular disease • Risk assessment • Management • Congenital heart disease • Valvular heart disease • Hypertension • Heart failure • Arrhythmia • Pulmonary hypertension • Aortic pathology • Cardiomyopathy • Drug therapy • Pharmacology

Table of Contents

Table of Contents ... 3166
List of tables ... 3168
Abbreviations and acronyms ... 3168
1. Preamble ... 3169
2. Introduction ... 3171
2.1 Why do we need new Guidelines on the management of cardiovascular diseases in pregnancy? ... 3171
2.2 New format of the Guidelines ... 3171
2.3 Why these Guidelines are important ... 3171
2.4 Methods ... 3171
2.5 What is new? ... 3172
3. General considerations ... 3173
3.1 Epidemiology ... 3173
3.2 Physiological adaptations to pregnancy ... 3174
3.3 Pre-pregnancy counselling ... 3174
3.3.1 Risk of maternal cardiovascular complications ... 3174
3.3.2 Risk of obstetric and offspring complications ... 3174
3.3.3 Pregnancy heart team ... 3176
3.4 Cardiovascular diagnosis in pregnancy ... 3176
3.4.1 Electrocardiography ... 3176
3.4.2 Echocardiography ... 3176
3.4.3 Exercise testing ... 3177
3.4.4 Ionizing radiation exposure ... 3177
3.4.5 Chest radiography and computed tomography ... 3177
3.4.6 Cardiac catheterization ... 3177
3.4.7 Magnetic resonance imaging ... 3177
3.5 Genetic testing and counselling ... 3177
3.5.1 Pre-natal diagnosis ... 3178
3.6 Foetal assessment ... 3178
3.6.1 Screening for congenital heart disease ... 3178
3.6.2 Assessing foetal wellbeing ... 3178
3.7 Interventions in the mother during pregnancy ... 3178
3.7.1 Percutaneous therapy ... 3178
3.7.2 Cardiac surgery with cardiopulmonary bypass ... 3178
3.8 Timing and mode of delivery: risk for mother and child ... 3179
3.8.1 Timing of delivery ... 3179
3.8.2 Labour induction ... 3179
3.8.3 Vaginal or caesarean delivery ... 3179
3.8.4 Delivery in anticoagulated women (not including mechanical valve; see section 5) ... 3179
3.8.5 Urgent delivery on therapeutic anticoagulation ... 3179
3.8.6 Haemodynamic monitoring during delivery ... 3180
3.8.7 Anaesthesia/analgesia ... 3180
3.8.8 Labour ... 3180
3.8.9 Perimortem caesarean section ... 3180

Downloaded from https://academic.oup.com/eurheartj/article-abstract/39/34/3165/5078465 by guest on 13 September 2018

3.8.10 Post-partum care. . . . 3180
3.8.11 Breastfeeding . . . 3180
3.9 Infective endocarditis . . . 3180
3.9.1 Prophylaxis. . . . 3180
3.9.2 Diagnosis and risk assessment . . . 3180
3.9.3 Treatment . . . 3180
3.10 Methods of contraception and termination of pregnancy, and in vitro fertilization. . . . 3181
3.10.1 Methods of contraception . . . 3181
3.10.2 Sterilization . . . 3181
3.10.3 Methods of termination of pregnancy . . . 3181
3.10.4 In vitro fertilization . . . 3181
3.11 Recommendations . . . 3182
4. Congenital heart disease and pulmonary hypertension . . . 3182
4.1 Introduction . . . 3182
4.2 Pulmonary hypertension and Eisenmenger's syndrome . . . 3183
4.2.1 Pulmonary hypertension . . . 3183
4.2.2 Eisenmenger's syndrome. . . . 3183
4.2.3 Cyanotic heart disease without pulmonary hypertension . . . 3184
4.3 Specific congenital heart defects . . . 3184
4.3.1 Left ventricular outflow tract obstruction . . . 3184
4.3.2 Atrial septal defect. . . . 3184
4.3.3 Ventricular septal defect . . . 3184
4.3.4 Atrioventricular septal defect . . . 3184
4.3.5 Coarctation of the aorta . . . 3184
4.3.6 Pulmonary valve and right ventricular outflow tract disease . . . 3184
4.3.7 Congenital aortic stenosis. . . . 3185
4.3.8 Tetralogy of Fallot . . . 3185
4.3.9 Ebstein's anomaly. . . . 3185
4.3.10 Transposition of the great arteries . . . 3185
4.3.11 Congenitally corrected transposition of the great arteries . . . 3185
4.3.12 Fontan circulation . . . 3186
4.4 Recommendations . . . 3186
5. Aortic diseases. . . . 3186
5.1 Maternal and offspring risk . . . 3187
5.2 Specific syndromes . . . 3187
5.2.1 Marfan syndrome. . . . 3187
5.2.2 Bicuspid aortic valve . . . 3187
5.2.3 Vascular Ehlers–Danlos syndrome . . . 3187
5.2.4 Turner syndrome. . . . 3187
5.2.5 Other autosomal dominant aortopathies . . . 3187
5.3 Management . . . 3187
5.3.1 Follow-up and medical therapy . . . 3187
5.3.2 Interventions . . . 3188
5.3.3 Delivery. . . . 3188
5.4 Recommendations . . . 3189
6. Valvular heart disease . . . 3190
6.1 Stenotic valve lesions . . . 3190
6.1.1 Mitral stenosis . . . 3190
6.1.2 Valvular aortic stenosis . . . 3190
6.2 Regurgitant lesions . . . 3191
6.2.1 Mitral and aortic regurgitation . . . 3191
6.2.2 Tricuspid regurgitation. . . . 3191
6.3 Atrial fibrillation in native heart valve disease. . . . 3191
6.4 Prosthetic valves . . . 3191
6.4.1 Choice of valve prosthesis . . . 3191
6.4.2 Pregnancy risk with bioprostheses. . . . 3192
6.5 Mechanical prostheses and anticoagulation . . . 3192
6.5.1 Maternal risk . . . 3192
6.5.2 Obstetric and offspring risk . . . 3192
6.5.3 Management . . . 3193
6.6 Recommendations . . . 3195
7. Coronary artery disease. . . . 3197
7.1 Aetiology . . . 3197
7.2 Presentation and diagnosis . . . 3197
7.3 Management . . . 3197
7.4 Pharmacotherapy . . . 3197
7.5 Intervention. . . . 3197
7.5.1 Stent choice and antiplatelet therapy . . . 3197
7.6 Pre-existing CAD . . . 3198
7.7 Labour and delivery . . . 3198
7.8 Recommendations . . . 3198
8. Cardiomyopathies and heart failure . . . 3198
8.1 Peripartum cardiomyopathy . . . 3198
8.1.1 Diagnosis . . . 3198
8.1.2 Prognosis and counselling . . . 3198
8.2 Dilated cardiomyopathy . . . 3198
8.2.1 Prognosis and counselling . . . 3199
8.3 Management of heart failure during and after pregnancy . . . 3199
8.3.1 Acute/subacute heart failure and cardiogenic shock during or after pregnancy . . . 3199
8.3.2 Bromocriptine and peripartum cardiomyopathy . . . 3201
8.3.3 Devices and transplantation. . . . 3201
8.3.4 Anticoagulation . . . 3201
8.3.5 Delivery and breastfeeding. . . . 3201
8.4 Hypertrophic cardiomyopathy. . . . 3201
8.4.1 Management . . . 3201
8.4.2 Delivery. . . . 3202
8.5 Recommendations . . . 3202
9. Arrhythmias . . . 3203
9.1 Introduction . . . 3203
9.2 Maternal risk . . . 3203
9.3 Obstetric and offspring risk . . . 3203
9.4 Supraventricular tachycardia . . . 3203
9.5 Atrial fibrillation and atrial flutter . . . 3203
9.5.1 Anticoagulation . . . 3203
9.6 Ventricular tachycardia . . . 3203
9.7 Bradyarrhythmias . . . 3204

Downloaded from https://academic.oup.com/eurheartj/article-abstract/39/34/3165/5078465 by guest on 13 September 2018

9.7.1 Sinus node dysfunction ... 3204
9.7.2 Atrioventricular block ... 3204
9.8 Interventions ... 3204
9.8.1 Electrical cardioversion ... 3204
9.8.2 Catheter ablation ... 3204
9.8.3 Implantable cardioverter-defibrillator and pacing ... 3204
9.9 Recommendations ... 3206
10. Hypertensive disorders ... 3207
10.1 Diagnosis and risk assessment ... 3207
10.1.1 Blood pressure measurement ... 3207
10.1.2 Laboratory tests ... 3207
10.2 Definition and classification of hypertension in pregnancy ... 3207
10.3 Prevention of hypertension and pre-eclampsia ... 3207
10.4 Management of hypertension in pregnancy ... 3208
10.4.1 Background ... 3208
10.4.2 Non-pharmacological management ... 3208
10.4.3 Pharmacological management ... 3208
10.5 Delivery ... 3208
10.6 Prognosis after pregnancy ... 3209
10.6.1 Blood pressure post-partum ... 3209
10.6.2 Hypertension and lactation ... 3209
10.6.3 Risk of recurrence of hypertensive disorders in a subsequent pregnancy ... 3209
10.6.4 Long-term cardiovascular consequences of gestational hypertension ... 3209
10.6.5 Fertility treatment ... 3209
10.7 Recommendations ... 3209
11. Venous thrombo-embolic disease during pregnancy and the puerperium ... 3210
11.1 Epidemiology and maternal risk ... 3210
11.2 Risk factors for pregnancy-related venous thrombo-embolism and risk stratification ... 3210
11.3 Prevention of venous thrombo-embolism ... 3210
11.4 Management of acute venous thrombo-embolism ... 3210
11.4.1 Pulmonary embolism ... 3210
11.4.2 Acute deep vein thrombosis ... 3211
11.5 Recommendations ... 3211
11.5.1 Management of delivery ... 3211
12. Drugs during pregnancy and breastfeeding ... 3212
12.1 General principles ... 3212
12.1.1 Pharmacokinetics in pregnancy ... 3212
12.1.2 Drug classes in pregnancy ... 3213
12.2 US Food and Drug Administration classification ... 3214
12.3 Internet databases ... 3214
12.4 Pharmaceutical industry ... 3214
12.5 Recommendations ... 3214
13. Gaps in the evidence ... 3231
14. Key messages ... 3231
15. 'What to do' and 'what not to do' messages from the Guidelines ... 3233
16. Appendix ... 3236
References ... 3237

List of tables

Table 1. Classes of recommendation ... 3170
Table 2. Level of evidence ... 3171
Table 3. Modified World Health Organization classification of maternal cardiovascular risk ... 3175
Table 4. Predictors of maternal and neonatal events ... 3176
Table 5. Aortic diseases ... 3188
Table 6. Recommended surveillance levels at time of delivery in women with arrhythmias ... 3205
Table 7. Drugs and safety data ... 3215

Abbreviations and acronyms

ABPM	Ambulatory blood pressure monitoring
ACE	Angiotensin-converting enzyme
ACE-I	Angiotensin-converting enzyme inhibitor
ACR	Albumin:creatinine ratio
ACS	Acute coronary syndromes
AF	Atrial fibrillation
AHF	Acute heart failure
AMI	Acute myocardial infarction
aPTT	Activated partial thromboplastin time
ARB	Angiotensin receptor blocker
ARNI	Angiotensin receptor neprilysin inhibitor
AS	Aortic stenosis
ASD	Atrial septal defect
ASI	Aortic size index
AT	Atrial tachycardia
AUC	Area under the curve
AV	Atrioventricular
BMI	Body mass index
BP	Blood pressure
BSA	Body surface area
CAD	Coronary artery disease
CARPREG	CARdiac disease in PREGnancy
CCB	Calcium channel blocker
CI	Confidence interval
CO	Cardiac output
CoA	Coarctation of the aorta
CPG	Committee for Practice Guidelines
CT	Computed tomography
CVD	Cardiovascular disease
DBP	Diastolic blood pressure
DCM	Dilated cardiomyopathy

Downloaded from https://academic.oup.com/eurheartj/article-abstract/39/34/3165/5078465 by guest on 13 September 2018

DES	Drug-eluting stent
DVT	Deep vein/venous thrombosis
ECG	Electrocardiogram
EF	Ejection fraction
ESC	European Society of Cardiology
FDA	US Food and Drug Administration
HCM	Hypertrophic cardiomyopathy
HF	Heart failure
HFrEF	Heart failure with reduced ejection fraction
5-HT1A	5-hydroxytryptamine (serotonin)
HTAD	Heritable thoracic aortic disease
ICD	Implantable cardioverter-defibrillator
ICU	Intensive care unit
IE	Infective endocarditis
INR	International normalized ratio
i.v.	Intravenous
KLH	Keyhole limpet haemocyanin
LMWH	Low molecular weight heparin
LQTS	Long QT syndrome
LV	Left ventricular
LVEF	Left ventricular ejection fraction
MCS	Mechanical circulatory support
mGy	Milligray
MI	Myocardial infarction
MR	Mitral regurgitation
MRA	Mineralocorticoid receptor antagonist
MRHD	Maximum recommended human dose
MRI	Magnetic resonance imaging
MS	Mitral stenosis
mWHO	Modified World Health Organization
NSTE-ACS	Non-ST-elevation acute coronary syndrome
NSTEMI	Non-ST-elevation myocardial infarction
NT-proBNP	N-terminal pro B-type natriuretic peptide
NYHA	New York Heart Association
OAC	Oral anticoagulant
OHSS	Ovarian hyperstimulation syndrome
OR	Odds ratio
PAH	Pulmonary arterial hypertension
PAP	Pulmonary arterial pressure
PCI	Percutaneous coronary intervention
PE	Pulmonary embolism
PGE	Prostaglandin E
PH	Pulmonary hypertension
PLLR	Pregnancy and Lactation Labelling Rule
PPCM	Peripartum cardiomyopathy
PS	Pulmonary (valve) stenosis
P-SCAD	Pregnancy-related spontaneous coronary artery dissection
PSVT	Paroxysmal supraventricular tachycardia
RAAS	Renin–angiotensin–aldosterone system
RHD	Recommended human dose
ROPAC	Registry Of Pregnancy And Cardiac disease
RV	Right ventricular
SBP	Systolic blood pressure
SCD	Sudden cardiac death
SD	Standard deviation
sFlt1	Soluble fms-like tyrosine kinase 1
STEMI	ST-elevation myocardial infarction
SVT	Supraventricular tachycardia
TAPSE	Tricuspid annular plane systolic excursion
TdP	Torsade de pointes
TGA	Transposition of the great arteries
TR	Tricuspid regurgitation
UFH	Unfractionated heparin
UPA	Ulipristal acetate
VKA	Vitamin K antagonist
VSD	Ventricular septal defect
VT	Ventricular tachycardia
VTE	Venous thrombo-embolism
WCD	Wearable cardioverter-defibrillator
WPW	Wolff–Parkinson–White

1. Preamble

Guidelines summarize and evaluate available evidence with the aim of assisting health professionals in selecting the best management strategies for an individual patient with a given condition. Guidelines and their recommendations should facilitate decision making of health professionals in their daily practice. However, the final decisions concerning an individual patient must be made by the responsible health professional(s) in consultation with the patient and caregiver as appropriate.

A great number of guidelines have been issued in recent years by the European Society of Cardiology (ESC), as well as by other societies and organisations. Because of the impact on clinical practice, quality criteria for the development of guidelines have been established in order to make all decisions transparent to the user. The recommendations for formulating and issuing ESC Guidelines can be found on the ESC website (http://www.escardio.org/Guidelines-&-Education/Clinical-Practice-Guidelines/Guidelines-development/Writing-ESC-Guidelines). ESC Guidelines represent the official position of the ESC on a given topic and are regularly updated.

Members of this Task Force were selected by the ESC, including representation from its relevant ESC sub-specialty groups, in order to represent professionals involved with the medical care of patients with this pathology. Selected experts in the field undertook a comprehensive review of the published evidence for management of a given condition according to ESC Committee for Practice Guidelines (CPG) policy. A critical evaluation of diagnostic and therapeutic procedures was performed, including assessment of the risk–benefit ratio. The level of evidence and the

Downloaded from https://academic.oup.com/eurheartj/article-abstract/39/34/3165/5078465 by guest on 13 September 2018

strength of the recommendation of particular management options were weighed and graded according to predefined scales, as outlined in *Tables 1 and 2*.

The experts of the writing and reviewing panels provided declaration of interest forms for all relationships that might be perceived as real or potential sources of conflicts of interest. These forms were compiled into one file and can be found on the ESC website (http://www.escardio.org/guidelines). Any changes in declarations of interest that arise during the writing period were notified to the ESC and updated. The Task Force received its entire financial support from the ESC without any involvement from the healthcare industry.

The ESC CPG supervises and coordinates the preparation of new Guidelines. The Committee is also responsible for the endorsement process of these Guidelines. The ESC Guidelines undergo extensive review by the CPG and external experts. After appropriate revisions the Guidelines are approved by all the experts involved in the Task Force. The finalized document is approved by the CPG for publication in the European Heart Journal. The Guidelines were developed after careful consideration of the scientific and medical knowledge and the evidence available at the time of their dating.

The task of developing ESC Guidelines also includes the creation of educational tools and implementation programmes for the recommendations including condensed pocket guideline versions, summary slides, booklets with essential messages, summary cards for non-specialists and an electronic version for digital applications (smartphones, etc.). These versions are abridged and thus, if needed, one should always refer to the full text version, which is freely available via the ESC website and hosted on the EHJ website. The National Societies of the ESC are encouraged to endorse, translate and implement all ESC Guidelines. Implementation programmes are needed because it has been shown that the outcome of disease may be favourably influenced by the thorough application of clinical recommendations.

Surveys and registries are needed to verify that real-life daily practice is in keeping with what is recommended in the guidelines, thus completing the loop between clinical research, writing of guidelines, disseminating them and implementing them into clinical practice.

Health professionals are encouraged to take the ESC Guidelines fully into account when exercising their clinical judgment, as well as in the determination and the implementation of preventive, diagnostic or therapeutic medical strategies. However, the ESC Guidelines do

Table 1 Classes of recommendation

Classes of recommendations	Definition	Suggested wording to use
Class I	Evidence and/or general agreement that a given treatment or procedure is beneficial, useful, effective.	Is recommended/is indicated
Class II	Conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the given treatment or procedure.	
Class IIa	*Weight of evidence/opinion is in favour of usefulness/efficacy.*	Should be considered
Class IIb	*Usefulness/efficacy is less well established by evidence/opinion.*	May be considered
Class III	Evidence or general agreement that the given treatment or procedure is not useful/effective, and in some cases may be harmful.	Is not recommended

©ESC 2018

Downloaded from https://academic.oup.com/eurheartj/article-abstract/39/34/3165/5078465 by guest on 13 September 2018

Table 2 Level of evidence

Level of evidence A	Data derived from multiple randomized clinical trials or meta-analyses.
Level of evidence B	Data derived from a single randomized clinical trial or large non-randomized studies.
Level of evidence C	Consensus of opinion of the experts and/or small studies, retrospective studies, registries.

©ESC 2018

not override in any way whatsoever the individual responsibility of health professionals to make appropriate and accurate decisions in consideration of each patient's health condition and in consultation with that patient or the patient's caregiver where appropriate and/or necessary. It is also the health professional's responsibility to verify the rules and regulations applicable to drugs and devices at the time of prescription.

2. Introduction

2.1 Why do we need new Guidelines on the management of cardiovascular diseases in pregnancy?

Since the previous version of these Guidelines was published in 2012, new evidence has accumulated, particularly on diagnostic techniques, risk assessment, and the use of cardiovascular drugs. This made a revision of the recommendations necessary.

2.2 New format of the Guidelines

The new Guidelines have been adapted to facilitate their use in clinical practice and to meet readers' demands by focusing on condensed, clearly presented recommendations. At the end of each section, 'recommendations' summarize the essentials. 'Gaps in the evidence' are listed in section 13 to propose topics for future research. The Guidelines document is harmonized with the simultaneously published chapter on the management of cardiovascular diseases (CVDs) in pregnancy of the ESC Textbook of Cardiology (http://oxfordmedicine.com/view/10.1093/med/9780199566990.001.0001/med-9780199566990-chapter-33). Background information and a detailed discussion of the data that have provided the basis for the recommendations can be found in the relevant book chapter.

2.3 Why these Guidelines are important

Pregnancy is complicated by maternal disease in 1–4% of cases. New data about the prevalence and incidence of pregnancy-related heart disease are limited from most parts of the world. Sudden adult death syndrome, peripartum cardiomyopathy (PPCM), aortic dissection, and myocardial infarction (MI) were the most common causes of maternal death in the UK over the period 2006–08.[1–5] Knowledge of the risks associated with CVDs during pregnancy and their management in pregnant women who suffer from serious pre-existing conditions is of pivotal importance for advising patients before pregnancy.[6] Since all measures concern not only the mother but the foetus as well, the optimum treatment of both must be targeted. A therapy favourable for the mother can be associated with potential harm to the developing child and, in extreme cases, treatment measures that protect the survival of the mother can cause the death of the foetus. On the other hand, therapies to protect the child may lead to a suboptimal outcome for the mother. Because prospective or randomized studies are frequently absent, recommendations in these Guidelines mostly correspond to evidence level C. Therefore, registries and prospective studies are urgently needed to improve current knowledge.[4,7] At the European level, the Registry Of Pregnancy And Cardiac disease (ROPAC) registry of the ESC and the European Surveillance of Congenital Anomalies network are providing data on epidemiology and drug exposure in pregnancy.[4,8]

2.4 Methods

The current Guidelines are based on the previously published ESC Guidelines on the management of CVDs during pregnancy,[9] the literature found in a systematic search from 2011–16 in the National Institutes of Health database (PubMed), and on recent publications and recommendations from the American Heart Association and the American College of Cardiology.[10] Furthermore, we considered related Guidelines of the ESC published in 2012–15 on the topics of congenital heart disease, aortic disease, valvular heart disease, cardiomyopathies and heart failure (HF), coronary artery disease (CAD), hypertension, pericardial diseases, pulmonary hypertension (PH), infective endocarditis (IE), ventricular arrhythmias, and acute coronary syndromes, and on the topics of cancer treatment and cardiovascular toxicity, dyslipidaemias, atrial fibrillation (AF), and CVD prevention published in 2016 (https://www.escardio.org/Guidelines/Clinical-Practice-Guidelineshomepage).

Downloaded from https://academic.oup.com/eurheartj/article-abstract/39/34/3165/5078465 by guest on 13 September 2018

2.5 What is new in the 2018 CVD in Pregnancy Guidelines? (*Figure 1*)

Selected revised recommendations and selected new recommendations	
Comment/comparison with 2011 version	**2018**
Strengthening mWHO classification of maternal risk.	It is recommended to perform risk assessment in all women with cardiac diseases of childbearing age and before conception, using the mWHO classification of maternal risk[11] (IC).
Upgrade in class of recommendation; patients with severe MS should undergo intervention before pregnancy.	Intervention is recommended before pregnancy in patients with MS and valve area <1.0 cm² (IC).
In 2011, OACs were recommended during the second and third trimesters until the 36th week. Now, separate recommendations for women with low and high dose are given for VKA use during the second and third trimesters.	During the second and third trimesters until the 36th week, VKAs are recommended in women needing a low dose (low-dose VKA: warfarin <5 mg/day, phenprocoumon <3 mg/day, or acenocoumarol <2 mg/day) (IC).
Sotalol deleted.	Flecainide or propafenone are recommended for prevention of SVT in patients with WPW syndrome[12] (IC).
Changed in high-risk patients from UFH to LMWH. Dosing based on body weight introduced.	LMWH is the drug of choice for the prevention and treatment of VTE in all pregnant patients[13] (IB). It is recommended that the therapeutic dose of LMWH is based on body weight[14] (IC).
Changes: dose adjustment of UFH or LMWH dose within 36 h now recommended.	In pregnant women on LMWH or UFH, it is recommended to perform weekly anti-Xa level monitoring or aPTT monitoring with dose adjustment (within 36 h) (IC).
Upgrade of recommendation: IIb to IIa.	Catheter ablation with electroanatomical systems should be considered in experienced centres in case of drug-refractory and poorly tolerated SVT[15–17] (IIaC).
Change from D-dimers to imaging as the first line of investigation, as D-dimers are unreliable in pregnancy.	If compression ultrasound is negative, magnetic resonance venography should be considered to diagnose VTE[18] (IIaC).
FDA categories A–X were used for all drugs in 2011.	Decision-making based on former FDA categories is no longer recommended (IIIC).
'Pre-pregnancy surgery' is now deleted. Now also information on Turner syndrome with aortic diameter corrected for BSA	Pregnancy is not recommended in patients with severe dilatation of the aorta (heritable thoracic aortic disease such as Marfan syndrome >45 mm, bicuspid aortic valve >50 mm, >27 mm/m² BSA, or Turner syndrome ASI >25 mm/m² BSA)[19,20] (IIIC).
Selected new recommendations	
Right heart catheterization is recommended to confirm the diagnosis of PAH. This can be performed during pregnancy but with very strict indications[10] (IC).	
LMWH in therapeutic dose is recommended in pregnant patients with chronic thrombo-embolic pulmonary hypertension (IC).	

Figure 1 Selected revised and new recommendations.

Downloaded from https://academic.oup.com/eurheartj/article-abstract/39/34/3165/5078465 by guest on 13 September 2018

© ESC 2018

In patients with pulmonary embolism, thrombolytic therapy is recommended only in severe hypotension or shock[21] (IC).
In women at high risk for thrombo-embolism, it is recommended to convert LMWH to UFH at least 36 h prior to delivery and stop the UFH infusion 4–6 h prior to anticipated delivery. aPTT should be normal before regional anaesthesia[22] (IC).
In women at low risk for thrombo-embolism on therapeutic LMWH, induction or caesarean section is recommended to be performed 24 h after the last dose of LMWH[22] (IC).
In women considering pregnancy and requiring heart valve surgery, it is recommended to choose the prosthesis in consultation with a pregnancy heart team (IC).
It is recommended to manage pregnancy in women with mechanical heart valves in a centre with a pregnancy heart team (IC).
In treatment-naive pregnant PAH patients, initiating treatment should be considered[23] (IIaC).
In patients with (history of) aortic dissection, caesarean delivery should be considered (IIaC).
Beta-blocker therapy throughout pregnancy should be considered in women with Marfan syndrome and other heritable thoracic aortic diseases (IIaC).
Induction of labour should be considered at 40 weeks gestation in all women with cardiac disease (IIaC).
In patients with PPCM, bromocriptine treatment may be considered to stop lactation and enhance recovery (LV function)[24,25] (IIbB).
Pregnancy is not recommended in patients with vascular Ehlers–Danlos syndrome[26] (IIIC).
Breastfeeding is not recommended in mothers who take antiplatelet agents other than low-dose aspirin (from section 7, see section 12) (IIIC).
New concepts
Enforcing mWHO classification of maternal risk.
Introduction of the pregnancy heart team.
More attention for assisted reproductive therapy.
Discussion of the use of bromocriptine in PPCM.
Introduction of specific levels of surveillance based on low/medium/high risk for arrhythmia with haemodynamic compromise at delivery.
New information on pharmacokinetics in pregnancy, more detailed information on pharmacodynamics in animal experiments on all drugs (Supplementary Data)
Perimortem caesarean section is discussed.
Advice on contraception and the termination of pregnancy in women with cardiac disease is now provided.

© ESC 2018

Figure 1 Continued.

3. General considerations

3.1 Epidemiology

In the western world, the risk of CVD in pregnancy has increased due to increasing age at first pregnancy. According to World Atlas,[27] the 10 countries where mean age at first birth is highest record a mean age between 28.8–31.2 years. The mild increase in maternal age does not justify an increase in CVD during pregnancy because of maternal age. However, pregnancies in the late reproductive years (or between ages of 40–50 years) are more frequently associated with an increasing prevalence of cardiovascular risk factors, especially diabetes, hypertension, and obesity. Additionally, an increasing number of women with congenital heart disease reach childbearing age.[5]

In western countries, maternal heart disease is the major cause of maternal death during pregnancy.[2,28]

Hypertensive disorders are the most frequent cardiovascular disorders during pregnancy, occurring in 5–10% of all pregnancies (see section 10). Among the other disease conditions, congenital heart disease is the most frequent CVD present during pregnancy in the western world (75–82%).[29,30] Rheumatic valvular disease dominates in non-western countries, comprising 56–89% of all CVDs in pregnancy.[29,31]

Peripartum intensive care unit (ICU) admissions are increasing in frequency, with affected women-who suffer from serious pre-existing conditions, are older, and present with multiple comorbidities and also congenital heart disease-being more frequently

Downloaded from https://academic.oup.com/eurheartj/article-abstract/39/34/3165/5078465 by guest on 13 September 2018

admitted than in previous years.[6] The admission rate to ICUs was 6.4 per 1000 deliveries, corresponding to 1 admission per 156 deliveries, in Vienna, Austria during the period 2011–14. A 5% mortality rate was also observed in the study and is considered as appropriate in comparison to the literature.[6]

Cardiomyopathies are rare, but represent severe causes of cardiovascular complications in pregnancy.[32]

3.2 Physiological adaptations to pregnancy

Pregnancy induces changes in the cardiovascular system to meet the increased metabolic demands of the mother and foetus. Plasma volume and cardiac output (CO) reach a maximum of 40–50% above baseline at 32 weeks of gestation, while 75% of this increase has occurred by the end of the first trimester. The increase in CO is achieved by an increase in stroke volume in the first-half of pregnancy and a gradual increase in heart rate thereafter. Atrial and ventricular diameters increase while ventricular function is preserved. In women with heart disease, left ventricular (LV) and right ventricular (RV) adaptation to pregnancy can be suboptimal.[33–36] Maternal cardiac dysfunction is related to impaired uteroplacental flow and suboptimal foetal outcome.[35–37] Systemic and pulmonary vascular resistances decrease during pregnancy.

Pregnancy is a hypercoagulable state associated with increased risk of thrombo-embolism. Increased activity of liver enzyme systems, glomerular filtration rate, and plasma volume, protein binding changes, and decreased serum albumin levels contribute to changes in the pharmacokinetics of many drugs.[36,38] Uterine contractions, positioning (left lateral vs. supine), pain, anxiety, exertion, haemorrhage, and uterine involution cause significant haemodynamic changes during labour and post-partum. Anaesthesia, haemorrhage, and infection may induce additional cardiovascular stress. Blood pressure (BP) and CO increase during labour and post-partum. In conclusion, the physiological adaptations to pregnancy influence the evaluation and interpretation of cardiac function and clinical status.

3.3 Pre-pregnancy counselling

All women with known cardiac or aortic disease who wish to embark on pregnancy require timely pre-pregnancy counselling.[39] Informed maternal decision-making is crucial and there is a clear need for individualized care, taking into account not only the medical condition but also the emotional and cultural context, psychological issues, and ethical challenges. Especially in patients with a high-risk or possible contraindication for pregnancy, the risk of pregnancy and the necessity of careful planning of pregnancy should be discussed at a young age. However, it is also important to explain that many women can go through pregnancy with low-risks.

For risk estimation, as a minimum, an electrocardiogram (ECG), echocardiography, and an exercise test should be performed. In case of aortic pathology, complete aortic imaging by computed tomography (CT) scanning or magnetic resonance imaging (MRI) is necessary for appropriate pre-conception counselling. Peak heart rate and peak oxygen uptake are both known to be predictive of maternal cardiac events in pregnancy.[40] A pregnancy exercise capacity >80% is associated with a favourable pregnancy outcome.

Several aspects must be discussed, including long-term prognosis, fertility and miscarriage rates, risk of recurrence of congenital disease, drug therapy, estimated maternal risk and outcome, expected foetal outcomes, and plans for pregnancy care and delivery. A multidisciplinary management plan should be constructed and discussed with the patient. In addition, attention to unhealthy habits including being overweight, smoking, and consuming alcohol is important, as these can have a clear impact on maternal and foetal outcomes. Pregnancy is a very suitable time for recommending a healthy lifestyle, including smoking cessation.

3.3.1 Risk of maternal cardiovascular complications

The risk of complications in pregnancy depends on the underlying cardiac diagnosis, ventricular and valvular function, functional class, presence of cyanosis, pulmonary artery pressures, and other factors. Comorbidities, including for example rheumatoid and musculoskeletal diseases as well as mental disorders, should also be taken into account. Therefore, risk estimation should be individualized.

To assess the maternal risk of cardiac complications during pregnancy, the condition of the woman should be assessed, taking into account medical history, functional class, oxygen saturation, natriuretic peptide levels, echocardiographic assessment of ventricular and valvular function, intrapulmonary pressures and aortic diameters, exercise capacity, and arrhythmias. Disease-specific risk should be assessed using the modified World Health Organization (mWHO) classification (*Table 3*) and as described in the respective sections dealing with specific diseases in these Guidelines. Risk estimation should be further refined by taking into account predictors that have been identified in studies that included large populations with various diseases, such as the CARPREG (CARdiac disease in PREGnancy), ZAHARA, and ROPAC (Registry Of Pregnancy And Cardiac disease) studies (*Table 4*).[29,41–43]

The mWHO classification is currently the most accurate system of risk assessment, although it is probably more appropriate for developed, rather than developing, countries.[4,11,44] The general principles of this classification, and follow-up and management during pregnancy according to this mWHO classification, are presented in *Table 3*. Indications for intervention (surgical or catheter) do not differ in women who contemplate pregnancy compared with other patients. The few exceptions to this rule are women with at least moderate mitral stenosis and women with aortic dilatation. See also the disease-specific sections of these Guidelines. Fertility treatment is contraindicated in women with mWHO class IV, and should be carefully considered in those who have mWHO class III disease or who are anticoagulated.[45]

The risk estimation needs to be re-evaluated during each pre-pregnancy visit, because the risk of complications may change over time. Natriuretic peptide levels are associated with the occurrence of cardiac events, with N-terminal pro B-type natriuretic peptide (NT-proBNP) >128 pg/mL at 20 weeks pregnancy being predictive of events later in the pregnancy.[46,47] Pre-eclampsia is associated with HF in women with heart disease.[43]

3.3.2 Risk of obstetric and offspring complications

Women with cardiac disease have an increased risk of obstetric complications, including premature labour, pre-eclampsia, and post-partum haemorrhage.

Offspring complications occur in 18–30% of patients with heart disease, with neonatal mortality between 1–4%.[29] Maternal and

Downloaded from https://academic.oup.com/eurheartj/article-abstract/39/34/3165/5078465 by guest on 13 September 2018

Table 3 Modified World Health Organization classification of maternal cardiovascular risk

	mWHO I	mWHO II	mWHO II–III	mWHO III	mWHO IV
Diagnosis (if otherwise well and uncomplicated)	Small or mild – pulmonary stenosis – patent ductus arteriosus – mitral valve prolapse Successfully repaired simple lesions (atrial or ventricular septal defect, patent ductus arteriosus, anomalous pulmonary venous drainage) Atrial or ventricular ectopic beats, isolated	Unoperated atrial or ventricular septal defect Repaired tetralogy of Fallot Most arrhythmias (supraventricular arrhythmias) Turner syndrome without aortic dilatation	Mild left ventricular impairment (EF >45%) Hypertrophic cardiomyopathy Native or tissue valve disease not considered WHO I or IV (mild mitral stenosis, moderate aortic stenosis) Marfan or other HTAD syndrome without aortic dilatation Aorta <45 mm in bicuspid aortic valve pathology Repaired coarctation Atrioventricular septal defect	Moderate left ventricular impairment (EF 30–45%) Previous peripartum cardiomyopathy without any residual left ventricular impairment Mechanical valve Systemic right ventricle with good or mildly decreased ventricular function Fontan circulation. If otherwise the patient is well and the cardiac condition uncomplicated Unrepaired cyanotic heart disease Other complex heart disease Moderate mitral stenosis Severe asymptomatic aortic stenosis Moderate aortic dilatation (40–45 mm in Marfan syndrome or other HTAD; 45–50 mm in bicuspid aortic valve, Turner syndrome ASI 20–25 mm/m^2, tetralogy of Fallot <50 mm) Ventricular tachycardia	Pulmonary arterial hypertension Severe systemic ventricular dysfunction (EF <30% or NYHA class III–IV) Previous peripartum cardiomyopathy with any residual left ventricular impairment Severe mitral stenosis Severe symptomatic aortic stenosis Systemic right ventricle with moderate or severely decreased ventricular function Severe aortic dilatation (>45 mm in Marfan syndrome or other HTAD, >50 mm in bicuspid aortic valve, Turner syndrome ASI >25 mm/m^2, tetralogy of Fallot >50 mm) Vascular Ehlers–Danlos Severe (re)coarctation Fontan with any complication
Risk	No detectable increased risk of maternal mortality and no/mild increased risk in morbidity	Small increased risk of maternal mortality or moderate increase in morbidity	Intermediate increased risk of maternal mortality or moderate to severe increase in morbidity	Significantly increased risk of maternal mortality or severe morbidity	Extremely high risk of maternal mortality or severe morbidity
Maternal cardiac event rate	2.5–5%	5.7–10.5%	10–19%	19–27%	40–100%
Counselling	Yes	Yes	Yes	Yes: expert counselling required	Yes: pregnancy contraindicated: if pregnancy occurs, termination should be discussed
Care during pregnancy	Local hospital	Local hospital	Referral hospital	Expert centre for pregnancy and cardiac disease	Expert centre for pregnancy and cardiac disease
Minimal follow-up visits during pregnancy	Once or twice	Once per trimester	Bimonthly	Monthly or bimonthly	Monthly
Location of delivery	Local hospital	Local hospital	Referral hospital	Expert centre for pregnancy and cardiac disease	Expert centre for pregnancy and cardiac disease

ASI = aortic size index; EF = ejection fraction; HTAD = heritable thoracic aortic disease; mWHO = modified World Health Organization classification; NYHA = New York Heart Association; WHO = World Health Organization.

© ESC 2018

Downloaded from https://academic.oup.com/eurheartj/article-abstract/39/34/3165/5078465 by guest on 13 September 2018

Table 4 Predictors of maternal and neonatal events

Predictors of maternal cardiovascular events	Predictors of neonatal events
Prior cardiac event (heart failure, transient ischaemic attack, stroke, arrhythmia)[4,28,43,47,48]	NYHA class III/IV or cyanosis during baseline pre-natal visit
NYHA class III/IV[29,42,43,48,49]	Maternal left heart obstruction
Left heart obstruction (moderate to severe)[29,42]	Smoking during pregnancy
Reduced systemic ventricular systolic function (ejection fraction <40%)[29,43,49]	Low maternal oxygen saturation (<90%)
Reduced subpulmonary ventricular function[47,50] (TAPSE <16 mm)[49,51]	Multiple gestations Use of anticoagulants throughout pregnancy
Systemic atrioventricular valve regurgitation (moderate to severe)[42]	Cardiac medication before pregnancy 'At birth' cyanotic heart disease
Pulmonary atrioventricular valve regurgitation (moderate to severe)[42]	Mechanical valve prosthesis
Pulmonary arterial hypertension[43,48,49]	Maternal cardiac event during pregnancy
Cardiac medication before pregnancy[42,46]	Maternal decline in cardiac output during pregnancy
Cyanosis (O_2 saturation <90%)[29,49]	Abnormal uteroplacental Doppler flow
Natriuretic peptide levels (NT-proBNP >128 pg/mL at 20 weeks predictive of event later in pregnancy)[42,46]	
Smoking history[51]	
Mechanical valve prosthesis[42,47]	
Repaired or unrepaired cyanotic heart disease[42]	

Predictors identified in references[29,35,42,43,51]
NT-proBNP = N-terminal pro B-type natriuretic peptide; NYHA = New York Heart Association; TAPSE = tricuspid annular plane systolic excursion.

© ESC 2018

offspring events are highly correlated.[29,42,43] Though predictors of offspring complications have been identified (*Table 4*), there are no validated prediction models.[4]

3.3.3 Pregnancy heart team

In women with a moderate or high-risk of complications during pregnancy (mWHO II–III, III, and IV), pre-pregnancy counselling and management during pregnancy and around delivery should be conducted in an expert centre by a multidisciplinary team: the pregnancy heart team. The minimum team requirements are a cardiologist, obstetrician, and anaesthetist, all with expertise in the management of high-risk pregnancies in women with heart disease. Additional experts that may be involved, depending on the individual situation, are a geneticist, cardiothoracic surgeon, paediatric cardiologist, foetal medicine specialist, neonatologist, haematologist, nurse specialist, pulmonary specialist, and others where appropriate. In this team patients from other centres can also be discussed, so not every hospital needs to have its own pregnancy heart team. The conclusions and recommendations should be filed and made available 24 h per day.

3.4 Cardiovascular diagnosis in pregnancy

During pregnancy it can be more difficult to diagnose HF, for example, because the physiological changes that occur during pregnancy (section 3.2) may mimic CVD. However, many disorders can be identified by taking a careful history and a thorough physical examination. When disproportionate or unexplained dyspnoea occurs during pregnancy and/or when a new pathological murmur (all audible diastolic murmurs are abnormal) is heard, echocardiography is indicated. BP should be measured using a standardized method (section 10). Proteinuria should be sought, especially with a history or family history of hypertension or pre-eclampsia. Oximetry should be performed in patients with congenital heart disease.

3.4.1 Electrocardiography

In most pregnant patients, the heart rotates to the left with a 15–20° leftward axis deviation on the ECG. Common additional findings include transient ST/T wave changes, a Q wave and inverted T waves in lead III, an attenuated Q wave in lead aVF, and inverted T waves in V1, V2, and occasionally V3. Changes may mimic LV hypertrophy and other structural heart diseases. Holter monitoring should be performed in patients with known previous paroxysmal/persistent arrhythmia [ventricular tachycardia (VT), AF, or atrial flutter] or reporting palpitations.

3.4.2 Echocardiography

Transthoracic echocardiography is the preferred imaging method in pregnancy. This reproducible, widely available, relatively cheap diagnostic modality can be used both in the outpatient clinic and at the

Downloaded from https://academic.oup.com/eurheartj/article-abstract/39/34/3165/5078465 by guest on 13 September 2018

cardiology ward, and also at the emergency department, ICU, and obstetric ward, and should be used with a low threshold. During pregnancy, some changes in echo parameters are expected, such as mild dilatation of the chambers, a change in LV wall thickness, and an increase in valve gradient.[34,52] Transoesophageal echocardiography is relatively safe; however, the risk of vomiting/aspiration and sudden increases in intra-abdominal pressure should be considered, and foetal monitoring performed.

3.4.3 Exercise testing

Physiological exercise testing is an integral part of follow-up in adult congenital heart disease and valve disease,[29,53] and should be performed in patients with known heart disease who plan pregnancy. This Task Force recommends submaximal exercise testing (80% of predicted maximal heart rate) in asymptomatic patients with suspected heart disease if already pregnant. There is no evidence that it increases the risk of spontaneous miscarriage.[30] Stress echocardiography using bicycle ergometry may improve diagnostic specificity.[54] Dobutamine stress is rarely indicated during pregnancy and, because pregnancy in itself is a stress test, its use should be avoided when other options are available.

3.4.4 Ionizing radiation exposure

The potential risks of ionizing radiation exposure to the foetus depend on the stage of pregnancy and the absorbed dose. Risks are highest during organogenesis and the early foetal period, less in the second trimester, and least in the third trimester.[55] Malformations are typically associated with the central nervous system. Early in pregnancy (including 0–8 days pre-implantation), the high incidence of spontaneous abortion makes the evaluation of radiation-induced pre-natal death difficult, although it occurs at other stages of gestation with doses >250 mGy. Observed radiation-induced abnormalities (typically at doses of 100–200 mGy) include growth restriction, intellectual disability, malignancies, and neurological effects.[56,57] The periods of greatest vulnerability include growth retardation at 8–56 days, microcephaly at 14–105 days, and intellectual deficit/seizures/severe mental impairment at 56–105 days.[58] An increased risk of childhood cancer with in utero doses of approximately 20 mGy has been reported, with an estimated 1–2 cases of childhood cancer occurring per 3000 children exposed to 10 mGy of radiation in utero.[59] If possible, procedures should be delayed until at least the completion of the period of major organogenesis (>12 weeks after menses).

All medical radiation doses must be kept 'as low as reasonably achievable'. If ionizing radiation is required, risks and benefits should be communicated to the mother, and informed consent obtained. The radiation dose to the foetus should be kept as low as possible (preferably <50 mGy) with clear documentation, particularly if the foetus is in the field of view (see section 3.7.1).

3.4.5 Chest radiography and computed tomography

Although the foetal dose from chest radiography is <0.01 mGy, it should only be performed if other methods fail to clarify the cause of symptoms. Lung ultrasound is a promising alternative imaging modality, although its use in pregnancy has yet to be clarified. CT is usually not necessary for cardiac disease during pregnancy and is not recommended, except for the diagnosis or exclusion of pulmonary embolism (PE) or aortic pathology where other diagnostic tools are insufficient (section 10), and where low radiation CT with 0.01–0.66 mGy can be used.[53,60]

3.4.6 Cardiac catheterization

Cardiac catheterization is seldom needed for diagnostic purposes, but can be necessary to guide interventional procedures.

The mean radiation exposure to the unshielded abdomen is 1.5 mGy, and <20% of this reaches the foetus. For example, successful closure of a patent foramen ovale was achieved with the Helex device in three patients in the second trimester. Radiation doses, as assessed by dose area product, were 260, 58, and 19 cGy/cm^2, with estimated uterine (foetal) doses of <0.005, <0.001, and <0.0005 mGy, respectively.[61] The radial approach by an experienced operator is preferable. Most electrophysiological studies should only be performed if arrhythmias are medically refractory and cause haemodynamic compromise. Electroanatomical mapping systems should be used to reduce the radiation dose (section 3).

3.4.7 Magnetic resonance imaging

MRI is advised if other non-invasive diagnostic measures are not sufficient for definitive diagnosis, and is preferred to ionizing radiation-based imaging modalities when possible.[53,55] Evidence regarding gadolinium-based contrast in pregnancy is controversial and its use should be avoided if possible, especially in the first trimester. Excretion of gadolinium-based agents into breast milk is limited [<0.04% of an intravenous (i.v.) dose within the first 24 h, with 1–2% absorption].[62] Data suggest that it is safe to continue breastfeeding after the administration of such agents.

3.5 Genetic testing and counselling

The risk of inheriting cardiac defects is raised significantly in comparison with parents without CVD, where the risk is approximately 1%.[63,64] Heritability varies between 3 and 50% depending on the type of parental heart disease.

Children of parents with an autosomal dominant condition [e.g. Marfan syndrome, hypertrophic cardiomyopathy (HCM), or long QT syndrome (LQTS)] have an inheritance risk of 50%.

The final phenotype will also be determined by incomplete penetrance and pleiotropic effects, and may vary significantly.[65] For defects that are inherited in a polygenic manner, recurrence risk is less clearly defined. Genetic testing in cardiomyopathies is not appropriate for pre-natal diagnosis in dilated cardiomyopathies, except for selected disorders or high-risk situations in the setting of expert teams after detailed clinical and family assessment.[66]

In patients with venous thrombo-embolism (VTE), genetic testing is considered to be justified only for relatives of probands with a deficiency of natural anticoagulants or after recurrent VTEs.[67]

Downloaded from https://academic.oup.com/eurheartj/article-abstract/39/34/3165/5078465 by guest on 13 September 2018

Genetic counselling by an expert in the specific genetic disorder is highly recommended for patients and their family members in the situations below, and has the rationale of identifying at-risk asymptomatic or disease-free relatives and guiding clinical surveillance for disease onset.[68–70] It is advocated in patients with known genetic disorders, especially if treatment options are available.[68]

Genetic counselling and parental testing may be useful:

- In cases of known carrier status of hereditary pulmonary arterial hypertension (PAH) or pulmonary veno-occlusive disease[71]
- In cardiomyopathies and channelopathies (e.g. LQTS)[72]
- In congenital heart disease that is known to be associated with genetic abnormalities (e.g. conotruncal defects or bicuspid valve), when the patient has dysmorphic features, developmental delay/mental retardation, or when other non-cardiac congenital abnormalities are present in syndromes such as in Marfan or other heritable thoracic aortic disease (HTAD), 22q11 deletion, Williams–Beuren, Alagille, Noonan, and Holt–Oram syndromes[68]
- In thoracic aortic pathology
- When other family members are affected.

3.5.1 Pre-natal diagnosis

Presently, options for pre-natal genetic testing are increasingly available for those patients with an identified genetic defect (either chromosomal defects such as insertions/deletions/translocations or single-gene defects). This includes (i) pre-gestational diagnosis or (ii) pre-natal diagnosis, chorionic villus sampling, or amniocentesis. Counselling should be provided by an experienced centre with an interdisciplinary expert team.

An individualized approach to each family is required to ensure autonomous choice and informed consent regarding pre-natal diagnostic testing within the local ethical and legal framework.[73]

3.6 Foetal assessment

3.6.1 Screening for congenital heart disease

Measurement of nuchal fold thickness around the 12th week of pregnancy to screen for chromosome abnormalities also screens for foetal congenital heart disease.[74] For major congenital heart disease, a 12-week ultrasound has a sensitivity and specificity of 85 [95% confidence interval (CI) 78–90%] and 99% (95% CI 98–100%), respectively. The incidence of congenital heart disease with normal nuchal fold thickness is about 1/1000.[75] The earlier diagnosis of a major malformation allows parents to consider all options, including termination of pregnancy.[76]

All women with congenital heart disease should be offered foetal echocardiography in the 19th–22nd weeks of pregnancy, with 45% of all congenital cardiac malformations identified.[77,78] Foetal echocardiography should be performed by experienced specialists.[79,80]

When a foetal cardiac anomaly is suspected, it is mandatory to obtain the following:

- Full foetal echocardiography
- Detailed scanning to identify associated anomalies (digits and bones)
- Family history
- Maternal medical history: medical disorders, viral illness, or teratogenic medication
- Foetal karyotype (e.g. deletion in 22q11.2 with conotruncal anomalies)
- Referral to a foetal medicine specialist, paediatric cardiologist, geneticist, and neonatologist
- Delivery at an institution that can provide neonatal cardiac care.

3.6.2 Assessing foetal wellbeing

In the context of foetal growth restriction, the aim is to determine the optimal time for delivery, balancing foetal and neonatal risks. The chance of disability-free survival increases by ~2% per day between 24 and 28 weeks, and 1% per day thereafter until 32 weeks. Delivery should be determined by umbilical artery and ductus venosus blood flow patterns.[81–83]

3.7 Interventions in the mother during pregnancy

3.7.1 Percutaneous therapy

If an intervention is absolutely necessary, the best time is after the 4th month in the second trimester. By this time, organogenesis is complete, the foetal thyroid is still inactive, and the uterine volume is still small, so there is a greater distance between the foetus and the chest than in later months. ST-elevation MI (STEMI) management in pregnancy mainly relies on primary percutaneous coronary intervention (PCI). Thrombolysis may be a bailout, just as in non-pregnant patients, and recombinant tissue plasminogen activator does not cross the placenta but may induce bleeding complications (subplacental bleeding). Procedures should follow the 'as low as reasonably achievable' principle. Manoeuvres to minimize radiation are: (i) use echo guidance when possible; (ii) place the source as distant as possible from the patient and the receiver as close as possible to the patient; (ii) use only low-dose fluoroscopy; (iv) favour anteroposterior projections; (v) avoid direct radiation of the abdominal region; (vi) collimate as tightly as possible to the area of interest; (vii) minimize fluoroscopy time; and (viii) utilize an experienced cardiologist.[84,85] Abdominal shielding lowers the radiation dose to the foetus to some degree; however, the presence of lead in the field of the primary beam may on the other hand increase scattered radiation. As the benefit of shielding is limited, it should not interfere with an optimal intervention. Monitoring and recording of radiation exposure facilitates the future assessment of possible effects on the foetus. Unfractionated heparin (UFH) has to be given at 40–70 U/kg i.v., targeting an activated clotting time of 250 s (200–300 s) or an activated partial thromboplastin time (aPTT) two times that which is normal.

3.7.2 Cardiac surgery with cardiopulmonary bypass

Maternal mortality during cardiopulmonary bypass is now similar to that in non-pregnant women. However, foetal mortality remains high (~20%).[86] Cardiac surgery is recommended only when medical therapy or interventional procedures fail and the mother's life is

Downloaded from https://academic.oup.com/eurheartj/article-abstract/39/34/3165/5078465 by guest on 13 September 2018

threatened. The best period for surgery is between the 13th and 28th weeks. With full maternal and foetal monitoring and attention to cardiopulmonary bypass, particularly the use of pulsatile perfusion, the risks to both the mother and the foetus can be minimized. Gestational age has a large impact on neonatal outcome.[87,88] Caesarean delivery may be considered before cardiopulmonary bypass if gestational age is >26 weeks.[86] Whether or not delivery is advantageous for the baby at this gestational age depends on gender, estimated weight, prior administration of corticosteroids before delivery, and the outcome statistics of the neonatal unit concerned. When gestational age is ≥28 weeks, delivery before surgery should be considered. Before surgery, a full course (two doses of betamethasone 12 mg intramuscularly 12 h apart) of corticosteroids should be administered to the mother, whenever possible. During cardiopulmonary bypass, foetal heart rate and uterine tone should be monitored, and cardiopulmonary bypass time should be minimized for better foetal outcomes.[89,90]

3.8 Timing and mode of delivery: risk for mother and child

A delivery plan should be made with details of induction, management of labour, delivery, and post-partum surveillance. The emotional context, psychological care, and ethical challenges should also be taken into account. This delivery plan should be widely disseminated and placed in the patient's hand-held notes. Specific expertise and collaborative management by a pregnancy heart team in specialist centres is mandatory for all moderate- and high-risk patients.

3.8.1 Timing of delivery

Induction of labour should be considered at 40 weeks of gestation in all women with cardiac disease; this reduces the risk of emergency caesarean section by 12% and the risk of stillbirth by 50% in women without heart disease, and the benefit is likely to be greater for women with heart disease[91] who have higher rates of obstetric complications.[92] Timing of induction will depend on cardiac status, obstetric evaluation including cervical assessment, foetal well-being, and foetal lung maturity.

3.8.2 Labour induction

Both misoprostol [25 μg, prostaglandin E_1 (PGE_1)] or dinoprostone [1–3 mg or slow-release formulation of 10 mg (PGE_2)] can be used safely to induce labour. Reassuringly, in women without heart disease, high-dose (600 μg) misoprostol has no effect on cardiac parameters,[93] although there remains a theoretical risk of coronary vasospasm and arrhythmias. Dinoprostone may cause profound hypotension, but only when injected blindly into the myometrium,[94] and this route of administration should be avoided. Mechanical methods such as a cervical ripening balloon might be preferable in patients where a drop in systemic vascular resistance would be detrimental.[95] Artificial rupture of membranes and infusion of oxytocin can be used safely in women with heart disease.

3.8.3 Vaginal or caesarean delivery

The ROPAC data show that elective caesarean section carries no maternal benefit and results in earlier delivery and lower birth weight.[96] Vaginal delivery is associated with less blood loss and lower risk of infection, venous thrombosis, and embolism, and should be advised for most women. Caesarean section should be considered for obstetric indications and for patients presenting in labour on oral anticoagulants (OACs), with aggressive aortic pathology, and in acute intractable HF. Caesarean section is advised in severe forms of PH (including Eisenmenger's syndrome).

3.8.4 Delivery in anticoagulated women (not including mechanical valve; see section 5)

For women with a planned caesarean section, therapeutic low molecular weight heparin (LMWH) dosing can be simply omitted for 24 h prior to surgery. If delivery has to be performed earlier, then anti-Xa activity can guide the timing of the procedure. In high-risk women, therapeutic UFH can be restarted at 6 h post-delivery. In women at moderate or low-risk, a single prophylactic dose of LMWH-for example, in the case of enoxaparin, 20 mg if weight is <50 kg, 40 mg if 50–90 kg, and for women with a raised body mass index (BMI) 0.5 mg/kg-can be given at 6 h post-delivery, before restarting therapeutic LMWH 12 h later.

If vaginal delivery is planned, moderate- and high-risk patients can be converted to an infusion of UFH with regular checks of aPTT to optimize control, and the infusion stopped at least 4–6 hours prior to insertion of regional anaesthesia or anticipated delivery. For women at low-risk, therapeutic LMWH can be omitted for 24 h prior to anticipated delivery. Anticoagulation can be restarted as above.

3.8.5 Urgent delivery on therapeutic anticoagulation

Delivery in a patient taking therapeutic anticoagulation carries a high-risk of maternal haemorrhage. For UFH, protamine sulfate should be given, the exact dose depending on the mode of administration and time since the last dose of UFH (please refer to the European Medicines Agency statement: https://www.medicines.org.uk/emc/product/8). In the case of LMWH, protamine sulfate should be given; however, not only may antifactor Xa activity remain prolonged and bleeding tendency persist,[97] but the half-life of LMWH is longer and absorption after subcutaneous injection is prolonged, such that repeated doses or an infusion of protamine sulfate may be required. If the patient is on OACs, caesarean section is preferred to reduce the risk of foetal intracranial haemorrhage.

Reversal of anticoagulation is better with four-factor prothrombin complex concentrate, best given as an individualized dose dependent on maternal weight, initial international normalized ratio (INR), and target INR[98] than fresh frozen plasma (12–15 mL/kg),[99] and should be given prior to caesarean delivery to achieve an INR ≤1.5; however, none of the available algorithms have been validated in pregnant women. Vitamin K (5–10 mg i.v.) may also be given, but may take up to 8–12 h to reverse the INR and has a persistent effect making re-anticoagulation more difficult. The foetus may remain anticoagulated

Downloaded from https://academic.oup.com/eurheartj/article-abstract/39/34/3165/5078465 by guest on 13 September 2018

for 8–10 days after discontinuation of maternal OACs, and may need to be given fresh frozen plasma as well as vitamin K.

3.8.6 Haemodynamic monitoring during delivery

Maternal BP and heart rate should be monitored in all patients with cardiac disease. In women with more severe heart disease, an arterial line provides more accurate data. Pulse oximetry and continuous ECG monitoring are advised to detect early signs of decompensation, and to identify those in whom delivery should be expedited. A Swan-Ganz catheter is of uncertain benefit, is associated with complications, and should be avoided in most cases.[100] In some high-risk patients (PH), right atrial pressure monitoring may be considered.

3.8.7 Anaesthesia/analgesia

Epidural analgesia reduces labour pain and can be used to provide anaesthesia for caesarean section if necessary. However, it can cause systemic hypotension (10%) and must be carefully titrated, especially in patients with obstructive valve lesions or diminished ventricular function who may benefit from invasive BP monitoring. All i.v. fluids need to be used carefully.[101]

3.8.8 Labour

Mobilization may facilitate foetal head descent and a lateral decubitus position can attenuate the haemodynamic impact of cava compression by the gravid uterus.[102] The active phase of the second stage should be delayed for 2 h to allow maximal descent of the foetal head, as this will shorten the active phase of the second stage.[103,104] Assisted delivery with forceps or a ventouse may be used to further reduce maternal effort, as indicated by the underlying cardiac lesion. Continuous electronic foetal heart rate monitoring is recommended.

3.8.9 Perimortem caesarean section

In the case of an acute life-threatening maternal event, immediate delivery should be considered. The aim of delivery is to improve the chance of successfully resuscitating the mother and, only secondarily, of improving foetal survival. It should be considered from 24 weeks of gestation, as prior to this time the degree of uterine vena cava compression is limited and the baby is not considered to be viable. The delivery should be performed within 4 min of the cardiac arrest.

3.8.10 Post-partum care

A slow i.v. infusion of oxytocin (2 U of oxytocin given over 10 min immediately after birth, followed by 12 mU/min for 4 h) reduces the risk of post-partum haemorrhage and has a minimal impact on cardiovascular parameters.[105] PGE[106] analogues [sulprostone (100–500 μg/h) and misoprostol (200–1000 μg)] can be used to treat post-partum haemorrhage; however, ergometrine and prostaglandin F analogues should be avoided.[107,108] Sulprostone should be used with caution, given its association with cardiovascular or respiratory symptoms. Meticulous leg care, elastic support stockings, and early ambulation are important to reduce the risk of thrombo-embolism. The post-partum period is associated with significant haemodynamic changes and fluid shifts, particularly in the first 24–48 h after delivery, which may precipitate HF. Haemodynamic monitoring should therefore be continued for at least 24–48 h in those at risk.[43] With preceding beta-blockade, infant monitoring for 48 h is recommended.[109]

3.8.11 Breastfeeding

Lactation is associated with a low-risk of bacteraemia secondary to mastitis and should be encouraged in patients with heart disease whenever possible. Any specific concerns or contraindications are discussed in the disease section (i.e. section 8). Most drugs used in patients enter the milk and could thus contraindicate breastfeeding (see *Table 7* for details of drugs and safety data). If needed, inhibition of lactation can be obtained with standard doses of cabergoline (0.25 mg every 12 h for 2 days), or bromocriptine (2.5 mg on the day of delivery, followed by 2.5 mg twice daily for 14 days) if cabergoline is not available.

3.9 Infective endocarditis

IE is rare, with an overall annual incidence estimated at 1 per 1000 in patients with congenital heart disease,[110,111] and between 3 and 12 per 1000 in patients with prosthetic valves.[112]

3.9.1 Prophylaxis

The same measures apply as in non-pregnant patients.[112] During delivery, the indication for prophylaxis has been controversial and, given the lack of convincing evidence, antibiotic prophylaxis is not recommended during vaginal or caesarean delivery. Non-specific hygiene and asepsis measures are also important to prevent endocarditis.[112]

3.9.2 Diagnosis and risk assessment

The diagnosis of IE during pregnancy involves the same criteria as in the non-pregnant patient.[112] The scarcity of data accounts for wide ranges in estimations of maternal and foetal mortality of 11–33 and 14–29%, respectively.[111,113,114]

Unlike chronic valvular regurgitations, acute regurgitations due to IE are poorly tolerated and often cause severe HF. Cerebral and peripheral embolisms are also frequent.[111] Every pregnant patient with IE should be discussed by an endocarditis team.

3.9.3 Treatment

IE should be treated in the same way as in the non-pregnant patient.[112] Antibiotics should be given according to guidelines, guided by culture and antibiotic sensitivity results, considering the potential foetotoxic effects of antibiotics (see *Table 7* for details of drugs and safety data).[115] Antibiotics that can be given during all trimesters of pregnancy are penicillin, ampicillin, amoxicillin, daptomycin, erythromycin, mezlocillin, oxacillin, and cephalosporins. There is a definite risk to the foetus in all trimesters of pregnancy with aminoglycosides

Downloaded from https://academic.oup.com/eurheartj/article-abstract/39/34/3165/5078465 by guest on 13 September 2018

and tetracyclines, and they should therefore only be used for vital indications.[115]

Given the inherent foetal risk, decision-making for valve surgery during pregnancy is particularly difficult.[112] Urgent surgery is mandatory in cardiogenic shock or refractory HF due to acute regurgitation. When surgery is indicated for uncontrolled infection or prevention of embolism, an individual approach should weigh the foetal risk of surgery and the risk of maternal complications under medical therapy alone. A viable foetus should be delivered prior to surgery where possible. These patients should be managed in tertiary centres, and the endocarditis and pregnancy teams should interact closely.

3.10 Methods of contraception and termination of pregnancy, and in vitro fertilization

3.10.1 Methods of contraception

The risk of using a particular type of contraception needs to be balanced against the risk of pregnancy, estimated using the modified WHO classification (see above),[116] which assesses the risk with each method for a given medical condition.[117] Advice is best provided by cardiologists with appropriate training or obstetricians, and should be given from the time of menarche since an unplanned pregnancy has to be avoided. The average age of first intercourse in the UK is 17 years, with ≤30% before 15 years,[118] regardless of the presence of heart disease.[119] The key issues are reliability and the potential for complications, with thrombosis and infection being the most important. Hormonal contraception can have important non-contraceptive benefits, including the control of menstruation, prevention of anaemia, reduction of dysmenorrhoea, and of hyperandrogenism.[120]

Ethinyloestradiol-containing contraceptives have the greatest risk of thrombosis[121,122] and are not advised in women with high-risk of thrombo-embolic disease; they also increase BP and are contraindicated in pre-existing hypertension.[117] Progestin-only contraceptives are an alternative, since they have little (implant or depot injection) or no (levonorgestrel-loaded intrauterine device or oral desogestrel) effect on coagulation factors, BP, and lipid levels.[123] Oral desogestrel inhibits ovulation, which could be an advantage for patients with polycystic ovary syndrome, endometriosis, or dysfunctional uterine bleeding.

Levonorgestrel-based long-acting reversible contraception implants or intrauterine devices are the safest and most effective contraceptives. However, intrauterine device insertion may cause a vasovagal response; consequently, this should be performed in a hospital setting, particularly for Fontan and Eisenmenger's syndrome patients. The levonorgestrel-releasing intrauterine device reduces periods, causing amenorrhoea in ≤60% of women, in contrast to copper intrauterine devices, which cause heavier periods. The newer, smaller levonorgestrel-based intrauterine devices are easier to insert, reducing the risk of pain and therefore vasovagal response.

Barrier methods are unreliable but reduce the risk of pelvic inflammatory disease. A good approach is the combination of barrier methods and long-acting reversible contraception (levonorgestrel-based long-acting reversible contraception, progestin-releasing implant, or progestin-releasing intrauterine devices).

For emergency contraception, a copper intrauterine device is most effective and additionally provides ongoing contraception. Alternatively, a single dose of 1.5 mg levonorgestrel is effective if taken within 72 h after unprotected sex (1.1% failure rate),[124] with no evidence of increased rates of thrombosis.[125] The progesterone receptor modulator ulipristal acetate (UPA) has been shown to be more effective than levonorgestrel. UPA is not associated with an increased risk of thrombosis.[126,127]

3.10.2 Sterilization

Sterilization by tubal ligation is not unreasonable if pregnancy is contraindicated or the family is complete. Laparoscopy is not without risks in patients with PAH, cyanosis, and a Fontan circulation, and the risks are probably lower with the hysteroscopic method performed under regional anaesthesia.[128] Vasectomy is an effective option.

3.10.3 Methods of termination of pregnancy

Pregnancy termination should be discussed if there is a high-risk of maternal morbidity or mortality, and/or of foetal abnormality. Both medical and surgical methods are effective with similar rates of major complications, but the greater need for unanticipated operative evacuation (2.1 vs. 0.6%) favours the surgical approach in this group of women.[129] High-risk patients should be managed in an experienced centre with on-site cardiac surgery. Antibiotics are given to reduce the risk of endometritis and these should be modified to provide endocarditis prophylaxis. Medical terminations can be considered up to 9 weeks of gestation using a reduced misoprostol dose of 100 μg.

3.10.4 In vitro fertilization

The rates of subfertility in most women with heart disease are likely to those of the general population,[130] but their management is more complex. Hysteroscopy and laparoscopy can be life-threatening procedures in women with some forms of heart disease (PH and Fontan), and should be undertaken in an experienced centre with appropriate support. Assisted reproduction has added risks above those of pregnancy alone; superovulation is pro-thrombotic and can be complicated by ovarian hyperstimulation syndrome (OHSS), with marked fluid shifts and an even greater risk of thrombosis. The risk of OHSS can be reduced by careful cycle monitoring, using low-dose follicle-stimulating hormone in combination with a gonadotropin-releasing hormone antagonist, freezing all embryos, or only transferring a single embryo.[131] The last option is strongly advised in women with heart disease, since conceiving a multiple pregnancy is associated with greater cardiovascular changes[132] and more maternal and foetal complications.133 Pregnancy, and consequently fertility treatment, is contraindicated in women with mWHO class IV. In women with mWHO class III or those who are anticoagulated, the risk of superovulation is very high and the alternative of natural cycle in vitro fertilization should be considered.

Downloaded from https://academic.oup.com/eurheartj/article-abstract/39/34/3165/5078465 by guest on 13 September 2018

3.11 Recommendations

General recommendations

Recommendations	Class[a]	Level[b]
Pre-pregnancy risk assessment and counselling is indicated in all women with known or suspected congenital or acquired cardiovascular and aortic disease.[39]	I	C
It is recommended to perform risk assessment in all women with cardiac diseases of childbearing age before and after conception, using the mWHO classification of maternal risk.[11]	I	C
It is recommended that high-risk patients are treated in specialized centres by a multidisciplinary pregnancy heart team.[39]	I	C
Foetal echocardiography by experienced specialists is recommended when there is an elevated risk of foetal abnormalities.[76–80]	I	C
Echocardiography is recommended in any pregnant patient with unexplained or new cardiovascular signs or symptoms.	I	C
If cardiac surgery is to be performed after 24 weeks and before 37 weeks of gestation, then corticosteroids are recommended for the mother.[134]	I	C
Vaginal delivery is recommended as the first choice in most patients; for most important exceptions see below.[96]	I	C
Induction of labour should be considered at 40 weeks of gestation in all women with cardiac disease.	IIa	C
Genetic counselling should be considered in women with congenital heart disease or congenital arrhythmia, cardiomyopathies, aortic disease, or genetic malformations associated with CVD.[68,71]	IIa	C
MRI (without gadolinium) should be considered if echocardiography is insufficient for a definite diagnosis.	IIa	C
In patients with severe hypertension, vaginal delivery with epidural analgesia and elective instrumental delivery should be considered.	IIa	C
Delivery before necessary surgery should be considered when gestational age is ≥26 weeks.[86–88,135]	IIa	C
Caesarean delivery should be considered for obstetrical indications or for patients with dilatation of the ascending aorta >45 mm, severe aortic stenosis, pre-term labour while on oral anticoagulants, Eisenmenger's syndrome, or severe heart failure.	IIa	C
A chest radiograph may be considered if other methods are not successful in clarifying the cause of dyspnoea.	IIb	C
Cardiac catheterization may be considered with very strict indications.	IIb	C
CT and electrophysiological studies may be considered in selected patients for vital indications.	IIb	C
Coronary bypass surgery or valvular surgery may be considered during pregnancy when conservative and medical therapy has failed, and in situations that threaten the mother's life or that are not amenable to percutaneous treatment.	IIb	C
Prophylactic antibiotic therapy to prevent endocarditis during delivery is not recommended.[112]	III	C

© ESC 2018

CT = computed tomography; CVD = cardiovascular disease; MRI = magnetic resonance imaging; mWHO = modified World Health Organization.
[a]Class of recommendation.
[b]Level of evidence.

Downloaded from https://academic.oup.com/eurheartj/article-abstract/39/34/3165/5078465 by guest on 13 September 2018

4. Congenital heart disease and pulmonary hypertension

4.1 Introduction

Congenital heart disease is present in 0.8–0.9% of live births.[63,136] Lesions vary in severity, but even patients with complex lesions now survive to childbearing years.[137] In large international surveys of pregnancy and heart disease, two-thirds of cases have congenital heart disease and 5% have PH.[92,138] However, congenital heart disease and PH are rare causes of maternal death.[3]

In most women with congenital heart disease, pregnancy is well tolerated. The risk of pregnancy depends on the underlying heart

defect as well as on additional factors such as ventricular function, functional class, and cyanosis. Maternal cardiac complications are present in ~10% of completed pregnancies and are more frequent in mothers with complex disease. Patients who experience complications during pregnancy may also be at higher risk of late cardiac events after pregnancy.[139] Obstetric complications such as (pre-) eclampsia are more often encountered. Offspring complications, including miscarriage, prematurity, and neonatal death, are increased.

Diagnosis. In most cases, congenital heart disease is diagnosed well before pregnancy, giving the opportunity for a full pre-pregnancy risk assessment. The mWHO classes (*Table 3*) outline the broad risk categories.

4.2 Pulmonary hypertension and Eisenmenger's syndrome

4.2.1 Pulmonary hypertension

4.2.1.1 Introduction

PH has many causes and is defined by an elevation in mean pulmonary arterial pressure (PAP) ≥25 mmHg at right heart catheterization. The term PAH describes a subset of PH characterized by an LV filling pressure ≤15 mmHg and a pulmonary vascular resistance >3 Wood Units.[23] Untreated, idiopathic PH results in death within a median of 2.8 years. PAH is frequently encountered in females and the first clinical manifestations may be seen in pregnancy.[140]

4.2.1.2 Maternal risk

Maternal outcome, which varies according to the PH subset, has improved with the availability of new targeted therapies and the use of a team-based, multidisciplinary approach.[141–143] While pregnancy appears safer today, mortality remains high in women with PAH (16–30% maternal mortality).[137,138] Therefore, the recommendation to avoid pregnancy remains and, when pregnancy occurs, termination should be discussed. The greatest period of risk is the puerperium and early post-partum. These women should be managed by a multidisciplinary team, with a PH expert included, in an expert centre for pregnancy and cardiac disease. Pulmonary hypertensive crisis, pulmonary thrombosis, and right HF are the most common causes of death. This may occur even in patients with few symptoms prior to pregnancy. Risk factors for maternal death are: severity of PH, late hospitalization, and perhaps the use of general anaesthesia.[144] Even moderate forms of pulmonary vascular disease can worsen during pregnancy.[138] Although there is no safe cut-off for elevated PAP risk, it is thought to be less in those with only mildly increased pressure.[138]

4.2.1.3 Obstetric and offspring risk

There is increased foetal and neonatal (0–30%) mortality, particularly if there is preterm delivery, reduced maternal CO, and/or hypoxaemia.

4.2.1.4 Management

The usual diagnostic algorithm of PH should be followed when a pregnant patient presents with new PH. Echocardiography is key and other diagnostic steps, in keeping with the PH guideline, are planned individually. Invasive right heart catheterization is recommended if there is diagnostic uncertainty and to assist important therapeutic decisions. If this is required, it should be performed in a specialist centre. Genetic counselling is appropriate in familial cases.

A multidisciplinary team is required to care for the pregnant PH patient. This should be tailored to the patient, but will require very regular follow-up (often weekly in the third trimester). A full assessment, including oxygen saturation and assessment of RV function, should occur at each visit. Bed rest may be required in symptomatic patients and additional risk factors (such as air travel) avoided.

Thrombo-embolism is a major risk and anticoagulation should be considered (see section 11). Diuretics may be needed in patients with HF and iron deficiency should be treated.

Pregnancy in PAH patients is a high-risk condition and a proactive approach should be taken to commencing advanced therapies. Risk stratification should be performed as in non-pregnant patients. There is no evidence of benefit comparing a stepwise approach vs. early combination therapy in pregnant patients, although the latter is often favoured, as per our Guidelines. Bosentan and other endothelin receptor antagonists are associated with embryopathy, and should be discontinued unless doing so would greatly increase maternal risk. An individualized approach is required and many units start therapy with oral sildenafil. The subset of patients with true vasodilator responsiveness who are well controlled on calcium channel blocker (CCB) therapy may be at lower risk and this therapy should be continued, as should all i.v. therapies. Section 12 discusses specific medications, including potential interactions with contraceptive drugs and anticoagulants.

4.2.1.5 Delivery

A detailed delivery plan, including the optimal mode and timing of delivery, should be decided by the pregnancy heart team. This should include the post-partum need for intensive care and mechanical support. Regional anaesthesia is usually favoured over general anaesthesia.[145] Meticulous fluid balance and optimization of RV function are important determinants of a good outcome. Patients remain at high-risk for many months post-delivery, and individualized counselling is needed to discuss the need for ongoing therapies and the avoidance of future pregnancies. Therapies should not be discontinued in the early post-delivery period.

4.2.2 Eisenmenger's syndrome

4.2.2.1 Maternal risk

Eisenmenger patients require special consideration because of the additional complications of cyanosis, right-to-left shunting, and paradoxical embolism. During pregnancy, systemic vasodilatation increases the right-to-left shunt and decreases pulmonary flow, leading to increased cyanosis and a low CO. Maternal mortality is high (20–50%) and termination of pregnancy should be discussed.[146] However, termination also carries a risk.

4.2.2.2 Foetal risk

Foetal and neonatal risks are increased and relate to maternal CO and cyanosis. Miscarriage is common. Maternal hypoxaemia is the most important predictor of outcome.

4.2.2.3 Management

Many of the principles of caring for non-Eisenmenger PAH apply. However, patients with Eisenmenger's syndrome are at increased risk of thrombocytopenia, deficiencies in vitamin K-dependent

Downloaded from https://academic.oup.com/eurheartj/article-abstract/39/34/3165/5078465 by guest on 13 September 2018

clotting factors, and bleeding. Caution is therefore needed if prescribing antiplatelet therapy or LMWH. The evidence base for using advanced therapies is less developed. However, sildenafil (and other phosphodiesterase inhibitors such as tadalafil and vardenafil) is often prescribed, with the addition of prostanoids in patients who remain symptomatic.[147] Care should be exercised if prescribing drugs that may lead to sudden systemic vasodilation or a risk of paradoxical air embolism (i.v. therapies). Advanced therapies for Eisenmenger patients should only be prescribed by experienced pregnancy heart teams including a PH expert. The principles guiding delivery are as per other forms of PH as above.

4.2.3 Cyanotic heart disease without pulmonary hypertension

4.2.3.1 Maternal risk

Cyanotic congenital heart disease is usually repaired before pregnancy, but some balanced, inoperable, or palliated cases do reach childbearing age.[148] Maternal complications (HF, thrombosis, arrhythmias, and endocarditis) occur in ≥15% of cyanotic pregnant patients. Maternal outcome will be determined by the underlying condition and the ventricular function rather than the saturation level.

4.2.3.2 Foetal risk

If oxygen saturation is >90%, then there is usually a better foetal outcome (10% foetal loss). If oxygen saturation is <85%, foetal growth restriction, prematurity, and foetal death are common and pregnancy should be discouraged (live birth rate of only 12%).[149]

4.3 Specific congenital heart defects

4.3.1 Left ventricular outflow tract obstruction

The principles for managing supravalvular or subvalvular LV outflow tract obstruction are the same as those for valvular aortic stenosis (AS) (section 5). However, balloon valvuloplasty is not a therapeutic option.

4.3.2 Atrial septal defect

4.3.2.1 Maternal risk

Pregnancy is well tolerated by most women with repaired atrial septal defect (ASD) (WHO risk class I). In unrepaired ASDs, thromboembolic complications have been described (5%). Atrial arrhythmias occur, especially when the ASD is unrepaired or closed at an older age.[150]

4.3.2.2 Obstetric and offspring risk

In women with unrepaired ASD, pre-eclampsia and growth restriction may occur more frequently.

4.3.2.3 Management

For a secundum defect, catheter device closure can be performed during pregnancy but is rarely indicated. If device closure is performed, antiplatelet therapy will be required. Closure for the prevention of paradoxical emboli is not indicated. In women with a residual shunt, prevention of venous stasis (compression stockings and minimizing bed rest) is important and extra care should be taken to avoid air in i.v. lines.

4.3.3 Ventricular septal defect

4.3.3.1 Maternal risk

Small or repaired ventricular septal defects (VSDs) (without left heart dilatation or ventricular dysfunction) have a low-risk of complications during pregnancy (mWHO I and II).

4.3.3.2 Obstetric and offspring risk

There is no evidence of increased obstetric risks.

4.3.3.3 Management

Patients should usually be reviewed once or twice during pregnancy with surveillance for PH.

4.3.4 Atrioventricular septal defect

4.3.4.1 Maternal risk

After ASD repair, pregnancy is usually well tolerated (WHO risk class II–III). However, arrhythmias and worsening atrioventricular (AV) valve regurgitation have been described. The risk of HF is low, and only exists in women with severe regurgitation or impaired ventricular function.

4.3.4.2 Obstetric and offspring risk

Offspring mortality has been reported in 6% of cases, primarily due to the recurrence of congenital heart disease.

4.3.4.3 Management

Follow-up is advisable at least once each trimester. This should be increased to monthly or bimonthly in patients with significant valve regurgitation or impaired ventricular function.

4.3.5 Coarctation of the aorta

4.3.5.1 Maternal risk

Pregnancy is often well tolerated in women after repair of coarctation of the aorta (CoA) (WHO risk class II). In women with unrepaired CoA and those repaired who have systemic hypertension, residual CoA or aortic aneurysms have an increased risk of complications including dissection. Other risk factors include aortic dilatation and bicuspid aortic valve.

4.3.5.2 Obstetric and offspring risk

An excess of hypertensive disorders, including pre-eclampsia and miscarriages, has been reported.

4.3.5.3 Management

Close surveillance of BP is warranted and follow-up, at least every trimester, is indicated. Hypertension should be treated and care should be taken to avoid placental hypoperfusion in those with residual coarctation. Percutaneous intervention for re-CoA (using a covered stent) is possible during pregnancy, but should only be performed for refractory hypertension or maternal or foetal compromise.

4.3.6 Pulmonary valve and right ventricular outflow tract disease

4.3.6.1 Maternal risk

Pulmonary (valve) stenosis (PS) is generally well tolerated. However, severe stenosis may result in complications including RV failure and

Downloaded from https://academic.oup.com/eurheartj/article-abstract/39/34/3165/5078465 by guest on 13 September 2018

arrhythmias. Severe pulmonary regurgitation has been identified as an independent predictor of maternal complications, especially in patients with impaired RV function.

4.3.6.2 Obstetric and offspring risk
There is no evidence of increased obstetric risks.

4.3.6.3 Management
Mild and moderate PS are low-risk lesions (WHO risk classes I and II) and two or three follow-up sessions are sufficient. In patients with severe PS, monthly or bimonthly cardiac evaluations are advised, focusing on RV function. In severely symptomatic PS, which is unresponsive to medical therapy and bed rest, percutaneous valvuloplasty can be appropriate.

4.3.7 Congenital aortic stenosis
AS, aortic dilatation, and bicuspid aortic disease are discussed in sections 5 and 6.

4.3.8 Tetralogy of Fallot
4.3.8.1 Maternal risk
Women with repaired tetralogy of Fallot usually tolerate pregnancy well (WHO risk class II). Cardiac complications have been reported in 8% of repaired patients, especially in those taking cardiac medication prior to pregnancy.[151] Arrhythmias and HF are the most common complications. Thrombo-embolism and endocarditis are rarer. Dysfunction of the RV and/or moderate to severe pulmonary regurgitation are risk factors. Previous pregnancy may be associated with a persisting increase in RV size and long-term cardiac events.

4.3.8.2 Obstetric and offspring risk
The risk of offspring complications is increased, in particular foetal growth restriction.[152] Maternal screening for 22q11 deletion should be undertaken prior to pregnancy.

4.3.8.3 Management
Follow-up every trimester is sufficient in most patients. In women with severe pulmonary regurgitation, monthly or bimonthly cardiac evaluation is indicated. If RV failure occurs during pregnancy, treatment with diuretics should be started and bed rest advised. Early delivery or, rarely, transcatheter valve implantation could be considered in those who do not respond to conservative treatment.

4.3.9 Ebstein's anomaly
4.3.9.1 Maternal risk
In women with uncomplicated Ebstein's anomaly, pregnancy is often tolerated well (WHO risk class II). Symptomatic patients with cyanosis and/or HF should be counselled against pregnancy. The haemodynamic problems seen largely depend on the severity of tricuspid regurgitation (TR) and on RV function. Cyanosis (due to ASD/patent foramen ovale) and arrhythmias due to accessory pathways are common. There is also an increased risk of HF and pre-term delivery.[153]

4.3.9.2 Obstetric and offspring risk
Foetal and neonatal outcomes are related to maternal oxygen saturation and CO.

4.3.9.3 Management
Even severe TR with HF can usually be managed medically during pregnancy. Women with interatrial shunting can develop progressive cyanosis during pregnancy and be at increased risk of paradoxical emboli, and these should be assessed at each visit.

4.3.10 Transposition of the great arteries
4.3.10.1 Maternal risk
In patients with transposition of the great arteries (TGA), the risks associated with pregnancy are mainly attributable to women with a previous atrial (Senning and Mustard) switch, not an arterial switch. Though many women with an atrial switch operation tolerate pregnancy relatively well, there is an increased risk of developing arrhythmias (sometimes life-threatening) and HF (WHO risk class III). An irreversible decline in RV function and worsening TR are also described.[154,155] Patients with more than moderate impairment of RV function or greater than moderate TR should be advised against pregnancy.

4.3.10.2 Obstetric and offspring risk
The risk of low birth weight and pre-term delivery is 38%.

4.3.10.3 Management
Monthly or bimonthly review focusing on systemic RV function and arrhythmia is required. Diuretics and other HF therapies may be required.

4.3.10.4 Arterial switch operation
The risk of pregnancy seems low in these patients with good clinical condition pre-pregnancy and preserved ventricular function. Women with a dilated neo-aorta will require closer surveillance. Although this is now the most common operation for TGA, few data are available on pregnancy outcomes.

4.3.11 Congenitally corrected transposition of the great arteries
4.3.11.1 Maternal risk
In patients with congenitally corrected TGA (also called AV and ventriculoarterial discordance) risk depends on functional status, ventricular function, and the presence of arrhythmias and associated lesions (such as a VSD and pulmonary valve stenosis). Complications include arrhythmias and HF (WHO risk class III). These patients are also predisposed to developing AV block. Some 10% of patients have an irreversible decline in RV function.[148,156] Patients in New York Heart Association (NYHA) classes III or IV, with ventricular dysfunction [ejection fraction (EF) <40%], or severe TR should be counselled against pregnancy.

4.3.11.2 Obstetric and offspring risk
The rate of foetal loss is increased, especially if there is cyanosis.

4.3.11.3 Management
For follow-up, it is recommended that patients have frequent echo surveillance of systemic RV function (every 4–8 weeks) and assessment of symptoms and rhythm.

Downloaded from https://academic.oup.com/eurheartj/article-abstract/39/34/3165/5078465 by guest on 13 September 2018

4.3.12 Fontan circulation

4.3.12.1 Maternal risk

Patients with a Fontan circulation have an increased risk of fertility issues, but successful pregnancy can occur. However, these are high- to very high-risk pregnancies (WHO risk class III or IV). Atrial arrhythmias and NYHA class deterioration are not uncommon. Patients with saturations <85%, depressed ventricular function, moderate to severe AV regurgitation, refractory arrhythmia, or protein-losing enteropathy should be counselled against pregnancy (mWHO IV).

4.3.12.2. Obstetric and offspring risk

Fontan patients have a high-risk of miscarriage (30%).[157] Antenatal and peripartum bleeding is common.[158] There is an increased risk of premature birth, small for gestational age, and neonatal death.[159]

4.3.12.3 Management

It is recommended that Fontan patients have frequent surveillance during pregnancy (monthly) and in the first weeks after delivery. Fontan patients are at risk of thrombo-embolic complications and therapeutic anticoagulation should be considered (balanced with the risk of bleeding). Atrial arrhythmias should be treated promptly and this often requires electrical cardioversion.

4.4 Recommendations

Recommendations for pregnancy and pulmonary arterial hypertension

Recommendations	Class[a]	Level[b]
Right heart catheterization is recommended to confirm the diagnosis of PAH (group 1). This can be performed during pregnancy but with very strict indications.[10]	I	C
Treatment dose LMWH is recommended in pregnant patients with chronic thrombo-embolic pulmonary hypertension.	I	C
If a PAH patient conceives on targeted PH therapies, consideration should be given to withdrawing embryotoxic drugs, taking into account the risks of withdrawal.	IIa	C
In treatment-naive pregnant PAH patients, initiating treatment should be considered.[23]	IIa	C
Pregnancy is not recommended in patients with PAH.[119]	III	B

© ESC 2018

LMWH = low molecular weight heparin; PAH = pulmonary arterial hypertension; PH = pulmonary hypertension.
[a]Class of recommendation.
[b]Level of evidence.

Recommendations for congenital heart disease

Recommendations	Class[a]	Level[b]
Patients with a systemic right ventricle (Mustard/Senning or congenitally corrected TGA), in NYHA class III/IV, systemic ventricular dysfunction (EF <40%), or severe TR should be advised against pregnancy.	IIa	C
Anticoagulation treatment should be considered during pregnancy in Fontan patients.	IIa	C
Symptomatic patients with Ebstein's anomaly with saturations <85% and/or heart failure should be advised against pregnancy.	IIa	C
In patients with a Fontan circulation and saturations <85%, depressed ventricular function, moderate–severe AV regurgitation, refractory arrhythmia, or protein-losing enteropathy, pregnancy is not recommended.	III	C

© ESC 2018

AV = atrioventricular; EF = ejection fraction; NYHA = New York Heart Association; TGA = transposition of the great arteries; TR = tricuspid regurgitation.
[a]Class of recommendation.
[b]Level of evidence.

5. Aortic diseases

Several heritable disorders affect the thoracic aorta, predisposing patients to both aneurysm formation and aortic dissection. These include HTAD and either syndromic (Marfan syndrome, Loeys–Dietz syndrome, osteoaneurysm syndrome, and vascular Ehlers–Danlos syndrome) or non-syndromic HTAD (i.e. only aortic aneurysm). New genes are regularly discovered. Other forms of congenital heart disease (e.g. tetralogy of Fallot and CoA) may also be accompanied by aortic dilatation, and finally non-heritable aortic pathology may occur.[160] Risk factors for aortic dilatation are hypertension and advanced maternal age. Pregnancy is a high-risk period for all patients with aortic pathology, which is rare during pregnancy but associated with very high mortality.[161,162] Most deaths occur in women not previously known to have an aortopathy. Most of these women will have heritable disease, so autopsy tissue should be saved for DNA analysis and families offered referrals for screening. Guidelines for the diagnosis and management of patients with thoracic aortic disease have been published.[163,164]

Downloaded from https://academic.oup.com/eurheartj/article-abstract/39/34/3165/5078465 by guest on 13 September 2018

5.1 Maternal and offspring risk

Haemodynamic and hormonal changes during pregnancy increase the susceptibility to dissection.[165] Dissection occurs most often in the last trimester of pregnancy (50%) or the early post-partum period (33%). All women with a genetically proven syndrome or familial aortic pathology should have counselling on the risk of dissection and the recurrence risk, and have a complete evaluation including imaging of the entire aorta before pregnancy (see section 3). When assessing aortic diameters, body surface area should be considered, especially in women of small stature. Parity seems associated with increased aortic diameter.[166] The effect of pregnancy on aortic dilatation is not clear.[167,168] The diagnosis of aortic dissection should be considered in all patients with chest pain during pregnancy.

5.2 Specific syndromes

Marfan syndrome is thought to affect 1 in 5000 individuals. Although bicuspid aortic valve is more common (1–2% of the population), associated aortic complications are uncommon, accounting for only 6% of type A dissections during pregnancy.[169]

5.2.1 Marfan syndrome

The overall risk of a woman with Marfan syndrome having an aortic dissection associated with pregnancy is ~3%.[170] Aortic size is a major determinant of risk, but even women with an aortic root <40 mm have a risk of dissection of 1%.[170,171] Although there are limited data, pregnancy should be avoided in Marfan patients with an aortic root diameter >45 mm as there is an increased risk of dissection. When the aorta is 40–45 mm, other factors should be considered, such as family history of dissection and rate of aortic growth.[163] Distal aortic dissection and dissection of other vessels are also a risk. For this reason, even after successful aortic root replacement, patients remain at risk of further events.[172] Studies focusing on the potential growth during pregnancy in Marfan patients demonstrated contradicting results; some demonstrated no significant growth, while others demonstrated growth ≥3 mm with a partial diameter decrease post-partum.[167,168,173]

Other important cardiac complications include progressive mitral regurgitation (MR) due to mitral valve prolapse, new arrhythmia, and HF due to ventricular dysfunction.[174,175] Obstetric complications are also increased, including premature rupture of membranes.[19]

5.2.2 Bicuspid aortic valve

Aortic dilatation occurs in ≤50% of patients with a bicuspid aortic valve and can occur even when valve function is normal. The dilatation can be in the distal ascending aorta, which cannot be adequately visualized by echocardiography. If not visible with echocardiography, MRI or CT should be performed pre-pregnancy. The risk of dissection is small. Risk factors are the type of bicuspid aortic valve morphology, aortic dilatation, and CoA.[176] Pregnancy should be avoided when the aorta diameter is >50 mm.

5.2.3 Vascular Ehlers–Danlos syndrome

Serious vascular complications occur almost exclusively in type IV Ehlers–Danlos syndrome (vascular). Maternal mortality is significant, and relates to uterine rupture and dissection of major arteries and veins. Pregnancy is therefore considered as a very high-risk undertaking and not advised.[177] These women should be engaged in a shared decision-making process when contemplating pregnancy.

5.2.4 Turner syndrome

Turner syndrome is associated with an increased risk of congenital heart disease, aortic dilatation, hypertension, diabetes, and atherosclerotic events.[178] Aortic dissection occurs rarely in Turner syndrome, but it is six times more common at younger ages than in the general population[179] Risk factors for aortic dissection include aortic dilation, bicuspid aortic valve, and CoA.[20,180] Pregnancy should be avoided when the aortic size index is >25 mm/m^2. Also, after aortic root surgery, the patient remains at risk of type B dissection.

Spontaneous pregnancy can occur in mosaic Turner patients (0.5–10%), but pregnancy is now most commonly secondary to assisted fertility techniques. Cardiovascular evaluation is recommended before starting fertility treatment. Good BP control and diabetes management is mandatory for all Turner patients, especially during pregnancy.[178]

5.2.5 Other autosomal dominant aortopathies

With improved genotyping, a series of new aortopathies are being reported. These includes syndromic and non-syndromic HTAD. These conditions are considered high-risk, especially when the aorta is dilated, and may also have multisystem involvement with additional risks such as uterine rupture.[181–184]

5.3 Management

5.3.1 Follow-up and medical therapy

Depending on the aortic diameter, patients with aortic pathology should be monitored by echocardiography at regular intervals throughout the pregnancy and 6 months post-partum. In women with a high-risk of dissection or an already severely dilated aorta, monitoring every month is warranted, while in low-risk women with only a mildly dilated aorta, monitoring every 12 weeks seems reasonable. When needed, cardiac MRI without contrast can be used. Pregnancy should be supervised by a cardiologist and obstetrician who are alert to the possible complications. Strict BP control is advised, and antihypertensive treatment that is safe for the foetus should be initiated if necessary.[185] In women with HTAD, beta-blocker therapy throughout pregnancy should be considered. In patients with Ehlers–Danlos syndrome type IV, celiprolol is recommended (also in normotensive women) because of the very high-risk of dissections and the benefit demonstrated in

Downloaded from https://academic.oup.com/eurheartj/article-abstract/39/34/3165/5078465 by guest on 13 September 2018

non-pregnant patients.[186] Foetal growth should be monitored when the mother is taking beta-blockers.

5.3.2 Interventions

When progressive dilatation occurs during pregnancy, before the foetus is viable, surgical treatment with the foetus *in utero* should be considered. When the foetus is viable, caesarean delivery followed directly by aortic surgery is recommended (section 3). Caesarean section should be performed in a hospital in which cardiothoracic surgery and neonatal intensive care facilities are available.

In patients with acute aortic complications during pregnancy, management includes medical therapy where appropriate, and surgical or catheter-based interventions where needed.

Stanford type A aortic dissection occurring during pregnancy is a surgical emergency. Experienced cardiothoracic, cardiology, obstetric, and cardio-anaesthetic physicians must act rapidly to deliver the foetus (if viable) by caesarean section in a specialized cardiothoracic centre and proceed directly to repair of the dissection. If the baby is not viable, aortic surgery with the foetus in place should be performed. Although maternal outcome is good, foetal mortality is 20–30%.[187]

In the case of uncomplicated type B aortic dissection, conservative treatment with strict BP control using medication allowed during pregnancy is recommended.[188]

Thoracic endovascular aortic repair has recently been proposed as a new approach for complicated type B aortic dissection. Promising mid-term outcomes have been reported.[189] However, the outcome of thoracic endovascular aortic repair during pregnancy is only described in a few cases,[190] and it is not recommended in the case of genetic aortopathy.[191–193]

5.3.3 Delivery

The primary aim of intrapartum management in patients with ascending aorta enlargement is to reduce the cardiovascular stress of labour and delivery. If the woman is taking beta-blockers during pregnancy, they should be continued in the peripartum period.

If the ascending aorta diameter is 40–45 mm, vaginal delivery with expedited second-stage and regional anaesthesia should be considered to prevent BP peaks, which may induce dissection. Caesarean delivery may also be considered in these patients, based on the individual situation. Caesarean delivery should be considered when the aortic diameter exceeds 45 mm, and is recommended in patients with vascular Ehlers–Danlos syndrome type IV or acute or chronic aortic dissection.

Table 5 provides an overview of the specific aortic disease syndromes.

Table 5 Aortic diseases

	Marfan[19,175]	Bicuspid aortic valve[176]	Loeys Dietz[182-184]	Turner[178,179]	Vascular Ehlers–Danlos[26]
Location of aneurysm/dissection	Everywhere (sinus of Valsalva)	Ascending aorta	Everywhere	Ascending aorta, arch and descending aorta	Everywhere
Risk of dissection	High: 1–10%	Low: <1%	High:1–10%	High: 1–10%	High: 1–10%
Comorbidity	Dural abnormalities Mitral regurgitation Heart failure Arrhythmias	Aortic stenosis or regurgitation	Dural abnormalities Mitral regurgitation	Low height Infertility Hypertension Diabetes Bicuspid aortic valve Coarctation	Dural abnormalities Uterine rupture
Advise not to become pregnant	Ascending aorta >45 mm (or >40 mm in family history of dissection or sudden death)	Ascending aorta >50 mm	Ascending aorta >45 mm (or >40 mm in family history of dissection or sudden death)	ASI >25 mm/m^2	All patients

ASI = aortic size index.

© ESC 2018

Downloaded from https://academic.oup.com/eurheartj/article-abstract/39/34/3165/5078465 by guest on 13 September 2018

5.4 Recommendations

Recommendations for the management of aortic disease

Recommendations	Class[a]	Level[b]
All aortic diseases		
It is recommended that women with aortic disease have counselling about the risk of aortic dissection.[19,178]	I	C
Imaging of the entire aorta (CT/MRI) is recommended before pregnancy in patients with a genetically proven aortic syndrome or known aortic disease.[53]	I	C
In bicuspid aortic valve patients, imaging of the ascending aorta is recommended before pregnancy.	I	C
When a woman with known aortic dilatation (history of) dissection or genetic predisposition for dissection becomes pregnant, strict blood pressure control is recommended.[185]	I	C
Repeated echocardiographic imaging every 4–12 weeks (depending on diagnosis and severity of dilatation) is recommended during pregnancy and 6 months post-partum in patients with ascending aorta dilatation.[194]	I	C
For imaging of pregnant women with dilatation of the distal ascending aorta, aortic arch, or descending aorta, MRI (without gadolinium) is recommended.[53]	I	C
It is recommended to deliver all women with aortic dilatation or (history of) aortic dissection in an experienced centre with a pregnancy heart team, where cardiothoracic surgery is available.	I	C
In patients with an ascending aorta <40 mm, vaginal delivery is recommended.[96]	I	C
In patients with an ascending aorta >45 mm, caesarean delivery should be considered.	IIa	C
In patients with (history of) aortic dissection, caesarean delivery should be considered.	IIa	C
Prophylactic surgery should be considered during pregnancy if the aorta diameter is >45 mm and increasing rapidly.	IIa	C
When the foetus is viable, delivery before necessary surgery should be considered.[96]	IIa	C
In patients with an aorta 40–45 mm, vaginal delivery with epidural anaesthesia and an expedited second stage should be considered.	IIa	C
In patients with an aorta 40–45 mm, caesarean section may be considered.	IIb	C
Pregnancy is not recommended in patients with (or history of) aortic dissection.	III	C
When possible, the use of ergometrine is not recommended in women with aortic disease.	III	C
Specific syndromes		
In patients with vascular Ehlers–Danlos syndrome, celiprolol is recommended.[186]	I	C
Beta-blocker therapy throughout pregnancy should be considered in women with Marfan syndrome and other heritable thoracic aortic diseases.	IIa	C
Pregnancy is not recommended in patients with severe dilatation of the aorta (heritable thoracic aortic disease such as Marfan syndrome >45 mm, bicuspid aortic valve >50 mm or >27 mm/m2 BSA, or Turner syndrome ASI >25 mm/m2 BSA).[19,20]	III	C
Pregnancy is not recommended in patients with vascular Ehlers–Danlos syndrome.[26]	III	C

ASI = aortic size index; BSA = body surface area; CT = computed tomography; MRI = magnetic resonance imaging.
[a]Class of recommendation.
[b]Level of evidence.

© ESC 2018

Downloaded from https://academic.oup.com/eurheartj/article-abstract/39/34/3165/5078465 by guest on 13 September 2018

6. Valvular heart disease

At childbearing age, valvular heart disease is often due to rheumatic heart disease, particularly in low–middle-income countries. Mechanical valve prostheses raise specific problems during pregnancy.[92,195,196] Risk assessment and management need to consider the resources available in high- and low–middle-income countries.

6.1 Stenotic valve lesions

In stenotic valve diseases, increased CO causes an increase in transvalvular gradient of ~50%, mainly between the first and second trimesters,[197] which increases the risk of maternal and foetal complications.[29,42,198]

6.1.1 Mitral stenosis

6.1.1.1 Maternal risk

Mild mitral stenosis (MS) is generally well tolerated.[198,199] HF occurs in one-third of pregnant women with a valve area ≤1.0 cm^2 and in one-half of those with a valve area ≤1.5 cm^2,[199] most often during the second trimester, even in the absence of symptoms before pregnancy.[198] Sustained AF, although rare (<10%), may precipitate HF and thrombo-embolic events.[199,200] Mortality is between 0–3% in western countries[198–200] and higher in low–middle-income countries.[201,202] NYHA class ≥ II, systolic PAP >30 mmHg, severe stenosis, and older age are associated with maternal complications.[199]

6.1.1.2 Obstetric and offspring risk

The risk of acute HF peripartum depends on symptoms and PAP.[194] Prematurity rates are 20–30%, intrauterine growth retardation 5–20%, and foetal death 1–5%.[198–200,203] Offspring risk is higher in women in NYHA class III/IV during pregnancy.[29,194]

6.1.1.3 Management

Diagnosis. MS is considered clinically significant if valve area is ≤1.5 cm^2.[204,205] The reference measurement of MS severity is planimetry; Doppler-derived pressure half-time is less reliable but can be used during pregnancy.[204,205] Mean gradient and PAP assess haemodynamic consequences and prognosis.[204,205] The assessment of mitral anatomy and associated regurgitation is important when percutaneous mitral commissurotomy is considered.[204,205] Before pregnancy, exercise testing is useful to assess objective exercise tolerance and exercise echocardiography may provide additional information.

Medical therapy. When symptoms or clinically significant PH (echocardiographically estimated systolic PAP ≥50 mmHg) develop, activity should be restricted and beta-1-selective blockers (preferably metoprolol or bisoprolol) commenced.[5] Diuretics may be used if symptoms persist, avoiding high doses (see table 'Recommendations for drug use in pregnancy').[5] Anticoagulation using UFH, LMWH, or vitamin K antagonist (VKA), according to the context and term, is recommended in the case of paroxysmal or permanent AF, left atrial thrombosis, or prior embolism.[5] Anticoagulation should be considered in women in sinus rhythm with significant MS and spontaneous echocardiographic contrast in the left atrium, large left atrium (≥ 60 mL/m^2), or congestive HF.

Interventions. All patients with significant MS should be counselled against pregnancy and intervention should be considered pre-pregnancy, favouring percutaneous intervention, even if asymptomatic, and even more so if the valve area is <1.0 cm^2.[198,204]

During pregnancy, percutaneous mitral commissurotomy is preferably performed after 20 weeks of gestation. It should only be considered in women with NYHA class III/IV and/or systolic PAP ≥50 mmHg, despite optimal medical treatment in the absence of contraindications (see table 'General Recommendations').[204] Closed commissurotomy remains an alternative in low–middle-income countries. Due to foetal risk, open-heart surgery should be reserved for cases in which all other measures have failed and the mother's life is threatened.[206]

Follow-up during pregnancy. Clinical and echocardiographic follow-up is indicated monthly or bimonthly depending on haemodynamic tolerance. In mild MS, evaluation is recommended every trimester and prior to delivery.

Labour and delivery. Vaginal delivery should be favoured in patients with mild MS, and in patients with significant MS in NYHA class I/II without PH. Caesarean section is generally considered in patients who are in NYHA class III/IV or have PH, or in whom percutaneous mitral commissurotomy cannot be performed or has failed.

Follow-up and prognosis after delivery. Close monitoring is needed in the days following delivery. Late prognosis depends mainly on the risk of stenosis progression or re-stenosis after commissurotomy, and justifies regular follow-up.[204]

6.1.2 Valvular aortic stenosis

The main cause of AS is bicuspid aortic valve followed by rheumatic heart disease.

6.1.2.1 Maternal risk

Cardiac morbidity is related to the baseline severity of AS and symptoms.[207] HF is rare (<10%) in women with moderate AS and in those who were asymptomatic before pregnancy, while it occurs in one out of four symptomatic patients.[207] Even in patients with severe AS, pregnancy is often well tolerated if prior exercise tolerance was normal. Mortality is now rare if careful management is provided.[194,198,207–209] Arrhythmias are rare.[206] Women with bicuspid aortic valve have a low-risk of aortic dissection if the aortic diameter is <50 mm (section 5.2).

6.1.2.2 Obstetric and offspring risk

Obstetric complications may be increased in patients with severe AS.[207,209] Pre-term birth, intrauterine growth retardation, and low birth weight occur in 20–25% of the offspring of mothers with moderate and severe AS, and are increased in severe AS.[207] Miscarriages and foetal death rates are <5%. The risk of genetic transmission of LV outflow tract malformations justifies the performance of foetal echocardiography in AS due to bicuspid aortic valve.[5]

6.1.2.3 Management

Diagnosis. The severity of AS is assessed by combining flow-dependent indices and valve area.[204,205] Exercise testing is recommended in asymptomatic patients before pregnancy to evaluate

Downloaded from https://academic.oup.com/eurheartj/article-abstract/39/34/3165/5078465 by guest on 13 September 2018

exercise tolerance, BP response, and arrhythmias, and exercise echocardiography may provide additional information. In women with bicuspid aortic valve, aortic diameters should be assessed before and during pregnancy.

Medical therapy. Medical treatment and restricted activities are indicated if HF occurs during pregnancy. Diuretics can be administered for congestive symptoms.

Interventions. All symptomatic patients with severe AS or asymptomatic patients with impaired LV function or a pathological exercise test should be counselled against pregnancy, and surgery should be performed pre-pregnancy.[10,204] Pregnancy should not be discouraged in asymptomatic patients, even with severe AS, when LV size and function and the exercise test are normal (see table 'General Recommendations'). There should also be no recent progression of AS.

During pregnancy in patients who are severely symptomatic despite medical therapy, percutaneous valvuloplasty can be undertaken by an experienced operator.[207] If this is not possible and patients have life-threatening symptoms, valve replacement should be considered after early delivery by caesarean section if this is an option (see table 'General Recommendations'). Given the foetal risk of surgery, transcatheter aortic valve implantation is a promising alternative, but experience during pregnancy is very limited.

Follow-up during pregnancy. Regular follow-up is required by an experienced team. In severe AS, monthly or bimonthly cardiac evaluations including echocardiography are advised.

Labour and delivery. In severe symptomatic AS, caesarean delivery should be preferred. An individual approach is recommended for asymptomatic severe AS. In non-severe AS, vaginal delivery is favoured.

Follow-up and prognosis after delivery. Disease progression is frequent after delivery and requires close follow-up.[204,208,210]

6.2 Regurgitant lesions

6.2.1 Mitral and aortic regurgitation

Mitral and aortic regurgitation can be of rheumatic, congenital, or degenerative origin.[92,199]

6.2.1.1 Maternal risk

Women with severe regurgitation and symptoms or compromised LV function are at high-risk of HF.[194,199] HF occurs in 20–25% of women with moderate or severe rheumatic MR.[199] Acute severe regurgitation is poorly tolerated. In women with congenital heart disease, significant left AV valve regurgitation is associated with cardiac complications during pregnancy. A persistent worsening of regurgitation may occur.[42]

6.2.1.2 Obstetric and offspring risk

No increased risk of obstetric complications has been reported. Intrauterine growth retardation occurs in 5–10%, and other offspring complications in <5%, of women with moderate or severe MR.[199]

6.2.1.3 Management

Diagnosis. Evaluation, preferably pre-conception, should include the assessment of symptoms and comprehensive echocardiographic evaluation of regurgitation severity, LV dimensions, and function.[204]

Ascending aortic diameters should be measured in women with aortic regurgitation, especially in those with bicuspid valves.

Medical therapy. Symptoms of fluid overload can usually be managed medically.

Interventions. Pre-pregnancy surgery favouring valve repair should be performed according to guidelines.[204]

In acute severe regurgitation with therapy-refractory HF, surgery is sometimes unavoidable during pregnancy. If the foetus is sufficiently mature, delivery should be undertaken prior to cardiac surgery (see table 'General Recommendations').

Follow-up during pregnancy. Follow-up is required every trimester in mild/moderate regurgitation, and more often in severe regurgitation.

Labour and delivery. Vaginal delivery with epidural anaesthesia and shortened second stage is advisable.

Follow-up and prognosis after delivery. The prognosis depends on the regurgitation severity and its consequences on symptoms, LV size, and function.

6.2.2 Tricuspid regurgitation

Secondary TR is more frequent than primary TR, which may be due to endocarditis or Ebstein's anomaly.

Maternal risk is usually determined by left-sided valve disease or PH. However, maternal risk can be increased in severe symptomatic TR or in women with RV dysfunction.[50] In women with congenital heart disease, moderate/severe AV valve regurgitation may be associated with maternal cardiac complications, which are mainly arrhythmias.[42]

Even severe TR with HF can usually be managed conservatively during pregnancy (see table 'General Recommendations'). When surgery is necessary for left-sided valve lesions, additional tricuspid repair is indicated in severe TR and should be considered in moderate TR with annular dilatation (≥ 40 mm).[204] In severe symptomatic TR, repair should be considered pre-pregnancy.

6.3 Atrial fibrillation in native heart valve disease

A high thrombo-embolic risk is associated with AF, particularly in clinically significant MS. Immediate anticoagulation is required, using LMWH at therapeutic doses in the first and last trimesters, and VKAs with the usual target INRs or LMWH for the second trimester. Non-VKA OACs are contraindicated throughout pregnancy. The choice between cardioversion and rate control using digoxin or beta-blockers depends on the severity of the underlying valve disease and the tolerance (see section 12).

6.4 Prosthetic valves

6.4.1 Choice of valve prosthesis

When implantation of a prosthetic valve is unavoidable in a woman who wants to become pregnant in the future, valve selection is

Downloaded from https://academic.oup.com/eurheartj/article-abstract/39/34/3165/5078465 by guest on 13 September 2018

challenging. Mechanical valves offer excellent haemodynamic performance and long-term durability, but the need for anticoagulation increases maternal and foetal mortality and morbidity, and the risk of major cardiac events during pregnancy is much higher than with bioprosthetic valves.[196,211,212] However, bioprosthetic valves in young women are associated with a high-risk of structural valve deterioration resulting in the risk of going through pregnancy with a dysfunctional valve, and eventually in the inevitable need for re-operation. Transcatheter valve implantation (currently especially in pulmonary valves) and the Ross procedure in aortic valve disease (pulmonary autograft in the aortic position and pulmonary homograft) are alternative options to be considered.[5] Data on pregnancy after a Ross procedure are scarce but indicate low-risk in the absence of aortic dilatation.[213] A desire for pregnancy is a class IIa indication for a biological valve.[204] In young women who wish to become pregnant in the future, the pregnancy heart team should be involved in the choice of a specific prosthesis. The final choice should be made after extensive sharing of information and discussion with the patient.

6.4.2 Pregnancy risk with bioprostheses

The risk of maternal cardiovascular complications in women with a bioprosthesis is low in those with no or minimal bioprosthesis dysfunction and uncompromised ventricular function. When significant bioprosthesis dysfunction is present, the risk of complications can be significant. Pre-pregnancy assessment and counselling, as well as follow-up, medical treatment, and indications for intervention, are comparable with those for pregnancies with native valve dysfunction.

6.5 Mechanical prostheses and anticoagulation

In women with mechanical valves, pregnancy is associated with a very high-risk of complications (WHO risk classification III). In the ROPAC registry, the chances of an event-free pregnancy with a live birth were 58% for women with a mechanical valve, compared with 79% for women with a bioprosthesis and 78% for women with heart disease but no valve prosthesis.[196] A recent study from the UK reported a favourable outcome for mother and baby in only 28% of cases.[214] The main risks are related to the need for anticoagulation therapy (valve thrombosis and haemorrhagic complications). Additional risks are related to ventricular and valvular dysfunction.

6.5.1 Maternal risk

The risk of valve thrombosis is markedly increased during pregnancy. The risk is lower with adequate dosing of anticoagulant therapy, and depends on the type and position of the mechanical valve, and on additional patient-related risk factors.[204] In the ROPAC registry, valve thrombosis occurred in 4.7% of 202 pregnancies and mortality was 20%.[196] In the UK study, maternal mortality related to thrombotic complications or valve dysfunction occurred in 9% and severe morbidity in 41% (16% thrombo-embolic complications).[214] The risk of valve thrombosis is relatively low with VKAs throughout pregnancy (0–4%).[196,215–219] Scarce evidence concerning UFH in the first trimester or throughout pregnancy indicates a high-risk of valve thrombosis (9–33%); additional risks are thrombocytopenia and osteoporosis.[215,218,219] LMWH is also associated with the risk of valve thrombosis.[196,214,215,219–222] Because the dose requirement markedly increases due to increased renal clearance, monitoring of anti-Xa levels with dose adjustment decreases the risk. LMWH throughout pregnancy with anti-Xa monitoring and dose adjustment according to peak levels carries a valve thrombosis risk of 4.4–8.7%.[219,223] Suboptimal target anti-Xa levels or poor compliance often contribute to valve thrombosis, but several valve thromboses occured with peak anti-Xa levels within the target range of 1.0–1.2 IU/mL.[221,222] Valve thrombosis occurs in 5.8–7.4% when LMWH is used in the first trimester only, which is similar to using LMWH throughout pregnancy.[196,215,219,223] However, the high-risk of valve thrombosis in the UK study was mainly related to the use of LMWH throughout pregnancy. The occurrence of valve thrombosis with adequate peak anti-Xa levels has raised concerns about the safety of this approach. Fast renal clearance can result in subtherapeutic trough (pre-dose) anti-Xa levels despite adequate peak levels, but data on pregnancies with LMWH dosing according to trough and peak anti-Xa levels are limited to case reports.[5,224–226] In conclusion, there are unresolved questions concerning LMWH in pregnant women with mechanical valves, including optimal anti-Xa levels, the importance of peak vs. trough levels, the best time intervals for anti-Xa monitoring, and the duration of use.

Current evidence (lacking adequate randomized studies) indicates that the use of VKAs throughout pregnancy, under strict INR control, is the safest regimen to prevent valve thrombosis.[196,215–219] LMWH is possibly superior to UFH for preventing valve thrombosis.[196,219,223]

6.5.2 Obstetric and offspring risk

All anticoagulation regimens carry an increased risk of miscarriage and haemorrhagic complications, including post-partum haemorrhage and retroplacental bleeding leading to premature birth and foetal death.[196,216,218,220,221] ROPAC shows that VKAs during the first trimester are associated with an increased risk of miscarriage compared with LMWH or UFH (28.6% vs. 9.2%), and the live birth rate is lower, in line with other literature.[196] Two systematic reviews concluded that the risk of foetal loss is dose-related (foetal loss rate with low-dose VKA is 13.4–19.2%, total foetal loss rate with VKA is 32.5%). Foetal loss rate with a combined heparin/VKA regimen is 22.7%,and with LMWH throughout pregnancy is 12.2%.[217,219] Comparison between studies is hampered by reporting differences, and conclusions concerning the safety of low-dose VKA are controversial.[5,196,217,219,223,227] VKA use in the first trimester results in embryopathy (limb defects, nasal hypoplasia) in 0.6–10% of cases.[216,218,219,228] UFH and LMWH do not cross the placenta, therefore substitution of VKA with UFH or LMWH in weeks 6–12 almost eliminates the risk of embryopathy. The embryopathy risk is also dose-dependent (0.45–0.9% with low-dose warfarin).[217,219] Additionally, there is 0.7–2% risk of foetopathy (e.g. ocular and central nervous system abnormalities, intracranial haemorrhage) with VKAs in the second and third trimester.[216,219,223,228–230] Foetopathy has been described with UFH but not with LMWH throughout pregnancy.[219,223] Vaginal delivery while the mother is on VKAs is contraindicated because of the risk of foetal intracranial bleeding.[228] Haemorrhagic complications in the mother occur with all regimens, but the incidence is lower with VKA throughout pregnancy than with LMWH/UFH throughout pregnancy.[219] Addition of low-dose aspirin to VKA or heparin has no proven advantage in preventing valve

Downloaded from https://academic.oup.com/eurheartj/article-abstract/39/34/3165/5078465 by guest on 13 September 2018

thrombosis but is associated with significantly more maternal bleeding complications, including fatal events.[196,219,222]

6.5.3 Management

Pre-pregnancy evaluation should include the assessment of symptoms and echocardiographic evaluation of ventricular function, as well as prosthetic and native valve function. The type and position of valve(s), as well as the history of valve thrombosis, should be taken into account. The option to avoid pregnancy should be discussed with the mother.

6.5.3.1 Medical therapy

The advantages and disadvantages of different anticoagulation regimen should be discussed extensively before pregnancy. The mother must understand that the use of VKAs is the most effective regimen to prevent valve thrombosis, and therefore the safest regimen for her, and that risks to the mother also jeopardize the baby. However, the increased risks of embryopathy, foetopathy, foetal loss, and foetal haemorrhage associated with the use of VKAs need to be discussed while considering the VKA dose. The higher risk of valve thrombosis and lower foetal risks associated with LMWH should be discussed. Compliance with prior anticoagulant therapy should be considered. The mother should understand that whatever anticoagulation regime is chosen, her strict compliance is crucial for a successful outcome of the pregnancy.

VKAs should be continued until pregnancy is achieved. Continuation of VKAs throughout pregnancy should be considered when the VKA dose is low (see *Table 7*). Because of the low risks of embryopathy, foetopathy (<2%), and foetal loss (<20%), VKAs are the most effective regimen to prevent valve thrombosis.[215,218,219] The target INR should be chosen according to current guidelines,[204] with INR monitoring weekly or every 2 weeks. Self-monitoring of INR in suitable patients is recommended. Alternatively, a switch to LMWH from weeks 6–12 under strict monitoring may be considered in patients with a low dose requirement, after full information has been given to the mother. When a higher dose of VKAs is required, discontinuation of VKAs between weeks 6 and 12, and replacement with adjusted-dose i.v. UFH or LMWH twice daily with dose adjustment according to peak anti-Xa levels, should be considered. See table 'Recommendations for the management of prosthetic heart valves' and *Figures 2–4* for details of dosing and monitoring. Alternatively, continuation of VKAs may be considered in these patients after fully informed consent. In addition to monitoring

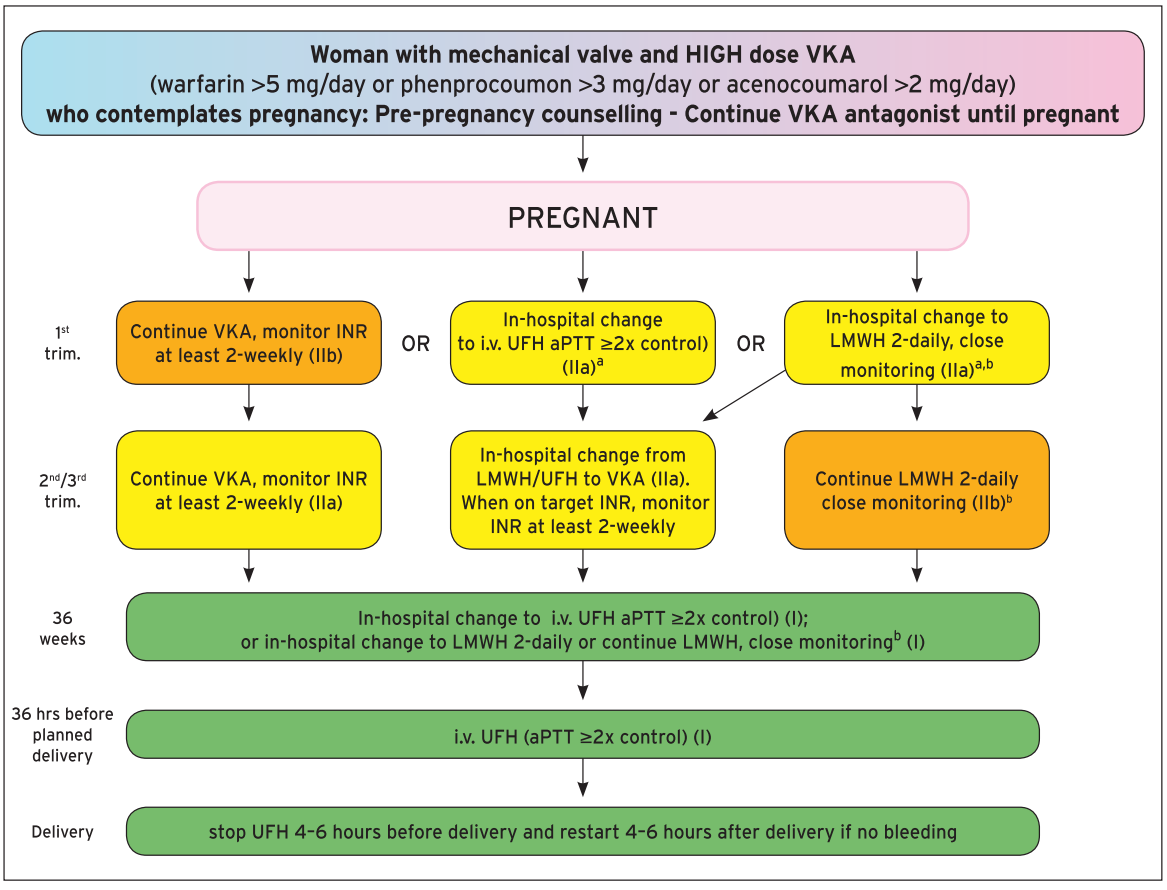

Figure 2 Flowchart on anticoagulation in mechanical valves and high-dose VKA [a]weeks 6–12 [b]monitoring LMWH: - starting dose for LMWH is 1 mg/kg body weight for enoxaparin and 100 IU/kg for dalteparin, twice daily subcutaneously; -in-hospital daily anti-Xa levels until target, then weekly (I); -target anti-Xa levels: 1.0–1.2 U/ml (mitral and right sided valves) or 0.8–1.2 U/ml (aortic valves) 46 hours post-dose (I); -pre-dose anti-Xa levels >0.6 U/ml (IIb). aPTT = activated partial thromboplastic time; INR = international normalized ratio; i.v. = intravenous; LMWH = low molecular weight heparin; LVEF = left ventricular ejection fraction; UFH = unfractionated heparin; VKA = vitamin K antagonist.

Downloaded from https://academic.oup.com/eurheartj/article-abstract/39/34/3165/5078465 by guest on 13 September 2018

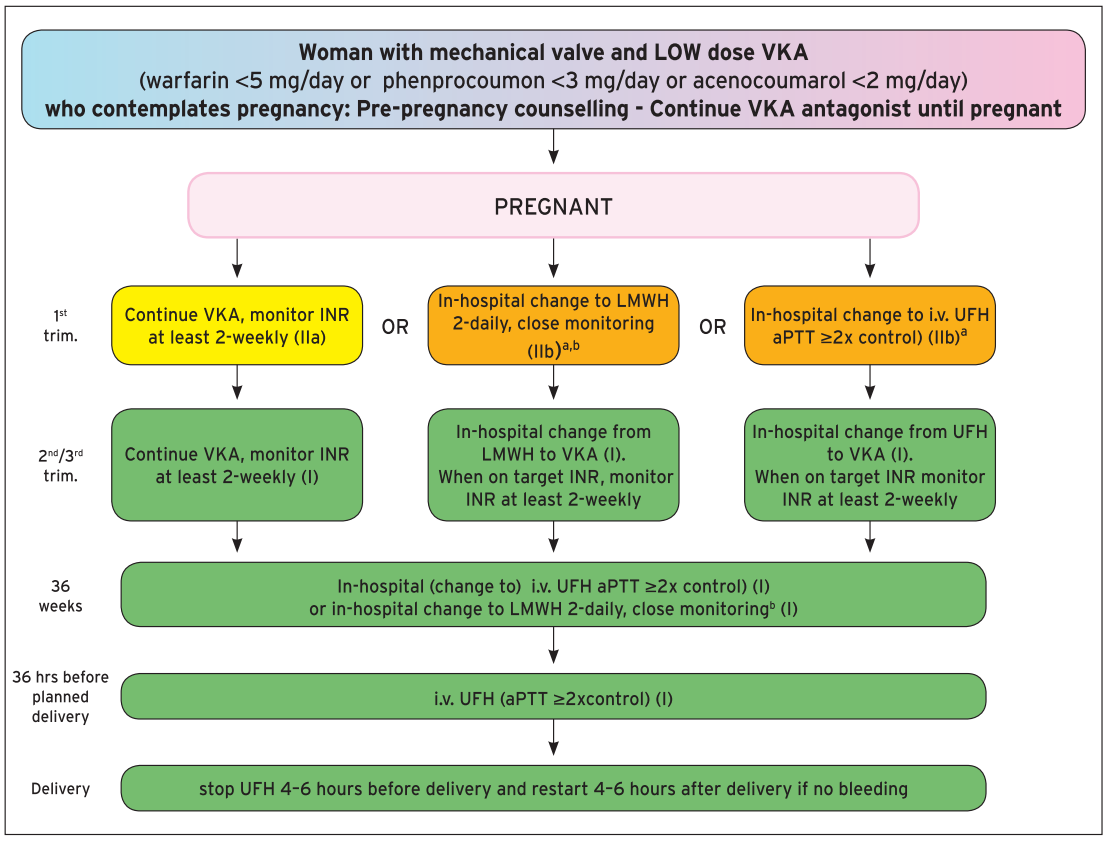

Figure 3 Flowchart on anticoagulation in mechanical valves and low-dose VKA [a]weeks 6–12 [b]monitoring LMWH: - starting dose for LMWH is 1 mg/kg body weight for enoxaparin and 100 IU/kg for dalteparin, twice daily subcutaneously; -in-hospital daily anti-Xa levels until target, then weekly (I); -target anti-Xa levels: 1.0–1.2 U/ml (mitral and right sided valves) or 0.8–1.2 U/ml (aortic valves) 4–6 hours post-dose (I); -pre-dose anti-Xa levels >0.6 U/ml (IIb). aPTT = activated partial thromboplastic time; INR = international normalized ratio; i.v. = intravenous; LMWH = low molecular weight heparin; LVEF = left ventricular ejection fraction; UFH = unfractionated heparin; VKA = vitamin K antagonist.

peak anti-Xa levels, monitoring of the trough (pre-dose) anti-Xa level and dose-adjustment to maintain this trough level at ≥0.6 IU/mL may be considered based on theoretical grounds, despite limited evidence.[5,224,225] The starting dose for LMWH is 1 mg/kg body weight for enoxaparin and 100 IU/kg for dalteparin, twice daily subcutaneously. The dose should be adjusted daily according to peak (or peak and trough) anti-Xa levels and weekly when the target anti-Xa level is achieved.[5,224,225] The routine addition of acetylsalicylic acid is not recommended.[196,219,222] When UFH is used, after a stable aPTT has been achieved, UFH should be monitored weekly using aPTT, with a prolongation of ≥2 times the control. During the second and third trimester, VKAs are the favoured therapy. For details on management see *Figures* 2–4.

6.5.3.2 Surveillance during pregnancy

These high-risk pregnancies should be managed by a pregnancy heart team in an expert centre. The effectiveness of the anticoagulation regimen should be monitored weekly or every 2 weeks depending on the anticoagulation regimen (see *Table* 7), and clinical follow-up including echocardiography should be performed monthly.

Target INR for mechanical prostheses		
Prothesis thrombogenicity	Patient-related risk factors[a]	
	None	≥1
Low[b]	2.5	3.0
Medium[c]	3.0	3.5
High[d]	3.5	4.0

©ESC 2018

Figure 4 Flowchart on anticoagulation in mechanical valves and target international normalized ratio for mechanical prostheses (modified from Baumgartner *et al.*[204]). INR = international normalized ratio; LVEF = left ventricular ejection fraction. [a]Mitral or tricuspid valve replacement, previous thrombo-embolism, atrial fibrillation, mitral stenosis of any degree, or LVEF <35%. [b]Carbomedics, Medtronic Hall, ATS, or Medtronic Open-Pivot, St Jude Medical, On-X, or Sorin Bicarbon. [c]Other bileaflet valves with insufficient data. [d]Lillehei-Kaster, Omniscience, Starr-Edwards (ball-cage), Björk-Shiley and other tilting-disc valves; any pulmonary valve prosthesis.

Downloaded from https://academic.oup.com/eurheartj/article-abstract/39/34/3165/5078465 by guest on 13 September 2018

6.5.3.3 Diagnosis and management of valve thrombosis

Dyspnoea and/or an embolic event are reasons for immediate transthoracic echocardiography to search for valve thrombosis, usually followed by transoesophageal echocardiography. Additionally, fluoroscopy can be performed with limited foetal risk. Management of valve thrombosis is comparable with management in non-pregnant patients. This includes optimizing anticoagulation with i.v. UFH and the resumption of oral anticoagulation in non-critically ill patients with recent subtherapeutic anticoagulation, and surgery when anticoagulation fails and for critically ill patients with obstructive thrombosis.[204] A molecular weight >1000 Da prevents most fibrinolytic items from easily crossing the placenta, though small amounts of streptokinase and fragments of urokinase may pass into the foetal circulation. Alteplase (a recombinant tissue plasminogen activator) has the highest molecular weight and does not cross the placenta. However, the risk of embolization (10%) and subplacental bleeding is a concern, and experience in pregnancy is limited. Fibrinolysis should be applied in critically ill patients when surgery is not immediately available, and it should be considered when the risk of surgery is high.[204] Because foetal loss is high (30%) with surgery, fibrinolysis may be considered instead of surgery in non-critically ill patients when anticoagulation fails.[231] Fibrinolysis is the therapy of choice in right-sided prosthetic valve thrombosis.[204] The mother should be informed about the risks.

6.5.3.4 Delivery

Planned delivery is necessary. Vaginal delivery requires a prior switch to i.v. heparin. The use of epidural anaesthesia requires a prolonged interruption of anticoagulant therapy, which may contraindicate its use in women with a mechanical prosthesis. A planned caesarean section may therefore be considered as an alternative, especially in patients with a high-risk of valve thrombosis, to keep the time without VKAs as short as possible. Caesarean section should be performed if labour onset occurs while the patient is still on VKAs.

6.6 Recommendations

Recommendations for the management of native valvular heart disease

Recommendations	Class[a]	Level[b]
Pre-pregnancy evaluation, including echocardiography, and counselling is recommended for any woman with known or suspected valvular disease.	I	C
Mitral stenosis		
In patients with symptoms or pulmonary hypertension, restricted activities and beta-1-selective blockers are recommended.[5,204]	I	B
Diuretics are recommended when congestive symptoms persist despite beta-blockers.[5]	I	B
Intervention is recommended before pregnancy in patients with MS and valve area <1.0 cm^2.	I	C
Therapeutic anticoagulation using heparins or VKA is recommended in case of atrial fibrillation, left atrial thrombosis, or prior embolism.	I	C
Intervention should be considered before pregnancy in patients with MS and valve area <1.5 cm^2.	IIa	C
Percutaneous mitral commissurotomy should be considered in pregnant patients with severe symptoms or systolic pulmonary artery pressure >50 mmHg despite medical therapy.	IIa	C
Aortic stenosis		
Intervention is recommended before pregnancy in patients with severe aortic stenosis if:		
• they are symptomatic	I	B
• OR LV dysfunction (LVEF <50%) is present[204]	I	C
• OR when they develop symptoms during exercise testing.	I	C
Intervention should be considered before pregnancy in asymptomatic patients with severe AS when a fall in blood pressure below baseline during exercise testing occurs.	IIa	C
Balloon aortic valvuloplasty should be considered during pregnancy in patients with severe aortic stenosis and severe symptoms.	IIa	C
Chronic regurgitant lesions		
Surgical treatment is recommended before pregnancy in patients with severe aortic or mitral regurgitation with symptoms of impaired ventricular function or ventricular dilatation.[204]	I	C
Medical therapy is recommended in pregnant women with regurgitant lesions when symptoms occur.	I	C

LV = left ventricular; LVEF = left ventricular ejection fraction; MS = mitral stenosis; VKA = vitamin K antagonist.
[a]Class of recommendation.
[b]Level of evidence.

Downloaded from https://academic.oup.com/eurheartj/article-abstract/39/34/3165/5078465 by guest on 13 September 2018

© ESC 2018

Recommendations for the management of prosthetic heart valves

Recommendations	Class[a]	Level[b]
It is recommended that the valve prosthesis for a woman contemplating pregnancy is chosen in consultation with a pregnancy heart team.	I	C
It is recommended to manage pregnancy in women with mechanical valves in a centre with a pregnancy heart team.	I	C
If delivery starts while on a VKA or in less than 2 weeks after discontinuation of a VKA, caesarean section is recommended.	I	C
It is recommended to discontinue VKAs and start adjusted-dose intravenous UFH (aPTT ≥2x control) or adjusted-dose LMWH[c] (see separate recommendations) at the 36th week of gestation.	I	C
In pregnant women on LMWH or UFH, it is recommended to perform weekly anti-Xa level monitoring or aPTT monitoring with dose adjustment (within 36 h).	I	C
In pregnant women on a VKA, it is recommended to perform INR monitoring weekly or every 2 weeks.	I	C
In pregnant women with LMWH, it is recommended to target anti-Xa levels 4–6 h post-dose at 0.8–1.2 U/l (aortic valve prosthesis) or 1.0–1.2 IU/mL (mitral and right-sided valve prostheses).	I	C
It is recommended to replace LMWH with intravenous UFH (aPTT ≥2x control) 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
It is recommended to anticipate the timing of delivery to ensure safe and effective peripartum anticoagulation.	I	C
Immediate echocardiography is recommended in women with mechanical valves presenting with dyspnoea and/or an embolic event.	I	C
It is recommended to implement changes in the anticoagulation regimen during pregnancy in hospital.	I	C
During the second and third trimesters until the 36th week, VKAs are recommended in women needing a low dose.[d]	I	C
A bioprostheses should be considered in young women contemplating pregnancy.	IIa	C
During the second and third trimesters until the 36th week, VKAs should be considered in women needing a high dose.[e]	IIa	C
Continuation of VKAs 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 VKAs between weeks 6 and 12, and replacement with adjusted-dose intravenous UFH (aPTT ≥2x control) or adjusted-dose LMWH[c] twice daily (see separate recommendations), should be considered in patients with a warfarin dose >5 mg/day (or phenprocoumon >3 mg/day or acenocoumarol >2 mg/day).	IIa	C
During the second and third trimesters, LMWH[c] with anti-Xa level monitoring and dose adjustment (see separate recommendations) may be considered in women who need a high dose of VKA[e] after patient information and consent.	IIb	C
In pregnant women with LMWH, in addition to monitoring peak anti-Xa levels, monitoring pre-dose levels targeted at ≥0.6 IU/mL may be considered.	IIb	C
LMWH is not recommended when weekly anti-Xa level monitoring and dose-adjustment is not available.	III	C

aPTT = activated partial thromboplastin time; INR = international normalized ratio; LMWH = low molecular weight heparin; UFH = unfractionated heparin; VKA = vitamin K antagonist.
[a]Class of recommendation.
[b]Level of evidence.
[c]The starting dose for LMWH is 1 mg/kg body weight for enoxaparin and 100 IU/kg for dalteparin, twice daily subcutaneously.
[d]Low-dose VKA: warfarin <5 mg/day (or phenprocoumon <3 mg/day or acenocoumarol <2 mg/day).
[e]High-dose VKA: warfarin >5 mg/day (or phenprocoumon >3 mg/day or acenocoumarol >2 mg/day).

© ESC 2018

Downloaded from https://academic.oup.com/eurheartj/article-abstract/39/34/3165/5078465 by guest on 13 September 2018

7. Coronary artery disease

The incidence of CAD in women of childbearing age is unclear and varies between countries.[232] Although acute MI (AMI)/acute coronary syndromes (ACS) complicating pregnancy is relatively uncommon (1.7–6.2/100 000 deliveries),[233–235] CAD accounts for >20% of all maternal cardiac deaths.[3]

7.1 Aetiology

Pregnancy is associated with a three- to four-fold increase in AMI risk compared with age-matched non-pregnant women.[232,234,236,237] Risk factors include smoking,[238] maternal age, hypertension, diabetes, obesity, and dyslipidaemia.[233,234,237,239,240] Additional risk factors include (pre-)eclampsia, thrombophilia, transfusion, post-partum infection, cocaine use, multiparity, and post-partum haemorrhage.[233,234] As the birth rate in women >40 years increases, ACS complicating pregnancy will become more common, as for every year increase in maternal age there is a 20% increase in MI risk.[235] The aetiology of CAD in pregnancy differs from the general population; the majority of CAD has non-atherosclerotic mechanisms, including pregnancy-related spontaneous coronary artery dissection (P-SCAD) (43%), angiographically normal coronary arteries (18%), and coronary thrombosis (17%).[239,241]

P-SCAD-related AMI occurs most commonly in late pregnancy/early post-partum, and predominantly involves the left-sided coronaries, frequently with multivessel involvement.[237,239] Potential pregnancy-related precipitating factors include fluctuating oestrogen/progesterone levels resulting in structural changes in coronary vasculature, in background of fibromuscular dysplasia or connective tissue disease, and increased coronary shear stresses associated with labour.[242–244]

The mechanisms of AMI with angiographically normal coronary arteries remains unclear and include transient coronary spasm (increased vascular reactivity and/or use of ergot derivatives),[237,245] rather reflecting the limitations of this diagnostic technique.[246,247] Coronary thrombosis in the absence of atherosclerosis is most likely due to the hypercoagulability of pregnancy[248] and can result from paradoxical embolization.

Increasing survival in Kawasaki disease (in the USA it is predicted that by 2030, one in every 1600 adults will have suffered from Kawasaki disease) presents an additional challenge.[249] Relevant Kawasaki disease manifestations include aneurysms, coronary blood flow alteration, coronary stenoses, myocardial ischaemia/fibrosis, congestive cardiac failure, and valvular abnormalities.[249]

Coronary thrombosis in the absence of atherosclerosis is most likely due to the hypercoagulability of pregnancy[248] and can result from paradoxical embolization.

7.2 Presentation and diagnosis

Development of pregnancy-related ACS/AMI is most common during the third trimester [STEMI 25% and non-STEMI (NSTEMI) 32%] or post-partum (STEMI 45% and NSTEMI 55%). Clinical presentation is the same as in the non-pregnant population.[250,251] ECG interpretation can be challenging, with inverted T waves in the absence of coronary ischaemia, and anaesthesia induction for caesarean section associated with ST-segment depression.[237] A serum troponin rise should suggest myocardial ischaemia, even in pre-eclampsia.[252,253] Where the ECG is non-diagnostic, echocardiography may be helpful.[254] The main differential diagnoses include PE, aortic dissection, and pre-eclampsia. Potential complications include HF/cardiogenic shock (38%), arrhythmias (12%), recurrent angina/AMI (20%), maternal mortality (7%), and foetal death (7%).[239]

7.3 Management

AMI management in pregnancy is similar to that in the general population, including revascularization techniques. In P-SCAD, enhanced vascular vulnerability should be considered when applying revascularization strategies.[241,255] Management should be multidisciplinary, including emergency, obstetric, and cardiovascular teams, and any revascularization should be undertaken by the most experienced operator due to the attendant risks associated with coronary intervention in this patient population. In cardiogenic shock, there should be facilities for emergency mechanical circulatory support. Close monitoring of the mother and foetus is required, with a delivery strategy in place in case there is sudden maternal or foetal deterioration. In the event of maternal cardiac arrest, resuscitation (and delivery) should be performed according to existing guidelines.[256]

7.4 Pharmacotherapy

There is little information regarding the foetal safety of guideline-recommended drug therapy in AMI.[257] Low-dose aspirin appears to be safe, but there is little information regarding $P2Y_{12}$ inhibitors. Clopidogrel should be used only when strictly necessary and for the shortest duration.[239] In the absence of data regarding glycoprotein IIb/IIIa inhibitors-bivalirudin, prasugrel, and ticagrelor, their use is not recommended. Beta-blockade may be beneficial in reducing shear stress in P-SCAD. Recombinant tissue plasminogen activator does not cross the placenta but may induce bleeding complications (subplacental bleeding). The benefits of short-term heparinization during PCI probably outweigh the risk of bleeding complications.

7.5 Intervention

The effects of ionizing radiation should not prevent primary PCI in pregnant patients with standard indications for revascularization in AMI. However, the radiation dose must be minimized. In stable, low-risk NSTEMI, a non-invasive approach should be considered.[258] Although CT coronary angiography provides an alternative diagnostic method,[259] it requires radiation, potentially high-dose beta-blockade, and may fail to demonstrate limited P-SCAD.

7.5.1 Stent choice and antiplatelet therapy

The majority of reports regarding STEMI in pregnancy relate to bare-metal stents. However, new-generation drug-eluting stents (DES) are recommended according to the 2017 AMI STEMI Guidelines.[251] Because no complications have been reported in stented pregnant patients treated with clopidogrel and aspirin, and because pregnancy is a high bleeding-risk situation, use of a more potent $P2Y_{12}$ inhibitor should be considered with caution. The duration of dual antiplatelet therapy with a second/third-generation DES can be shortened, particularly in the absence of great thrombotic burden. Bioabsorbable stent usage has been reported in spontaneous coronary artery dissection; however, there is currently no evidence to recommend them in pregnancy.

Downloaded from https://academic.oup.com/eurheartj/article-abstract/39/34/3165/5078465 by guest on 13 September 2018

7.6 Pre-existing CAD

Women with pre-established CAD or ACS/MI are at risk of serious adverse cardiac events during pregnancy, the highest risk of which is seen in atherosclerotic coronary disease[260] with reported maternal mortality between 0–23%.[92,261,262] Adverse obstetric outcomes occur in ≤16%, with 30% of pregnancies complicated by an adverse foetal/neonatal event, most commonly in coronary atherosclerosis (50%).[260]

Pregnancy may be considered in patients with known CAD in the absence of residual ischaemia and clinical signs of LV dysfunction. There are no high-quality data defining how long pregnancy should be delayed post-AMI/ACS. However, recommending 12 months seems reasonable, individualized according to comorbidities, cardiovascular status, and the requirement for medical therapy. There is no definitive evidence that previous P-SCAD increases recurrence risk. However, avoidance of further pregnancy is advised[258] and, if the patient chooses to proceed, close monitoring is recommended.

7.7 Labour and delivery

Timing of delivery must be individualized. However, treatment of STEMI/NSTEMI should not be delayed for delivery. Delivery should be postponed (if possible) for at least 2 weeks post-AMI to facilitate maternal management.[237] Vaginal delivery is preferable (see section 3).

7.8 Recommendations

Recommendations for the management of coronary artery disease

Recommendations	Class[a]	Level[b]
ECG and measurement of troponin levels are recommended when a pregnant woman has chest pain.[225,227]	I	C
Primary coronary angioplasty is recommended as the preferred reperfusion therapy for STEMI during pregnancy.[226]	I	C
An invasive management strategy should be considered for NSTE-ACS with high risk criteria.[226]	IIa	C
Conservative management should be considered for stable NSTE-ACS with low risk criteria.	IIa	C
Follow-up should be considered over at least the next 3 months.	IIa	C
Breastfeeding is not recommended in mothers who take antiplatelet agents other than low-dose aspirin due to a lack of data (see section 12).	III	C

© ESC 2018

ECG = electrocardiogram; LV = left ventricular; NSTE-ACS = non-ST-elevation acute coronary syndrome; NSTEMI = non-ST-elevation myocardial infarction; STEMI = ST-elevation myocardial infarction.
[a]Class of recommendation.
[b]Level of evidence.

8. Cardiomyopathies and heart failure

The aetiology of pregnancy-associated cardiomyopathy includes acquired and inherited diseases, such PPCM, toxic cardiomyopathies, HCM, dilated cardiomyopathy (DCM), Takotsubo cardiomyopathy, and storage diseases. Although rare, they may cause severe complications in pregnancy.[263] HF with preserved EF, an important cause of HF in older patients, does not appear to be a major clinical problem in pregnancy; however, it may be underdiagnosed.

8.1 Peripartum cardiomyopathy

PPCM has recently been reviewed[32,263,264] and the EURObservational Research Programme international PPCM registry will provide fundamental data on this condition.[265,266] Important predisposing factors include multiparity, African ethnicity, smoking, diabetes, pre-eclampsia, malnutrition, advanced age, and teenage pregnancy.[32,263] The cause is uncertain, but potential aetiologies include inflammation and angiogenic imbalance, inducing vascular damage.[267–270] The biologically active 16 kDa prolactin and other factors, such as soluble fms-like tyrosine kinase 1 (sFlt1), may initiate and drive PPCM.[268,271,272]

8.1.1 Diagnosis

PPCM presents with HF secondary to LV systolic dysfunction towards the end of pregnancy and in the months following delivery, with the majority diagnosed post-partum. Careful history taking is necessary to identify and exclude other causes of HF.[273–276] The LV may be non-dilated, but the EF is usually <45%.[32,263,270] Symptoms and signs are often typical for HF with numerous phenotypes reported. Patients frequently present with acute HF, but also with ventricular arrhythmias and/or cardiac arrest.[277–280] Echocardiography is the imaging modality of choice. Initial LVEF <30%, marked LV dilatation (LV end-diastolic diameter ≥6.0 cm), and RV involvement are associated with adverse outcomes.[278,281,282]

8.1.2 Prognosis and counselling

Prospective larger cohort studies have mainly focused on 6 month outcomes, reporting a mortality ranging from 2.0% in Germany[277] to 12.6% in a large cohort of 206 patients with PPCM from South Africa.[283] A prospective study over 24 months from Turkey reported a 24% mortality.[284] When the EF has not recovered to >50–55%, subsequent pregnancy should be discouraged. Even with normalized EF, counselling is required due to potential recurrence. With expert interdisciplinary management and immediate bromocriptine treatment post-delivery, successful subsequent pregnancies, especially in patients with recovered EF, have been reported.[285]

8.2 Dilated cardiomyopathy

DCM encompasses a number of conditions resulting in LV dilatation and dysfunction including prior viral infection, drugs, and ischaemia. Some 50% of cases are idiopathic, of which 20–35% are hereditary.[276] Around 40% of the genetic causes of DCM have been identified, with >50 gene mutations described.[286] The prevalence of idiopathic DCM is 1:2500; however, this is likely an underestimate.[287]

Downloaded from https://academic.oup.com/eurheartj/article-abstract/39/34/3165/5078465 by guest on 13 September 2018

Patients may already be known to have DCM, or may present *de novo* during pregnancy. Distinguishing symptoms and signs of normal pregnancy from HF demands careful attention. Although PPCM and DCM are distinct disease entities, patients may share a genetic predisposition, and differentiation during pregnancy may be impossible.[273–276,287]

8.2.1 Prognosis and counselling

Pregnancy is poorly tolerated in some women with pre-existing DCM, with the potential for significant deterioration in LV function.[29] Predictors of maternal mortality are NYHA class III/IV and EF <40%.[288] Highly adverse risk factors include EF <20%, MR, RV failure, AF, and/or hypotension. All patients with DCM planning pregnancy require appropriate counselling and joint multidisciplinary care, as there is a high-risk of irreversible deterioration in ventricular function, maternal mortality, and foetal loss.

Pre-pregnancy management includes the modification of existing HF medications to avoid foetal harm. Angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), angiotensin receptor neprilysin inhibitors (ARNIs), mineralocorticoid receptor antagonists (MRAs), and ivabradine are contraindicated and should be stopped prior to conception, with close clinical and echocardiographic monitoring. However, beta-blockers should be continued and switched to beta-1-selective blockers (see section 12). If EF falls, then further discussion should occur, reconsidering the safety of pregnancy. If contraindicated drugs have been inadvertently taken during the first trimester, they should be stopped, and the patient monitored closely with maternal echocardiography and foetal ultrasound.

8.3 Management of heart failure during and after pregnancy

Assessment and management of pregnant patients with DCM or PPCM depends upon the clinical setting. However, all require joint cardiac and obstetric care, serial echocardiograms, serum B-type natriuretic peptide, and foetal ultrasound.[46]

8.3.1 Acute/subacute heart failure and cardiogenic shock during or after pregnancy

HF in DCM or PPCM can develop rapidly and Guidelines for the management of acute HF and cardiogenic shock apply.[286,289] For rapid diagnosis and decision-making, a pre-specified management algorithm and expert interdisciplinary team are crucial (*Figures 5 and 6*).[279,290]

8.3.1.1 Haemodynamic instability and cardiogenic shock

If a patient is in cardiogenic shock or dependent on inotropes or vasopressors, she should be transferred early to a facility where mechanical circulatory support teams are available.[279,289] Urgent delivery by caesarean section (irrespective of gestation) should be considered with mechanical circulatory support immediately available. PPCM patients

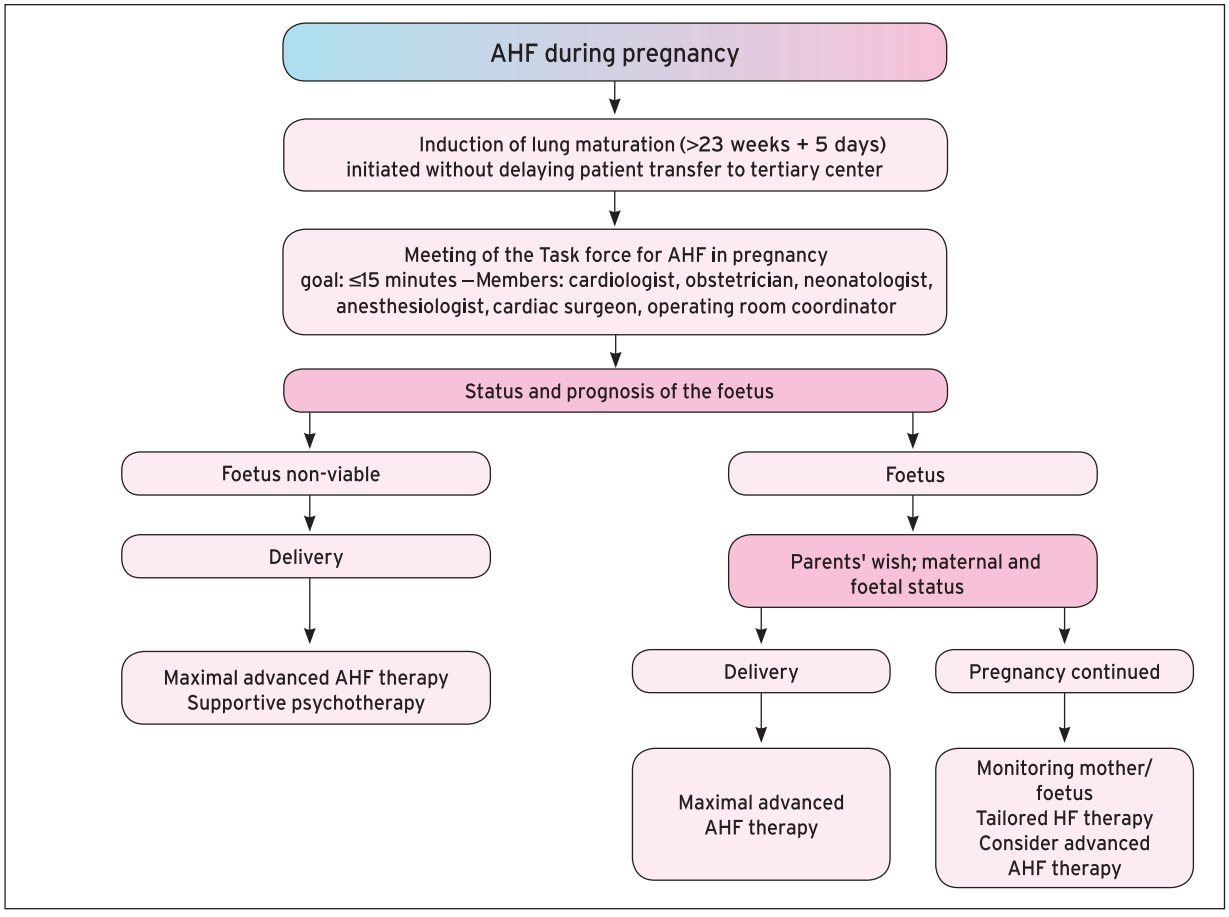

Figure 5 Management of acute heart failure during pregnancy: rapid interdisciplinary workup and treatment of mother and foetus (modified from Bauersachs *et al.*[280]). AHF = acute heart failure; HF = heart failure.

Downloaded from https://academic.oup.com/eurheartj/article-abstract/39/34/3165/5078465 by guest on 13 September 2018

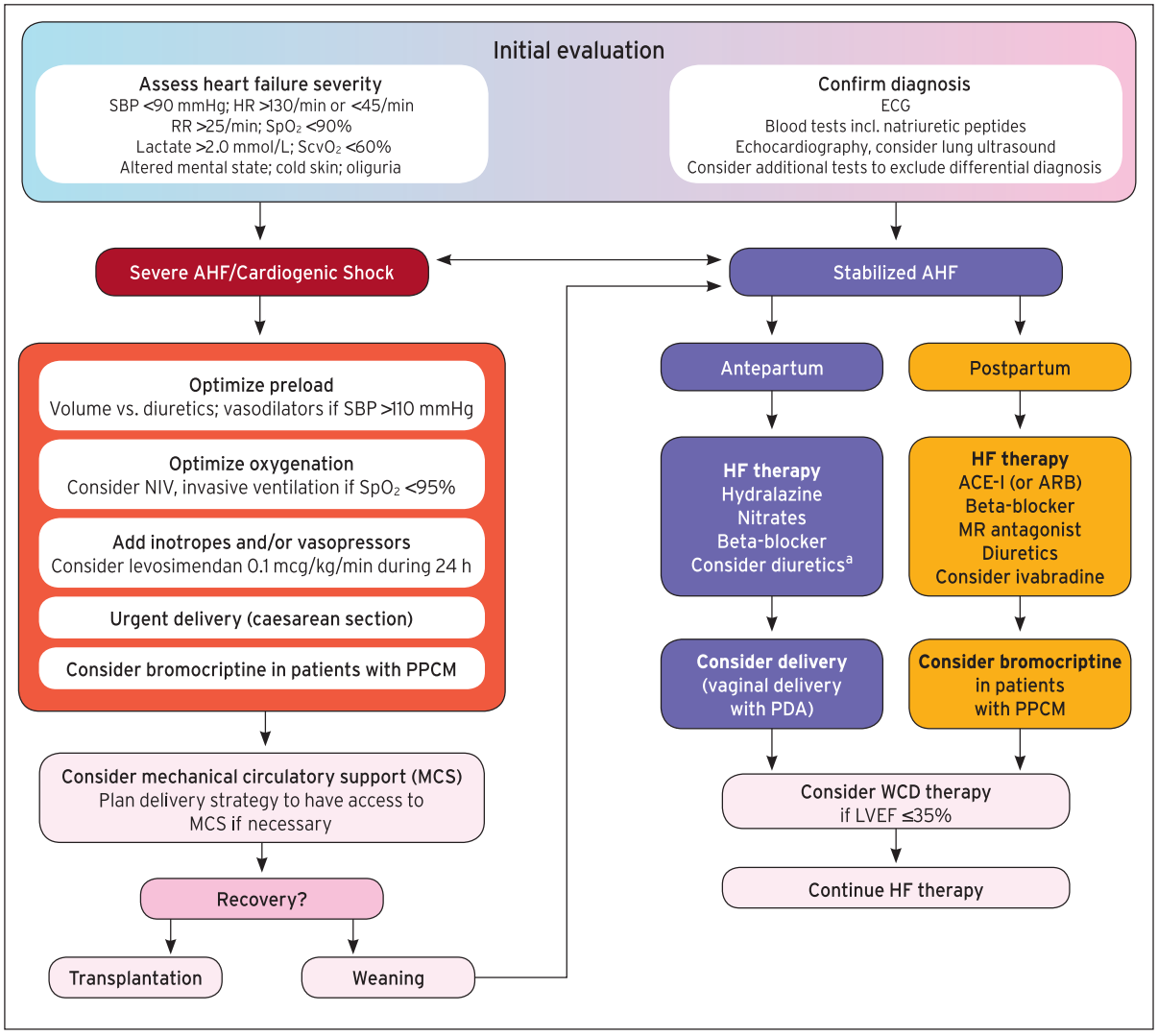

Figure 6 Management of acute heart failure during/after pregnancy (modified from Bauersachs *et al.*[280]). [a]Diuretics have to be used with caution due to potential reduction in placental blood flow. ACE-I = angiotensin-converting enzyme inhibitor; AHF = acute heart failure; ARB = angiotensin receptor blocker; ECG = electrocardiogram; HF = heart failure; HR = heart rate; LVEF = left ventricular ejection fraction; MCS = mechanical circulatory support; MR = mineralocorticoid receptor; NIV = non-invasive ventilation; PDA = Peridural analgesia; PPCM = peripartum cardiomyopathy; RR = respiratory rate; SBP = systolic blood pressure; $ScvO_2$ = central venous oxygen saturation; SpO_2 = peripheral oxygen saturation; WCD = wearable cardioverter-defibrillator.

are sensitive to the toxic effects of beta-adrenergic agonists, which should be avoided whenever possible. Levosimendan may be the preferred inotrope.[279,291,292]

8.3.1.2 Acute/subacute heart failure

Patients with symptoms and signs of acute HF should be evaluated according to acute HF Guidelines.[289] Differential diagnoses include uncomplicated pregnancy, pulmonary oedema (pre-eclampsia/eclampsia), PE, pneumonia, and MI, all of which should be diagnosed or excluded using standard algorithms.

Management goals are similar to non-pregnant acute HF, while avoiding foetotoxic agents (ACE inhibitors, ARB, ARNI, MRA, and atenolol). HF with pulmonary congestion is treated with loop diuretics and thiazides if required; however, diuretics should be avoided in the absence of pulmonary congestion, due to the potential reduction in placental blood flow.[290] Hydralazine and nitrates appear safe in pregnancy, although with less evidence for benefit than ACE inhibitors, and should only be used in the presence of hypertension, severe LV dysfunction, and/or evidence of congestion in decompensated HF. Beta-blockers should be initiated cautiously and gradually uptitrated to the maximum tolerated dose[266,286] (details in section 12). High resting heart rate is a predictor of adverse outcome in PPCM, and treatment with ivabradine may be useful if the patient is not pregnant or breastfeeding.[283,293] Relapse of PPCM has been observed after rapid tapering of HF therapies, and therefore treatment should continue for at least 6 months after full recovery of LV function followed by gradual tapering.[264]

Downloaded from https://academic.oup.com/eurheartj/article-abstract/39/34/3165/5078465 by guest on 13 September 2018

8.3.2 Bromocriptine and peripartum cardiomyopathy

Addition of bromocriptine to standard HF therapy may improve LV recovery and clinical outcome in women with acute severe PPCM.[24,25,277,278,294] Bromocriptine (2.5 mg once daily) for at least 1 week may be considered in uncomplicated cases, whereas prolonged treatment (2.5 mg twice daily for 2 weeks, then 2.5 mg once daily for 6 weeks) may be considered in patients with EF <25% and/or cardiogenic shock. Bromocriptine treatment must always be accompanied by anticoagulation with heparin (LMWH or UFH), at least in prophylactic dosages.[25,294,295] The essential therapies for patients with acute PPCM have been summarized under the BOARD label: Bromocriptine, Oral heart failure therapies, Anticoagulants, vasoRelaxing agents, and Diuretics.[296]

8.3.3 Devices and transplantation

Given the high rate of improvement of LV function during optimal HF drug therapy, early implantation of an implantable cardioverter-defibrillator (ICD) in patients with newly diagnosed PPCM or DCM is not appropriate. A wearable cardioverter-defibrillator (WCD) may prevent sudden cardiac death (SCD) during the first 3–6 months after diagnosis, especially in patients with EF <35%, allowing protected recovery from severe LV impairment.[279,297] In severe LV dysfunction during the 6–12 months following first presentation despite optimal medical therapy, implantation of an ICD and cardiac resynchronization therapy (for patients with left bundle branch block and QRS >130ms) are recommended.[286,298] However, mortality reduction in those with non-ischaemic cardiomyopathy is uncertain.[299]

Cardiac transplantation is reserved for patients where mechanical circulatory support is not possible or desirable, or for patients who do not recover after 6–12 months. Patients with PPCM have higher rates of graft failure and death after heart transplantation.[300]

8.3.3.1 Pregnancy post-cardiac transplantation

Despite successful pregnancies post-cardiac transplantation, data are limited. Multidisciplinary team management is required relating to the timing and management of pregnancy.[301] Pre-conception counselling includes the risks of graft rejection and dysfunction, infection, and the teratogenicity of immunosuppressive agents. Some centres recommend human leucocyte antigen testing prior to conception. If the donated heart and father have the same human leucocyte antigen, and the recipient has donor-specific antigens, the risk of autograft rejection is high.[302] PPCM recurrence rates in transplanted patients are unknown. However, as rejection risk in these patients is higher in the first year post-transplant and graft survival is shorter, many advise against pregnancy in such patients.[303]

Pregnancy should be avoided for at least 1 year post-transplantation, and discouraged in patients at high-risk of rejection and/or with poor baseline graft function before pregnancy.[303–305] Besides graft rejection or dysfunction and infection, hypertension is the most common maternal complication. Additional increased risks include hyperemesis and thrombo-embolic disease.[301] All immunosuppressive medications enter the foetal circulation, thus the management of immunosuppression in the pregnant post-transplant recipient is highly specialized.[301] As all immunosuppressive agents are excreted into breast milk with unknown long-term effects, the International Society for Heart and Lung Transplantation currently recommends against breastfeeding.[303]

8.3.4 Anticoagulation

Standard indications for anticoagulation in PPCM and DCM apply during and after pregnancy. The choice of anticoagulant agent depends upon the stage of pregnancy and patient preference (see section 12 and *Table 7*).[9,306] In PPCM patients with very low EF, prophylactic anticoagulation should be considered.[263]

8.3.5 Delivery and breastfeeding

Urgent delivery irrespective of gestation duration should be considered in women with advanced HF and haemodynamic instability despite treatment.[279] Caesarean section is recommended with central neuraxial anaesthesia. To prevent abrupt pressure or volume changes, epidural anaesthesia might be the method of choice but should be carefully titrated, guided by an expert anaesthetic team.[279,290] In stable congestive HF, vaginal delivery is preferred with spinal/epidural analgesia.

In HF with reduced EF (HFrEF), breastfeeding is discouraged in more severe cases (e.g. NYHA III/IV). Stopping lactation reduces the high metabolic demand and enables early optimal HF treatment.[24] For drug treatment during breastfeeding see section 12.

8.4 Hypertrophic cardiomyopathy

The true prevalence of HCM in different populations is a topic of debate, but a number of methodologically diverse studies in North America, Europe, Asia, and Africa have reported a prevalence of unexplained increase in LV thickness in the range of 0.02–0.23% in adults.[65] The observed incidence of HCM in pregnancy is <1:1000.[65,307]

Women with HCM usually tolerate pregnancy well. In a recent meta-analysis, maternal mortality was 0.5%, and complication or worsening of symptoms occurred in 29% of cases. Foetal mortality by spontaneous abortion (15%), therapeutic abortion (5%), or stillbirth (2%) is comparable to the general population; however, the risk of premature birth is increased (26%).[308,309] Risk is increased where women are symptomatic pre-pregnancy or exhibit a high-risk profile, including diastolic dysfunction, severe LV outflow tract obstruction, and arrhythmia.[310,311] Medication in the pre-pregnancy period, and a CARPREG or ZAHARA score ≥1, are risk factors for pregnancy/post-partum cardiac events.[312] Symptoms are typical for HF with pulmonary congestion and echocardiography is usually diagnostic.

8.4.1 Management

Women in WHO class II should be assessed each trimester, and those in class III assessed monthly or bimonthly.[9] Beta-blockers should be continued if they are already being taken (see section 12). They should be started when new symptoms occur, for rate control in AF, and to suppress ventricular arrhythmias, with verapamil as second choices when beta-blockers are not tolerated (with foetal monitoring for AV block).[65,313]

Cardioversion should be considered for poorly tolerated persistent AF.[314] Therapeutic anticoagulation is recommended for those with paroxysmal or persistent arrhythmias. Hypovolaemia is poorly tolerated. Patients with a past history or family history of sudden death need close surveillance with prompt investigation if they develop symptoms of palpitations or presyncope. When indicated, a device should be implanted [315,316]

Downloaded from https://academic.oup.com/eurheartj/article-abstract/39/34/3165/5078465 by guest on 13 September 2018

8.4.2 Delivery

Low-risk cases may have a spontaneous labour and vaginal delivery. Caesarean section should be considered in patients with severe LV outflow tract obstruction, pre-term labour while on OACs, or severe HF.[9] Epidural and spinal anaesthesia must be applied cautiously, especially with severe LV outflow tract obstruction, because of potential hypovolaemia, and single-shot spinal anaesthesia avoided.

During delivery, monitoring of heart rate and rhythm should be considered in patients with a high-risk of developing arrhythmias. Oxytocin should be given as a slow infusion and any i.v. fluids given judiciously.[9,317]

8.5 Recommendations

Recommendations for the management of cardiomyopathies and heart failure

Recommendations	Class[a]	Level[b]
Anticoagulation is recommended in patients with intracardiac thrombus detected by imaging or with evidence of systemic embolism.[286]	I	A
It is recommended to treat women with HF during pregnancy according to current guidelines for non-pregnant patients, respecting contraindications for some drugs in pregnancy[263](see *Table 7*).	I	B
It is recommended to inform women with HFrEF about the risk of deterioration of the condition during gestation and peripartum.[29]	I	C
Therapeutic anticoagulation with LMWH or vitamin K antagonists according to the stage of pregnancy is recommended for patients with atrial fibrillation.	I	C
In HFrEF, it is recommended that beta-blockers are continued in women who used them before pregnancy or are installed with caution, if clinically indicated.	I	C
In patients with PPCM and DCM, counselling for recurrence risk during subsequent pregnancy is recommended in all cases, even after recovery of LV function.	I	C
As rapid diagnosis and decision-making is crucial for all pregnant women with acute HF, a pre-specified management algorithm and an interdisciplinary team should be established.[279,290]	IIa	C
Patients in cardiogenic shock/dependent on inotropes should be transferred early to a facility where mechanical circulatory support is available.	IIa	C
Bromocriptine treatment should be accompanied by prophylactic (or therapeutic) anticoagulation.	IIa	C
Due to the high metabolic demands of lactation and breastfeeding, preventing lactation may be considered in patients with severe HF.[24]	IIb	B
In patients with PPCM, bromocriptine treatment may be considered to stop lactation and enhance recovery (LV function).	IIb	B
In women with PPCM and DCM, subsequent pregnancy is not recommended if LVEF does not normalize.[285]	III	C
HCM		
In patients with HCM, the same risk stratifications as for non-pregnant women are recommended.[313]	I	C
In patients with HCM, it is recommended that beta-blockers are continued in women who used them before pregnancy.[313]	I	C
In patients with HCM, beta-blockers should be started in women who develop symptoms due to outflow tract obstruction or arrhythmia during pregnancy.	IIa	C
In HCM, cardioversion should be considered for persistent atrial fibrillation.[306]	IIa	C

DCM = dilated cardiomyopathy; HCM = hypertrophic cardiomyopathy; HF = heart failure; HFrEF = heart failure with reduced ejection fraction; LMWH = low molecular weight heparin; LV = left ventricular; LVEF = left ventricular ejection fraction; PPCM = peripartum cardiomyopathy.
[a]Class of recommendation.
[b]Level of evidence.

© ESC 2018

Downloaded from https://academic.oup.com/eurheartj/article-abstract/39/34/3165/5078465 by guest on 13 September 2018

9. Arrhythmias

9.1 Introduction

Tachyarrhythmias, particularly AF,[318,319] may manifest for the first time and become more frequent during pregnancy, especially in older women[318,320] and in women with congenital heart disease.[41,321] AF (27/100 000) and paroxysmal supraventricular tachycardia (PSVT) (22 - 24/100 000) are, apart from premature beats, the most frequent arrhythmias.[318] Symptomatic exacerbations of PSVT[322] are usually benign and can be medically treated effectively.[12] Life-threatening VT and ventricular fibrillation are very rare during pregnancy,[318] as are bradyarrhythmias and conduction disturbances.

9.2 Maternal risk

AF is associated with an increased mortality risk[318] [odds ratio (OR) 13.13, 95% CI 7.77–22.21; P <0.0001], and a rapid ventricular response can lead to serious haemodynamic consequences for both the mother and the foetus. Diagnosis and treatment of underlying conditions are the first priorities. Patients with a known history of any symptomatic supraventricular tachycardia (SVT) or VT should be considered for catheter ablation prior to pregnancy.

SCD is recognized as an increasing risk factor in pregnancy and therefore cascade screening for channelopathies with genetic counselling[2,3,72] is important. Women with congenital LQTS are at substantial risk of cardiac events during the post-partum period.[323] New-onset VT warrants the exclusion of underlying structural heart disease,[324] as it is associated with increased risk of SCD for the mother (OR 40.89, 95% CI 26.08–64.1; P <0.0001).[318]

Bradyarrhythmias and conduction disturbances usually have a favourable outcome in the absence of underlying heart disease.

9.3 Obstetric and offspring risk

Pregnant PSVT subjects have worse obstetric and foetal outcomes, with higher adjusted ORs (1.54–3.52) for severe maternal morbidity, caesarean delivery, low birth weight, pre-term labour, foetal stress, and foetal abnormalities than those without PSVT.[325] Women with congenital heart disease are more likely to die during admission for delivery than those without (OR 6.7), arrhythmia being the most frequent cardiovascular event.[321] Recommendations for optimal surveillance levels during delivery for women with arrhythmias are outlined in 'Recommendations for the management of arrhythmias'.

9.4 Supraventricular tachycardia

Recommendations for acute termination of PSVT (AV nodal re-entry tachycardia and AV re-entry tachycardia)[326] are outlined in 'Recommendations for the management of arrhythmias' below. The i.v. administration of adenosine is recommended as the first drug of choice for acute conversion of PSVT (see table 'Recommendations for the management of arrhythmias').

For the prevention of PSVT, beta-blockers (except atenolol) or verapamil are first-line agents, except for patients with Wolff–Parkinson–White syndrome (see section 12).[12,32,327,328] The use of preventive drug therapy should be related to the severity of symptoms and haemodynamic compromise during tachycardia.

Focal atrial tachycardia (AT) can be associated with drug resistance and tachycardia-induced cardiomyopathy. Adenosine may aid in diagnosis and terminates focal AT in 30% of cases. AV nodal blocking drugs are recommended for long-term rate control. Flecainide, propafenone (in the absence of ischaemic heart disease), or sotalol should be considered for rhythm control if these agents fail (see *Table 7*).[12]

9.5 Atrial fibrillation and atrial flutter

Electrical cardioversion is recommended whenever ongoing AF is haemodynamically unstable or a considerable risk for the mother or the foetus.[306] Delivery of i.v. butilide or flecainide may be considered for the termination of atrial flutter and AF in stable patients with structurally normal hearts.[12,329] Cardioversion should generally be preceded by anticoagulation (see below).[306] The use of i.v. beta-blockers is recommended for rate control.

Rhythm control should be considered as the preferred treatment strategy during pregnancy, starting with a beta-blocker as the first option.[306] In the case of a rate control strategy, an oral beta-blocker is recommended (see *Table 7*).

Episodes of atrial flutter are usually not well tolerated in patients with congenital heart disease and electrical cardioversion should therefore be performed to restore sinus rhythm.[12] Beta-blockers, class I antiarrhythmic drugs, and sotalol should be used with caution if systemic ventricular function is impaired (see section 8).

9.5.1 Anticoagulation

The same rules for stroke risk stratification should be used as in non-pregnant patients.[306] Non-vitamin K oral anticoagulation drugs are prohibited during pregnancy (see *Table 7*).

9.6 Ventricular tachycardia

Inherited arrhythmogenic disorders should always be looked for with appropriate diagnostic tests during or after pregnancy.[72] PPCM should be ruled out in the case of new-onset VT during the last 6 weeks of pregnancy or in the early post-partum period.[266]

Recommendations for acute termination of VT[72] are outlined in 'Recommendations for the management of arrhythmias'.

The choice of prophylactic antiarrhythmic drug therapy relates to the presence of underlying structural heart disease and LV function

Downloaded from https://academic.oup.com/eurheartj/article-abstract/39/34/3165/5078465 by guest on 13 September 2018

(see table 'Recommendations for the management of arrhythmias'). Idiopathic RV outflow tract tachycardia is the most frequent VT type and may require prophylactic treatment with a beta-blocker, verapamil, or other antiarrhythmic drugs, and even catheter ablation if drug treatment fails.

ICD implantation is recommended if an indication emerges during pregnancy (see table 'Recommendations for the management of arrhythmias').[72,330,331] Implantation of an ICD in PPCM patients with VT or low EF should follow ESC Guidelines,[72] considering the relatively high rate (50%) of spontaneous recovery after delivery. Non-selective beta-blockers should be continued throughout pregnancy and during the post-partum period (at least 40 weeks after delivery)[323] in patients with congenital LQTS[332] and those with catecholaminergic polymorphic VT.[72,333] Exceptions may be LQTS patients without prior syncope or torsade de pointes (TdP), or any other risk profile, for whom a selective beta-blocker may be chosen. Management of cardiac arrest in pregnancy is described elsewhere.[256]

9.7 Bradyarrhythmias

9.7.1 Sinus node dysfunction

Rare cases of sinus bradycardia may be related to the supine hypotensive syndrome of pregnancy. Symptomatic bradycardia should be managed by changing the position of the mother to a left lateral decubitus position. For persistent symptoms, a temporary pacemaker may be necessary.

9.7.2 Atrioventricular block

Isolated congenital complete heart block in the mother has a favourable outcome during pregnancy, especially when the escape rhythm has a narrow QRS complex.[334,335] Temporary ventricular pacing during delivery is unnecessary in stable patients with complete heart block,[334] but recommended in selected women with symptoms due to the risk of bradycardia and syncope.

9.8 Interventions

9.8.1 Electrical cardioversion

Cardioversion seems safe in all phases of pregnancy as it does not compromise foetal blood flow,[336] and the risk of inducing foetal arrhythmias or initiating pre-term labour seems small.[337,338] The foetal heart rate should routinely be controlled after cardioversion.[339]

9.8.2 Catheter ablation

Catheter ablation should be postponed to the second trimester if possible, and performed at an experienced centre using non-fluoroscopic electroanatomical mapping and catheter navigation systems.[15,16] Catheter ablation of recurrent drug-refractory AV nodal re-entry tachycardia, AV re-entrant tachycardia, focal ATs, cavotricuspid isthmus-dependent atrial flutter, and certain benign right-sided VTs may be considered for ablation to avoid potentially harmful medications during pregnancy (see table 'Recommendations for the management of arrhythmias'),[12,15,17] but has no role for other macroreentry tachycardias or AF.[15,17]

9.8.3 Implantable cardioverter-defibrillator and pacing

The implantation of an ICD should be considered prior to pregnancy in patients with high-risk factors for SCD.[72,340] Treatment with an ICD during pregnancy does not cause an increased risk of major ICD-related complications and is recommended if an indication emerges (see table 'Recommendations for the management of arrhythmias').[330,340] Safety considerations regarding radiation during ICD implantation are similar to those discussed for catheter ablation. Subcutaneous ICD is limited by a lack of pacing capability and a higher risk of inappropriate shock, which may warrant ICD inactivation during delivery.[341,342] The use of WDCs in PPCM patients is limited[343] and deserves further study as it has not undergone clinical testing in pregnant patients. Routine ICD interrogation and advice is recommended prior to delivery.

Implantations, for ICD preferably one chamber, can be performed safely, especially if the foetus is beyond 8 weeks of gestation. Echocardiographic guidance or electroanatomical mapping may be helpful.[344]

Downloaded from https://academic.oup.com/eurheartj/article-abstract/39/34/3165/5078465 by guest on 13 September 2018

Table 6 Recommended surveillance levels at time of delivery in women with arrhythmias

Risk for arrhythmia with haemodynamic compromise at delivery		Level of surveillance[a]	Class[b]	Level[c]
Low-risk	PSVT, AF, idiopathic VT, low-risk LQTS, WPW syndrome	1	I	C
Medium-risk	Unstable SVT, VT, those with an implanted ICD, VT and structural heart disease, Brugada syndrome; moderate risk: LQTS, catecholaminergic polymorphic VT	2	I	C
High-risk for life threatening arrhythmia	Unstable VT in structural heart disease/congenital heart disease, unstable VT/TdP in high-risk LQTS patients, short QT syndrome, high-risk catecholaminergic polymorphic VT	3	I	C

Descriptions of actions to be planned	Surveillance level		
	Low 1	Medium 2	High 3
Consult cardiologist	×		
Consultation with multidisciplinary team including arrhythmologists at specialized centre		×	×
Mode and location of delivery as advised by obstetricians	×	×	
Caesarean delivery recommended			×
Monitor cardiac rhythm (telemetry, external rhythm monitor)		(×)	×
Intravenous line		×	×
Arterial line			×
Prepare for intravenous administration of adenosine		×	
Prepare for intravenous administration of a beta-blocker		×	×
Prepare for intravenous administration of selected antiarrhythmic drugs			×
External cardioverter defibrillator at site		×	×
Delivery at thoracic operating theatre			×
Prepare for transfer to cardiac intensive care unit post-partum if needed			×

This table has been developed by expert consensus.
AF = atrial fibrillation; ICD = implantable cardioverter-defibrillator; LQTS = long QT syndrome; PSVT = paroxysmal supraventricular tachycardia; SVT = supraventricular tachycardia; TdP = torsade de pointes; VT = ventricular tachycardia; WPW = Wolfe-Parkinson-White.
[a]The risk stratification should follow published Guidelines for the particular disease.
[b]Class of recommendation.
[c]Level of evidence.

© ESC 2018

Downloaded from https://academic.oup.com/eurheartj/article-abstract/39/34/3165/5078465 by guest on 13 September 2018

9.9 Recommendations

Recommendations for the management of arrhythmias

Recommendations	Class[a]	Level[b]
Acute management (intravenous administration of drugs) of SVT and AF		
Vagal manoeuvres and if these fails, adenosine are recommended for acute conversion of PSVT.[12,326,327]	I	C
Immediate electrical cardioversion is recommended for any tachycardia with haemodynamic instability and for pre-excited AF.[12,306,326,336–338]	I	C
Beta-1-selective blockers should be considered for acute conversion of PSVT.[12,326]	IIa	C
Ibutilide or flecainide may be considered for termination of atrial flutter and AF in stable patients with structurally normal hearts.[c] [12,329]	IIb	C
Long-term management (oral administration of drugs) of SVT and AF		
Beta-1-selective blockers or verapamil[d] is recommended for the prevention of SVT in patients without pre-excitation on resting ECG.[12,327]	I	C
Flecainide[e] or propafenone[e] are recommended for the prevention of SVT in patients with WPW syndrome.[12]	I	C
Beta-selective blockers are recommended for rate control of AT or AF.[12]	I	C
Flecainide[e], propafenone,[e] or sotalol[f] should be considered to prevent SVT, AT, and AF if AV nodal blocking agents fail.[12]	IIa	C
Digoxin[d] and verapamil[d] should be considered for rate control of AT or AF if beta-blockers fail.	IIa	C
Catheter ablation with electroanatomical systems should be considered in experienced centres in cases of drug-refractory and poorly tolerated SVT.[15–17]	IIa	C
Acute management (intravenous administration of drugs) of ventricular tachyarrhythmias		
Immediate electrical cardioversion is recommended for sustained both unstable and stable VT.[72,326,336–338]	I	C
For acute conversion of sustained, haemodynamically stable, monomorphic VT (e.g. idiopathic VT), a beta-blocker, sotalol,[f] flecainide,[e] procainamide, or overdrive ventricular pacing should be considered.[72]	IIa	C
Long-term management (oral administration of drugs) of ventricular tachyarrhythmias		
ICD (preferably one chamber) is recommended prior to pregnancy if clinically indicated. If indication emerges during pregnancy, ICD implantation is recommended using echocardiographic guidance or mapping, especially if the foetus is beyond 8 weeks of gestation.[72,330,340]	I	C
Beta-blocking agents are recommended during pregnancy and post-partum in patients with long QT syndrome or catecholaminergic polymorphic VT.[72,323]	I	C
Beta-blocking agents or verapamil[d,e] are recommended for the prevention of idiopathic sustained VT if associated with severe symptoms or haemodynamic compromise.[72,331]	I	C
In idiopathic sustained VT, sotalol[f] or flecainide[e] should be considered for prevention if other drugs fail.[72]	IIa	C
Catheter ablation with electroanatomical mapping systems may be considered in experienced centres in sustained drug-refractory and poorly tolerated VT if there are no other alternatives.[15–17]	IIb	C

AF = atrial fibrillation; AT = atrial tachycardia; AV = atrioventricular; ECG = electrocardiogram; ICD = implantable cardioverter-defibrillator; PSVT = paroxysmal supraventricular tachycardia; SVT = supraventricular tachycardia; TdP = torsade de pointes; VT = ventricular tachycardia; WPW = Wolff–Parkinson–White.

[a]Class of recommendation.

[b]Level of evidence.

[c]Cardioversion of AF and atrial flutter should generally be preceded by anticoagulation (see below).[306]

[d]AV nodal blocking agents should not be used in patients with pre-excitation on resting ECG or pre-excited AF.

[e]Flecainide and propafenone should be combined with AV nodal blocking agents for certain ATs, but structural heart disease, reduced left ventricular function, and bundle branch block should be excluded.

[f]Vaughan Williams class III antiarrhythmic drugs should not be used in patients with prolonged QTc.

© ESC 2018

Downloaded from https://academic.oup.com/eurheartj/article-abstract/39/34/3165/5078465 by guest on 13 September 2018

10. Hypertensive disorders

Hypertensive disorders in pregnancy are the most common medical complications, affecting 5–10% of pregnancies worldwide. They remain a major cause of maternal, foetal, and neonatal morbidity and mortality. Maternal risks include placental abruption, stroke, multiple organ failure, and disseminated intravascular coagulation. The foetus is at high-risk of intrauterine growth retardation (25% of cases of pre-eclampsia), pre-maturity (27% of cases of pre-eclampsia), and intrauterine death (4% of cases of pre-eclampsia).[345]

10.1 Diagnosis and risk assessment

Repeated BP readings should be performed, preferably on two occasions,[346] ≥15 min apart in severe hypertension (i.e. ≥160/110 mmHg in the obstetric literature).[9,347,348]

10.1.1 Blood pressure measurement

BP in pregnancy should be measured in the sitting position (or the left lateral recumbent during labour) with an appropriately-sized arm cuff at heart level and using Korotkoff V for diastolic BP (DBP). Mercury sphygmomanometers are still the gold standard for BP measurement in pregnancy. Automatic devices tend to under-record the true BP and are unreliable in severe pre-eclampsia. Therefore, only devices validated according to recognized protocols should be used in pregnancy.[349,350]

The diagnosis of hypertension in pregnancy by ambulatory BP monitoring (ABPM) is superior to routine BP measurement for the prediction of pregnancy outcome.[351,352] The devices used for ABPM are technically more accurate than those used for office or home BP measurement. ABPM avoids unnecessary treatment of white-coat hypertension, and is useful in the management of high-risk pregnant women with hypertension and those with diabetic or hypertensive nephropathy.

10.1.2 Laboratory tests

Basic laboratory investigations recommended for monitoring pregnant hypertensive patients include urinalysis, blood count, haematocrit, liver enzymes, serum creatinine, and serum uric acid (increased in clinically evident pre-eclampsia, hyperuricaemia in hypertensive pregnancies identifies women at increased risk of adverse maternal and foetal outcomes).[353]

All pregnant women should be assessed for proteinuria in early pregnancy to detect pre-existing renal disease and, in the second half of pregnancy, to screen for pre-eclampsia. A dipstick test of ≥1+ should prompt further investigations, including an albumin:creatinine ratio (ACR),[354] which can be quickly determined in a single spot urine sample. A value <30 mg/mmol can reliably rule out proteinuria in pregnancy,[355] but a positive test should possibly be followed by a 24 h urine collection. In cases of proteinuria >2 g/day, close monitoring is warranted. However, the result of a 24 h urine collection is often inaccurate[356] and delays the diagnosis of pre-eclampsia. Consequently, an ACR cut-off of 30 mg/mmol can be used to identify significant proteinuria.

In addition to basic laboratory tests, the following investigations may be considered:

- Ultrasound investigation of the adrenals, and plasma and urinary fractionated metanephrine assays in hypertensive pregnant women with a suggestive clinical presentation of pheochromocytoma in particular.
- Doppler ultrasound of uterine arteries (performed after 20 weeks of gestation) is useful to detect those at higher risk of gestational hypertension, pre-eclampsia, and intrauterine growth retardation.[357]
- An sFlt1 to placental growth factor (sFlt1:PlGF) ratio ≤38 can be used to exclude the development of pre-eclampsia in the next week when suspected clinically.[358,359]

10.2 Definition and classification of hypertension in pregnancy

The definition of hypertension in pregnancy is based only on office (or in-hospital) BP values [systolic BP (SBP) ≥140 mmHg and/or DBP ≥90 mmHg][360–362] and distinguishes mildly (140–159/90–109 mmHg) or severely (≥ 160/110 mmHg) elevated BP, in contrast to the grades used by the joint ESC/ESH Hypertension Guidelines.[348]

Hypertension in pregnancy is not a single entity but comprises:[9]

- **Pre-existing hypertension**: precedes pregnancy or develops before 20 weeks of gestation. It usually persists for more than 42 days post-partum and may be associated with proteinuria.
- **Gestational hypertension**: develops after 20 weeks of gestation and usually resolves within 42 days post-partum.
- **Pre-eclampsia**: gestational hypertension with significant proteinuria (>0.3 g/24 h or ACR ≥30 mg/mmol). It occurs more frequently during the first pregnancy, in multiple pregnancy, in hydatidiform mole, in antiphospholipid syndrome, or with pre-existing hypertension, renal disease, or diabetes. It is often associated with foetal growth restriction due to placental insufficiency and is a common cause of prematurity. The only cure is delivery.[363] As proteinuria may be a late manifestation of pre-eclampsia, it should be suspected when *de novo* hypertension is accompanied by headache, visual disturbances, abdominal pain, or abnormal laboratory tests, specifically low platelets and/or abnormal liver function.
- **Pre-existing hypertension plus superimposed gestational hypertension with proteinuria**.
- **Antenatally unclassifiable hypertension**: this term is used when BP is first recorded after 20 weeks of gestation and hypertension is diagnosed; re-assessment is necessary after 42 days post-partum.

10.3 Prevention of hypertension and pre-eclampsia

Women at high or moderate risk of pre-eclampsia should be advised to take 100–150 mg of aspirin daily from week 12 to weeks 36–37.[364,365]

Downloaded from https://academic.oup.com/eurheartj/article-abstract/39/34/3165/5078465 by guest on 13 September 2018

High risk of pre-eclampsia includes any of the following:

- hypertensive disease during a previous pregnancy
- chronic kidney disease
- autoimmune disease such as systemic lupus erythematosus or antiphospholipid syndrome
- type 1 or type 2 diabetes
- chronic hypertension.

Moderate risk of pre-eclampsia includes more than one of the following risk factors:

- first pregnancy
- age 40 years or older
- pregnancy interval of more than 10 years
- BMI of ≥35 kg/m^2 at first visit
- family history of pre-eclampsia
- multiple pregnancy.

Calcium supplementation (1.5–2 g/day, orally) is recommended for the prevention of pre-eclampsia in women with low dietary intake of calcium (<600 mg/day),[366] to be commenced at the first antenatal clinic.

Vitamins C and E do not decrease pre-eclampsia risk; on the contrary, they are more frequently associated with a birth weight <2.5 kg and adverse perinatal outcomes.[367–370]

10.4 Management of hypertension in pregnancy

10.4.1 Background

Management of hypertension in pregnancy depends on the BP, gestational age, and the presence of associated maternal and foetal risk factors.

Most women with pre-existing hypertension and normal renal function have non-severe hypertension (140–159/90–109 mmHg) and are at low-risk for cardiovascular complications. Some are able to withdraw their medication in the first half of pregnancy because of the physiological fall in BP.

Evidence-based data regarding treatment of hypertension in pregnancy are lacking. The only trial of treatment of hypertension in pregnancy with adequate infant follow-up (7.5 years) was performed 40 years ago with α-methyldopa.[371,372]

In terms of treatment benefit, tight vs. less-tight control of hypertension in pregnancy in the Control of Hypertension in Pregnancy Study was associated with less severe maternal hypertension, but no difference in the risk of adverse perinatal outcomes and overall serious maternal complications.[373] However, a secondary analysis of the data showed that women developing severe hypertension had higher rates of adverse maternal (pre-eclampsia, platelets <100 × 10^9/L, elevated liver enzymes with symptoms, and maternal length of hospital stay ≥10 days) and perinatal outcomes (perinatal death, high-level neonatal care for >48 h, birth weight <10th percentile, pre-eclampsia, and pre-term delivery).[374] Thus, there is no evidence currently supporting target BP values in pregnancy.[373,375]

10.4.2 Non-pharmacological management

Non-pharmacological management of hypertension during pregnancy has a limited role to play, with randomized studies of dietary and lifestyle interventions showing minimal effects on pregnancy outcome.[376] Regular exercise might be continued with caution and obese women (≥30 kg/m^2) are advised to avoid a weight gain of more than 6.8 kg.[377]

10.4.3 Pharmacological management

While the goal of treating hypertension is to reduce maternal risk, the agents selected must be effective and safe for the foetus.

10.4.3.1 Treatment of severe hypertension

There is no agreed definition of severe hypertension, with values ranging between 160–180 mmHg to >110 mmHg. This Task Force recommends considering an SBP ≥170 mmHg or DBP ≥110 mmHg in a pregnant woman an emergency, and hospitalization is indicated. The selection of the antihypertensive drug and its route of administration depend on the expected time of delivery. ACE inhibitors, ARBs, and direct renin inhibitors are strictly contraindicated (see section 12). Pharmacological treatment with i.v. labetalol, oral methyldopa, or nifedipine should be initiated; i.v. hydralazine is no longer the drug of choice as its use is associated with more perinatal adverse effects than other drugs.[378] However, hydralazine is still commonly used when other treatment regimens have failed to achieve adequate BP control as most obstetricians find its side effect profile acceptable.[379] Use of i.v. urapidil can also be considered. Sodium nitroprusside should only be used as the drug of last choice since prolonged treatment is associated with an increased risk of foetal cyanide poisoning.[51] The drug of choice when pre-eclampsia is associated with pulmonary oedema is nitroglycerin (glyceryl trinitrate), given as an i.v. infusion of 5 μg/min, and gradually increased every 3–5 min to a maximum dose of 100 μg/min.

10.4.3.2 Treatment of mild–moderate hypertension

Despite a lack of evidence, the European Guidelines[9,348,375] recommend *the initiation of drug treatment in all women with persistent elevation of BP ≥150/95 mmHg* and at values >140/90 mmHg in women with:

- gestational hypertension (with or without proteinuria)
- pre-existing hypertension with the superimposition of gestational hypertension
- hypertension with subclinical organ damage or symptoms at any time during pregnancy.

Methyldopa, beta-blockers (most data available for labetalol), and calcium antagonists (most data available for nifedipine) are the drugs of choice.[380,381] Beta-blockers appear to be less effective than calcium antagonists and may induce foetal bradycardia, growth retardation, and hypoglycaemia; consequently, their type and dose should be carefully selected, with atenolol best avoided (see section 12 and *Table 7*). Women with pre-existing hypertension may continue their current antihypertensive medication unless on ACE inhibitors, ARBs, and direct renin inhibitors, which are contraindicated due to adverse foetal and neonatal outcomes. The plasma volume is reduced in pre-eclampsia, therefore diuretic therapy is best avoided unless in the context of oliguria, when low-dose furosemide may be considered. Delivery of i.v. magnesium sulfate is recommended for the prevention of eclampsia and treatment of seizures, but should not be given concomitantly with CCBs (there is a risk of hypotension due to potential synergism).[382]

10.5 Delivery

Delivery is indicated in pre-eclampsia with visual disturbances or haemostatic disorders, and at 37 weeks in asymptomatic women.[383]

Downloaded from https://academic.oup.com/eurheartj/article-abstract/39/34/3165/5078465 by guest on 13 September 2018

10.6 Prognosis after pregnancy

10.6.1 Blood pressure post-partum

Post-partum hypertension is common in the first week. Methyldopa should be avoided because of the risk of post-partum depression.[384]

10.6.2 Hypertension and lactation

Breastfeeding does not increase BP in the nursing mother. Cabergoline, rather than bromocriptine, is recommended for lactation suppression. However, there is some evidence that bromocriptine might be beneficial in PPCM,[264] although it may induce hypertension.

All antihypertensive agents taken by the nursing mother are excreted into breast milk.[385] Most of the antihypertensive drugs are present at very low concentrations, except for propranolol and nifedipine, which have breast milk concentrations similar to those in maternal plasma.

10.6.3 Risk of recurrence of hypertensive disorders in a subsequent pregnancy

Women experiencing hypertension in their first pregnancy are at increased risk in a subsequent pregnancy. The earlier the onset of hypertension in the first pregnancy, the higher the risk of recurrence in a subsequent pregnancy.

10.6.4 Long-term cardiovascular consequences of gestational hypertension

Women who develop gestational hypertension or pre-eclampsia are at increased risk of hypertension, stroke, and ischaemic heart disease in later adult life.[386,387] Lifestyle modifications are primarily indicated to avoid complications in subsequent pregnancies and to reduce maternal cardiovascular risk in the future. Therefore, annual visits to a primary care physician to check BP and metabolic factors are recommended.

10.6.5 Fertility treatment

There is no clear evidence that fertility treatment increases the risk of hypertension or pre-eclampsia.[388]

10.7 Recommendations

Recommendations for the management of hypertension

Recommendations	Class[a]	Level[b]
Low-dose aspirin (100–150 mg daily) is recommended in women at high or moderate risk of pre-eclampsia from week 12 to weeks 36–37.[343,344]	I	A
In women with gestational hypertension or pre-existing hypertension superimposed by gestational hypertension, or with hypertension and subclinical organ damage or symptoms, initiation of drug treatment is recommended at SBP >140 mmHg or DBP >90 mmHg.[185] In all other cases, initiation of drug treatment is recommended if SBP ≥150 mmHg or DBP ≥95 mmHg.[348,375]	I	C
SBP ≥170 mmHg or DBP ≥110 mmHg in a pregnant woman is an emergency, and hospitalization is recommended.	I	C
Methyldopa (B), labetalol (C), and calcium antagonists (C) are recommended for the treatment of hypertension in pregnancy.[51,379,389]	I	B (methyldopa) C (labetalol and calcium antagonists)
In women with gestational hypertension or mild pre-eclampsia, delivery is recommended at 37 weeks.[383]	I	B
It is recommended to expedite delivery in pre-eclampsia and with adverse conditions such as visual disturbances or haemostatic disorders.	I	C
In pre-eclampsia associated with pulmonary oedema, nitroglycerin given as an intravenous infusion is recommended.[361]	I	C
In severe hypertension, drug treatment with intravenous labetalol, or oral methyldopa or nifedipine, is recommended.[51]	I	C
Limitation of weight gain to <6.8 kg should be considered in obese women.[377]	IIa	C
ACE inhibitors, ARBs, or direct renin inhibitors are not recommended.[51,185,361]	III	C

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; BP = blood pressure; DBP = diastolic blood pressure; SBP = systolic blood pressure.
[a]Class of recommendation.
[b]Level of evidence.

© ESC 2018

Downloaded from https://academic.oup.com/eurheartj/article-abstract/39/34/3165/5078465 by guest on 13 September 2018

11. Venous thrombo-embolic disease during pregnancy and the puerperium

11.1 Epidemiology and maternal risk

VTE, encompassing PE and deep vein/venous thrombosis (DVT), represents a significant cause of pregnancy-related morbidity and mortality. Pregnancy and the puerperium are associated with an increased incidence of VTE occurring in around 0.05–0.20% of all pregnancies,[390–393] and rates of PE of around 0.03%.[394,395] 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.[3] The case fatality rate is 3.5%.[396] The risk of VTE is highest in the immediate post-partum period with rates of nearly 0.5% reported,[394,397] and returns to the non-pregnant level after the sixth week post-partum.[390,394,397] In women with previous VTE, recurrence rates are 7.6%, and in a high-risk population rates are 5.5% despite the use of LMWH.[398,399] Consequently, a high index of suspicion and a low threshold for investigation must be maintained in pregnant women in general and in high-risk women specifically.

11.2 Risk factors for pregnancy-related venous thrombo-embolism and risk stratification

The presence of one risk factor increases the rate of VTE from 0.02 to 0.05%.[397,400] Consequently, all women should undergo a documented assessment of risk factors for VTE before pregnancy or in early pregnancy.[401] Based on this, women can be classified as being at high, intermediate, or low-risk of VTE and preventative measures applied accordingly.[401] Previous unprovoked recurrent VTEs and previous VTE—unprovoked or oestrogen-related—are considered high-risk factors.

11.3 Prevention of venous thrombo-embolism

Prospective, non-randomized studies have shown that in women with risk factors not receiving anticoagulation, the recurrence rate of VTE ranged from 2.4–12.2%, in comparison with 0–5.5% in patients who did receive anticoagulation.[399,402] LMWH has become the drug of choice for the prevention and treatment of VTE in pregnant patients.[13] It causes less bone loss than UFH, and the osteoporotic fracture rate is lower (0.04% of pregnant women treated with LMWH).[13] The initial dose of LMWH for thromboprophylaxis should be based on the booking weight (body weight at the first antenatal appointment with the gynaecologist, e.g. 8–10 weeks of pregnancy) since weight-based LMWH regimens have been shown to achieve prophylactic anti-Xa levels more effectively.[403] Consequently, patients at high-risk for VTE should receive prophylactic enoxaparin at 0.5 IU/kg of body weight once daily[403] or another LMWH at equivalent doses, according to local practice. In morbidly obese women, weight-based dosing instead of fixed dosing is more appropriate in order to achieve adequate anti-Xa concentrations.[404]

11.4 Management of acute venous thrombo-embolism

11.4.1 Pulmonary embolism

11.4.1.1 Clinical presentation

The symptoms and signs of PE during pregnancy are the same as in the non-pregnant state (dyspnoea, chest pain, tachycardia, haemoptysis, and collapse). However, subjective clinical assessment of PE is more difficult because dyspnoea and tachycardia are relatively common in normal pregnancy.

11.4.1.2 Diagnosis

Clinical prediction rules for assigning pre-test probabilities of VTE have been validated and diagnostic algorithms established in the non-pregnant patient. These include the use of D-dimer testing, compression ultrasonography, CT pulmonary angiography, and ventilation/perfusion lung scanning.[405] This is not the case in pregnant women.[406] A high index of suspicion is important, and all pregnant women with signs and symptoms suggestive of VTE should have objective testing performed urgently and receive therapeutic anticoagulation until the diagnosis is established.

D-dimer levels increase physiologically with each trimester. In one study, the mean [standard deviation (SD)] preconception D-dimer concentration was 0.43 (0.49) mg/L, and rose in the first, second, and third trimesters to 0.58 (SD 0.36), 0.83 (SD 0.46), and 1.16 (SD 0.57) mg/L, respectively, indicating a 39% relative increase in D-dimer concentration for each trimester.[407] Thus, a positive D-dimer test in pregnancy is not necessarily indicative of VTE and further objective testing is required. A negative D-dimer test helps to exclude VTE outside pregnancy, but normal D-dimer concentrations have been reported in pregnant women with VTE,[408] meaning that imaging remains the diagnostic test of choice during pregnancy.[409] Currently, the optimal diagnostic approach for the pregnant patient with suspected PE is uncertain.[410] A modified Wells score may be useful alone or in combination with D-dimer testing to stratify women into those needing imaging, allowing the remainder to avoid unnecessary radiation exposure,[411,412] but this awaits further study.

If the index of suspicion of DVT remains high, then compression ultrasound should be performed, and if this is abnormal then anticoagulation is indicated. If compression ultrasonography is negative, then further testing is required and MRI should be performed. Where PE is suspected and all other investigations are normal, low-dose CT should be undertaken.

1.4.1.3 Treatment

LMWH: LMWH has become the drug of choice for the treatment of VTE in pregnancy and the puerperium. In suspected DVT or PE, therapeutic LMWH should be given until the diagnosis is excluded by objective testing.

Dosage: 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.[413]

Downloaded from https://academic.oup.com/eurheartj/article-abstract/39/34/3165/5078465 by guest on 13 September 2018

Monitoring (see section 12).

UFH: Typically, UFH is used in the acute treatment of massive pulmonary emboli. For details on management, see section 12.

Thrombolysis: Thrombolytics should only be used in patients with severe hypotension or shock[405] (see section 12). When thrombolysis has been given, the loading dose of UFH should be omitted and an infusion started at a rate of 18 U/kg/h. After stabilization of the patient, UFH can be switched to LMWH.

Fondaparinux: Fondaparinux (7.5 mg once a day in normal-weight pregnant women) can be considered if there is an allergy or adverse response to LMWH (see section 12).

Vena cava filters: Indications for vena cava filters are the same as in non-pregnant patients. However, there is limited experience with their use and the risk associated with the procedure may be increased.[405,414]

Post-partum management: In patients with recent PE, prepartum heparin treatment should be restarted 6 h after a vaginal birth and 12 h after a caesarean delivery, if no significant bleeding has occurred, with subsequent overlap with VKAs for at least 5 days. VKAs may be started on the second day after delivery and continued for at least 3 months, or for 6 months if PE occurred late in pregnancy. The INR should be between 2 and 3 and needs regular monitoring, ideally every 1–2 weeks. VKAs do not enter the breast milk in active forms and are safe for nursing mothers.

11.4.2 Acute deep vein thrombosis

11.4.2.1 Clinical presentation

Leg swelling is a frequent finding in pregnancy, giving rise to the suspicion of DVT. Since DVT is left-sided in >85% of cases, due to compression of the left iliac vein by the left iliac artery and the gravid uterus, swelling of the left leg is more suspicious. Iliac vein thrombosis may manifest with isolated pain in the buttock, groin, flank, or abdomen. Three clinical variables-left leg presentation, >2 cm calf circumference difference, and first trimester-allowed a negative predictive value of 100% (95% CI 95.8–100%) if none of the three variables was present and ultrasound of the legs was negative.[415] However, this clinical decision rule needs to be validated in prospective studies.

11.4.2.2 Diagnosis

D-dimer: See section 11.4.1.2.

Compression ultrasound leg vein imaging: Compression ultrasound is the diagnostic imaging procedure of choice for suspected DVT in pregnancy with a high sensitivity and specificity for proximal DVT, but less so for distal and pelvic DVTs. Serial compression ultrasound evaluations at days 0, 3, and 7 in pregnancy give a high negative predictive value of 99.5% (95% CI 97–99%).[416] Women with a suspected DVT in pregnancy can be evaluated with D-dimer testing (see above) and compression ultrasonography. If a proximal DVT is detected, treatment should be continued. If the initial compression ultrasound is negative, then magnetic resonance venography may be considered to exclude a pelvic DVT. If the clinical suspicion is high and the initial compression ultrasonography negative, then anticoagulation should be continued and compression ultrasonography repeated on days 3 and 7. If the initial clinical suspicion is low, then anticoagulation can be stopped and compression ultrasonography repeated on days 3 and 7. If compression ultrasonography is persistently negative, a DVT can be excluded.

11.4.2.3 Treatment

In acute DVT, treatment with therapeutic doses of weight adjusted LMWH should be given twice daily (see treatment of PE).

11.5 Recommendations

11.5.1 Management of delivery

In women on therapeutic LMWH, delivery should be planned at around 39 weeks to avoid the risk of spontaneous labour while fully anticoagulated, as LMWH can only be partially reversed with protamine sulfate.

In high-risk women on therapeutic LMWH, LMWH should be converted to UFH at least 36 h prior to delivery and the infusion stopped some 4–6 hours prior to anticipated delivery. A normalized aPTT should guide the use of regional anaesthesia.

In low-risk women on therapeutic LMWH or women on high dose prophylaxis, assuming a typical twice-a-day regimen, the evening LMWH dose should be omitted and induction or caesarean section performed the next morning, with regional anaesthesia started more than 24 h after the last dose of LMWH and if no other drugs with impairment of coagulation are used.

Therapeutic anticoagulation is associated with an increased risk of post-partum haemorrhage, so the third stage of labour should always be actively managed with modified dose oxytocin. Recently, the effect of adding 2 IU oxytocin over 5 min to a standard treatment of low-dose infusion for 4 h [10 U of oxytocin in 500 mL of normal saline given i.v. at 36 mL/h for 4 h (12 mU/min)] was analysed. The addition of 2 IU of oxytocin was not associated with any greater derangement in cardiovascular measures, but with a significantly lower volume of blood loss.[105] We would advise using this regimen.

Downloaded from https://academic.oup.com/eurheartj/article-abstract/39/34/3165/5078465 by guest on 13 September 2018

Recommendations for the prevention and treatment of venous thrombo-embolism

Recommendations	Class[a]	Level[b]
LMWH is recommended for the prevention and treatment of VTE in pregnant patients.[13]	I	B
For high-risk women, it is recommended to give a weight-related prophylactic dose of LMWH (e.g. enoxaparin 0.5 mg/kg once daily).[13]	I	B
A documented assessment of risk factors for VTE before pregnancy or in early pregnancy is recommended in all women.[417]	I	C
It is recommended that the therapeutic dose of LMWH is based on body weight.[14]	I	C
Thrombolytics to manage patients with pulmonary embolism is only recommended in patients with severe hypotension or shock.[21]	I	C
In high-risk women, it is recommended to convert LMWH to UFH at least 36 h prior to delivery and stop the UFH infusion 4–6 h prior to anticipated delivery. aPTT should be normal before regional anaesthesia.[22]	I	C
In low-risk women on therapeutic LMWH, induction or caesarean section is recommended to be performed 24 h after the last dose of LMWH.[22]	I	C
For women after *in vitro* fertilization complicated by OHSS, thromboprophylaxis with LMWH is recommended during the first trimester.[418]	I	C
In women who are on antenatal anticoagulation, it should be considered to actively manage the third stage of labour with oxytocin.[105]	IIa	C
If compression ultrasound is negative, using magnetic resonance venography should be considered to diagnose pelvic thrombosis before using computed tomography pulmonary angiography or ventilation perfusion scanning.[18]	IIa	C
In women on therapeutic LMWH, planned delivery should be considered at around 39 weeks to avoid the risk of spontaneous labour while fully anticoagulated (LMWH is only partially reversed with protamine).[419]	IIa	C
Direct oral anticoagulants are not recommended in pregnancy.[420]	III	C

© ESC 2018

aPTT = activated partial thromboplastin time; LMWH = low molecular weight heparin; OHSS = ovarian hyperstimulation syndrome; UFH = unfractionated heparin; VTE = venous thrombo-embolism.
[a]Class of recommendation.
[b]Level of evidence.

12. Drugs during pregnancy and breastfeeding

12.1 General principles

This section summarizes all pertinent drugs and their potential use during pregnancy and breastfeeding. There are no uniform recommendations for the treatment of pregnant women yet. This also concerns the timing of treatment initiation and the selection of medications. Prescribing information for drugs on specific databases for pregnancy and lactation (for internet databases see section 12.3) should be consulted. As drug treatment in pregnancy concerns the mother and the foetus, optimum treatment of both must be targeted. Whether drug treatment is necessary is dependent on the urgency of the indication.

In case of emergency, drugs that are not recommended by international agencies for use during pregnancy and breastfeeding should not be withheld from the mother. The potential risk of a drug and the possible benefit of the therapy must be weighed against each other.

12.1.1 Pharmacokinetics in pregnancy

During pregnancy, profound physiological changes occur that potentially change the absorption, distribution, metabolism, and excretion of drugs.[36] The following list provides a summary of these changes:

Cardiovascular system, lungs and blood:

- increases in plasma volume, CO, stroke volume, and heart rate
- decreases in serum albumin concentration and serum colloid osmotic pressure
- increases in coagulation factors and fibrinogen
- compression of the inferior vena cava by the uterus
- increase in tidal volume and minute ventilation.

Liver, stomach, and intestines:

- changes in oxidative liver enzymes, such as increased activity of cytochrome P450 enzymes e.g. CYP2D6 and CYP3A4 nausea and vomiting
- delayed gastric emptying
- prolonged small bowel transit time
- gastrointestinal reflux.

Kidneys:

- increases in renal blood flow and glomerular filtration rate.

Different sources of evidence can be used for the risk classification of drugs applied during pregnancy.

Downloaded from https://academic.oup.com/eurheartj/article-abstract/39/34/3165/5078465 by guest on 13 September 2018

12.1.2 Drug classes in pregnancy

12.1.2.1 Anticoagulants

VKA and LMWH have advantages and disadvantages during pregnancy, which are also discussed in the sections related to specific indications. However, comparison between studies is hampered by reporting differences, and conclusions concerning the safety of low-dose VKA (warfarin <5 mg daily) in the current literature are controversial.[5,196,217,219,223,227] 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.[216,218,219,228] Substitution of a VKA with UFH or LMWH in weeks 6–12 almost eliminates the risk of embryopathy. 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.[217,219] 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.[216,219,223,228–230] Foetopathy has also been described with UFH but not with LMWH throughout pregnancy.[219,223] Vaginal delivery while the mother is on VKAs is contraindicated because of the risk of foetal intracranial bleeding.[228] Haemorrhagic complications in the mother occur with all regimens.[219]

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%).[13] In clinically suspected DVT or PE, therapeutic LMWH should be given until the diagnosis is excluded by objective testing.

Monitoring is essential in patients treated with LMWH with mechanical valves (see section 6), 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 U/mL),[224,421] 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.[396] 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.[225]

UFH does not cross the placenta either, but is associated with more thrombocytopenia (platelet levels should be measured every 2–3 days), osteoporosis, and more frequent dosing when given subcutaneously compared with LMWH. Typically, UFH is used in the acute treatment of massive pulmonary emboli. It is also used around the time of delivery if the maintenance of anticoagulation is critical and when the ability to reverse anticoagulation urgently using protamine is advantageous. In this circumstance, 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 complications.

12.1.2.2 Thrombolytics

Thrombolytics are considered to be relatively contraindicated during pregnancy and peripartum, and should only be used in high-risk patients with severe hypotension or shock.[405] The risk of haemorrhage, mostly from the genital tract, is around 8%.[422] There are more than 200 reported patients in whom streptokinase was mostly used and, more recently, recombinant tissue plasminogen activator (alteplase). Neither of these thrombolytics crosses the placenta in significant amounts. Foetal loss in 6% and pre-term delivery in 6% of cases were reported.[414] When thrombolysis is given, the loading dose of UFH should be omitted and an infusion started at a rate of 18 U/kg/h, and carefully adjusted according to the aPTT level. After stabilization of the patient, UFH can be switched to LMWH.

12.1.2.3 Factor Xa and thrombin inhibitors

No adequate, well-controlled studies in pregnant women are available.

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.[423] Its use can be considered if there is an allergy or adverse response to LMWH. One study showed minor transplacental passage of fondaparinux,[424] and more work is required to assess the risk of congenital malformations.

Rivaroxaban, a direct factor Xa inhibitor, crosses the placental barrier and therefore is not recommended in pregnancy. A systematic review of 137 pregnancies with pregnancy outcome data revealed a miscarriage rate of 23% (n = 31), elective terminations in 29% (n = 39) of cases, and possible embryopathy in 2.2% (n = 3) of cases.[425]

Most cases were on rivaroxaban, and in most pregnancies the duration of use was limited to the first trimester. Rivaroxaban is currently not recommended in pregnant patients. Other direct factor Xa inhibitors—such as apixaban, edoxaban, and the direct oral thrombin inhibitor dabigatran—should not be used in pregnant patients.

12.1.2.4 Beta-adrenergic blocking agents

Beta-adrenergic blocking agents are generally safe in pregnancy, but may be associated with increased rates of foetal growth restriction and also hypoglycaemia. Beta-1-selective drugs are preferred,[426] except in TdP (see section 9), as they are less likely to affect uterine contraction and peripheral vasodilation, and they have exhibited lower rates of foetal growth retardation.[427] Examples are metoprolol and bisoprolol. Unselective beta-blockers such as atenolol have been associated with higher rates of foetal growth retardation.[427,428] Among the alpha/beta-blockers, labetalol is a drug of choice for hypertension in pregnancy[380,381], and carvedilol used for HF therapy did not show any association with foetal growth retardation in a recently published small study with 13 patients receiving this drug.[427]

12.1.2.5 Renin–angiotensin–aldosterone system inhibitors: ACE inhibitors, ARBs, ARNIs, and aldosterone antagonists

ACE inhibitors and ARBs are teratogenic and contraindicated during pregnancy.[36] Renal or tubular dysplasia, renal failure, oligohydramnios, growth retardation, ossification disorders of the skull, lung hypoplasia, contractures, large joints, anaemia, and intrauterine foetal death have been described. In a systematic review, 48% of 118 foetuses exposed to ACE inhibitors and 87% of foetuses exposed to ARBs had complications related to the use of these medications.[36] These recommendations and data also apply to ARNIs (sacubitril/valsartan), since they contain ARBs.

Downloaded from https://academic.oup.com/eurheartj/article-abstract/39/34/3165/5078465 by guest on 13 September 2018

Spironolactone is not advised in humans during pregnancy.[36] Eplerenone has been associated with post-implantation losses at the highest administered doses in rabbits, and should only be used in pregnancy if clearly needed.

12.1.2.6 Calcium channel blockers

CCBs do not seem to be associated with an increased incidence of congenital anomalies in humans.[36] In one study with 721 pregnancies exposed to CCBs during the third trimester, an increased risk (relative risk 3.6, 95% CI 1.3–10.4) of neonatal seizures with CCBs was reported.[36,429] Diltiazem is teratogenic in animals and only limited data in humans exist; thus, its use is only recommended in pregnancy if the potential benefit justifies the potential risk to the foetus.[36] Verapamil is considered to be fairly safe during pregnancy, and is recommended as a second-line drug for rate control in AF and for the treatment of idiopathic sustained VTs in pregnant women.[36]

12.1.2.7 Statins

Statins should not be prescribed in pregnancy or during breastfeeding to treat hyperlipidaemia since their harmlessness is not proven. However, in a review published in 2012, no evidence of teratogenicity of statins was found, but a harmful effect could not be ruled out due to small sample sizes.[36,430] In a prospective case-control study of 249 foetuses exposed to statins, the rate of birth defects did not differ significantly between cases and controls.[36,431]

12.2 US Food and Drug Administration classification

On 30 June 2015, the US Food and Drug Administration (FDA) changed the previously used classification system for the counselling of pregnant women and nursing mothers requiring drug therapy.[432] The former A to X categories have been replaced by the Pregnancy and Lactation Labelling Rule (PLLR), which provides a descriptive risk summary and detailed information on animal and clinical data. PLLR applies immediately for prescription drugs approved after 30 June 2015, and the former FDA categories have to be removed for all other drugs until 29 June 2018. However, the former FDA categories will be present in the literature for a longer period of time, therefore *Table 7* provides information on both systems. For detailed up-to-date information on drugs used during pregnancy and breast feeding, please see the Supplementary Data/Web version of the guidelines. Detailed information can also be found on www.ema.europa.eu/, www.accessdata.fda.gov, http://www.embryotox.de, or from prescription labels provided by manufacturers.

The previous classification consisted of category A (safest) to X (known danger: do not use!). The following categories were used for drugs during pregnancy and breastfeeding, as outlined in the 2011 Guidelines.[9]

Category A: adequate and well-controlled studies have failed to demonstrate a foetal risk in the first trimester (and there is no evidence of risk in the later trimesters).

Category B: either animal reproduction studies have not demonstrated a foetal risk but there are no controlled studies in pregnant women, or animal reproduction studies have shown an adverse effect that was not confirmed in controlled studies in women.

Category C: either studies in animals have revealed adverse effects on the foetus and there are no controlled studies in women, or studies in women and animals are not available. Drugs should be given only if potential benefits justify the potential risk to the foetus.

Category D: there is evidence of human foetal risk, but the benefits from use in a pregnant woman may be acceptable despite the risk (e.g. treatment of life-threatening conditions).

Category X: studies in animals or humans have demonstrated foetal abnormalities, there is evidence of foetal risk based on human experience, or both, and the risk of drug use in pregnant women clearly outweighs any possible benefit. The drug is contraindicated in women who are or may become pregnant.

12.3 Internet databases

The authors of the database www.embryotox.de of the Pharmakovigilanz- und Beratungszentrum für Embryonaltoxikologie of the Berliner Betrieb für Zentrale Gesundheitliche Aufgabe base their recommendations on a combination of scientific sources, expert opinion that is mainly based on observational data, and personal experiences of women during pregnancy and breastfeeding.

The English database www.safefetus.com is arranged in a similar fashion to the German database.

12.4 Pharmaceutical industry

Manufacturers' instructions are mainly based on the fact that drugs are not tested sufficiently during pregnancy and breastfeeding. For this and for legal reasons, drugs are frequently considered prohibited during pregnancy and breastfeeding.

12.5 Recommendations

Recommendations for drug use in pregnancy

Recommendations	Class[a]	Level[b]
Before pharmacological treatment in pregnancy is started, it is recommended to check *Table 7* for clinical safety data.	I	C
In the absence of clinical safety data, it is recommended to check the electronic drug table (www.safefetus.com) for pre-clinical safety data.	I	C
In the absence of adequate human safety data, decision-making should be based on individual drug efficacy and safety profiles, and the available animal data, and the decision must be made together with the patient.	IIa	C
Decision-making based on former FDA categories alone is no longer recommended.[11]	III	C

FDA = US Food and Drug Administration.
[a]Class of recommendation.
[b]Level of evidence.

© ESC 2018

Downloaded from https://academic.oup.com/eurheartj/article-abstract/39/34/3165/5078465 by guest on 13 September 2018

Table 7 **Drugs and safety data**

Drugs	Classification (Vaughan Williams for antiarrhythmic drugs)	Former FDA category	Placenta permeable	Transfer to breast milk (foetal dose)	Pre-clinical/clinical safety data
Abciximab	Monoclonal antibody with antiplatelet effects	C	Unknown	Unknown	Inadequate human studies • use only if potential benefit outweighs potential risk Animal data: • no animal reproduction studies
ACE inhibitors[a]	ACE inhibitor	D	Yes	Yes[b] (maximum of 1.6%)	Contraindicated • renal or tubular dysplasia, oligohydramnios, growth retardation, ossification disorders of skull, lung hypoplasia, contractures, large joints, anaemia, intrauterine foetal death
Acenocoumarol	Vitamin K antagonist	D	Yes	Yes (no adverse effects reported)	Embryopathy (mainly first trimester), bleeding (see discussion in section 5)
Acetylsalicylic acid (low dose)	Antiplatelet drug	B	Yes	Well tolerated	No teratogenic effects • there is insufficient clinical experience regarding the use of doses between 100–500 mg/day
Adenosine[c]	Antiarrhythmic	C	No	No	No foetal adverse effects reported (limited human data)
Alirocumab	Lipid-lowering drug (monoclonal antibody)	-	Yes	Unknown	No human data: not recommended Animal data: • no adverse effects on foetal growth or development in rats and monkeys • maternal toxicity in rats • weaker secondary response to antigen challenge in the offspring of monkeys
Aliskiren	Renin inhibitor	D	Unknown	Yes (secreted in rat milk)	No use in first trimester; contraindicated in second and third trimesters • see other RAAS blockers Animal data: • no evidence of embryofoetal toxicity or teratogenicity at doses ≤600 mg/kg/day in rats or 100 mg/kg/day in rabbits • fertility, pre-natal development, and post-natal development were unaffected in rats at doses ≤250 mg/kg/day. The doses in rats and rabbits provided systemic exposures of 1–4× and 5× MRHD

Continued

Downloaded from https://academic.oup.com/eurheartj/article-abstract/39/34/3165/5078465 by guest on 13 September 2018

Ambrisentan	Endothelin receptor antagonist	X	Unknown	Unknown (contraindicated during breastfeeding)	Contraindicated • no human data Animal data: • teratogenic in rats (≥ 15 mg/kg/day) and rabbits (≥ 7 mg/kg/day). In both species, abnormalities of lower jaw, hard/ soft palate, heart and vascular malformation, thymus and thyroid abnormalities, ossification of the basisphenoid bone, displacement of the umbilical artery
Amiloride	Diuretic (potassium-sparing)	B	Yes	Yes (secreted in rat milk)	Inadequate human data Animal data: • no harm to foetus in teratogenicity studies in rabbits (20× RHD) and mice (25× RHD) • no impaired fertility in rats (20× RHD) • decreased rat pup growth and survival (5× or higher RHD)
Amiodarone	Antiarrhythmic (Class III)	`D	Yes	Yes	Thyroid insufficiency (9%), hyperthyroidism, goitre, bradycardia, growth retardation, premature birth
ARB (sartans)	ARB	D	Unknown	Unknown	Contraindicated • renal/tubular dysplasia, oligohydramnios, growth retardation, ossification disorders of skull, lung hypoplasia, contractures, large joints, anaemia, intrauterine foetal death
Penicillin, ampicillin, amoxicillin, erythromycin, mezlocillin, cephalosporins	Antibiotics	B	Yes	Yes	No foetal adverse effects reported
Vancomycin, imipenem, rifampicin, teicoplanin	Antibiotics	C	Unknown	Unknown	Limited data
Aminoglycosides, quinolones tetracyclines	Antibiotics	D	Unknown	Unknown	Foetal risk: use only when benefit outweighs risk
Apixaban	Anticoagulant	-	Transplacental passage in *ex vivo* studies of placental transfer	Extensive secretion into rat milk with the parent drug as the major component	No human data: not recommended Animal data: • no direct/indirect reproductive toxicity in animal studies • no foetal malformation in rodents • increased maternal bleeding incidence in rodents

Continued

Downloaded from https://academic.oup.com/eurheartj/article-abstract/39/34/3165/5078465 by guest on 13 September 2018

Atenolol[d]	Beta-blocker (Class II)	D	Yes	Yes	Hypospadias (first trimester), birth defects, low birth weight, bradycardia and hypoglycaemia in foetus (second and third trimesters)
Beraprost	Prostacyclin analogue	-	Unknown	Unknown	No human data
					Animal data: • no lethal or teratogenic effects in rats (<2.0 mg/kg/day) or rabbits (<1 mg/kg/day)
Bendroflumethiazide	Diuretic (thiazide)	C	Yes	Yes	Inadequate human data
Bisoprolol	Beta-blocker (Class II)	C	Yes	Yes	Foetal bradycardia and hypoglycaemia
Bosentan	Endothelin receptor antagonist	X	Unknown	Unknown	Contraindicated • no human data
					Animal data: • teratogenic in rats (≥ 60 mg/kg/day; 2× MRHD), malformations of the head, mouth, face, and large blood vessels; increased stillbirths and pup mortality (60/300 mg/kg/day; 2× and 10× MRHD) • no birth defects in rabbits (<1500 mg/kg/day)
Bumetanide	Diuretic (loop)	C	Unknown	Unknown	Inadequate human data
					Animal data: • in rodents, no teratogenicity with oral application • no teratogenic effects with i.v. application (rats/mice: 140× MRHD) • moderate growth retardation and increased incidence of delayed ossification of sternebrae in rats (at 3400× oral MRHD; not seen at 1000× oral MRHD)
Cangrelor	Antiplatelet drug	C	Unknown	Unknown	No human data • Animal data: • no malformations in rat or rabbit, no teratogenicity • foetal growth retardation in rats (at 5× less than the MRHD) • increased incidence of abortion and intrauterine losses, and foetal growth retardation in rabbits (12× MRHD)
Carvedilol	Αλπηα/βετα-blocker	C	Yes (data from rats; no human data available)	Yes • (data in rats, increased, no human data) • (increased mortality at 1 week post-partum in neonates from rats	No adequate human data • bradycardia and hypoglycaemia in foetus • use only if potential benefit outweighs potential risk
					Animal data: • increased post-implantation loss, decrease in foetal body weight, and delayed skeletal development in rats (50× MRHD). No developmental toxicity in rats at 10× MRHD

Continued

Downloaded from https://academic.oup.com/eurheartj/article-abstract/39/34/3165/5078465 by guest on 13 September 2018

				• treated with ≥10× MRHD last trimester through • day 22 of lactation)	• increased post-implantation loss in rabbits (25× MRHD). No developmental toxicity in rabbits at 5× MRHD
Clopidogrel	Antiplatelet drug	B	Unknown	Yes (secreted in rat milk)	No adequate human data
					Animal data: • no impaired fertility or foetotoxicity in rats (65× MRHD) and rabbits (78× MRHD)
Colestipol, cholestyramine	Lipid-lowering drugs	C	Unknown	Yes (lowering fat-soluble vitamins)	May impair absorption of fat-soluble vitamins, e.g. vitamin K → cerebral bleeding (neonatal)
Dabigatran	Anticoagulant	-	Transplacental passage in *ex vivo* studies of placental transfer	Unknown	No human data • use not recommend during pregnancy unless clearly necessary
					Animal data: • female fertility: decrease in implantations/increase in pre-implantation loss (plasma exposure five-fold higher compared with patients) • decrease in foetal body weight and embryofoetal viability in rodents (plasma exposure 5- to 10-fold higher compared with patients) • increased maternal bleeding (vaginal/uterine) in rodents
Danaparoid	Anticoagulant	B	No	No	Limited human data
					Animal data: • no impaired fertility or foetotoxicity in rats (8.7× RHD) and rabbits (6× RHD)
Digoxin[e]	Cardiac glycoside	C	Yes	Yes[b]	Serum levels unreliable, safe
Dihydralazine	Vasodilator	–	Unknown	Yes	Maternal side effects: reflex tachycardia, headache, tachyphylaxis • lupus-like symptoms (maternal/ foetal)
Diltiazem	Calcium channel blocker (Class IV)	C	No	Yes[b]	• possible teratogenic effects • use only when benefit outweighs risk
					Animal data: • embryo and foetal lethality in mice, rats, and rabbits (4–6× RHD), and abnormalities of the skeleton, heart, retina, and tongue • mice, rats, or rabbits: reductions in early individual pup weights and pup survival, prolonged delivery, and increased incidence of stillbirths

Continued

Downloaded from https://academic.oup.com/eurheartj/article-abstract/39/34/3165/5078465 by guest on 13 September 2018

Disopyramide	Antiarrhythmic (Class IA)	C	Yes	Yes[b]	Uterine contractions • use only when benefit outweighs risk
					Animal data: • no teratogenicity • decreased implantation sites, decreased pup growth and survival (20× RHD)
Dronedarone	Antiarrhythmic (Class III)	-	Yes (data from animals; no human data available)	Yes (data from animals; no human data available)	Not recommended: limited human data
					Animal data: • reproductive toxicity (post-implantation losses, reduced foetal and placental weights, and external, visceral and skeletal malformations)
Edoxaban	Anticoagulant	-	Unknown	Animal studies show excretion in breast milk; contraindicated in breastfeeding	Contraindicated: • human data: Hokusai-VTE study: 10 cases with exposure in first trimester, for up to 6 weeks. Results: six live births (four full term and two pre-term), one first trimester spontaneous abortion, and three elective terminations
					Animal data: • reproductive toxicity (gallbladder variations, increased post-implantation losses (49–65× MRHD) • vaginal haemorrhage at higher doses in rats/rabbits
Enoximone	Phosphodiesterase inhibitor	-	Unknown	Unknown	Inadequate human studies • use only if necessary
Eplerenone	Aldosterone antagonist	B	Unknown	Yes (data from animals; no human data available)	Inadequate human data • should be used during pregnancy only if clearly needed
					Animal data: • no teratogenic effects in rats or rabbits (exposures up to 32 and 31 times the human AUC, respectively); • decreased body weight in maternal rabbits • increased rabbit foetal resorptions and post-implantation loss at the highest administered dose
Epoprostenol	Prostacyclin analogue	B	Unknown	Unknown	Inadequate human data
					Animal data: • no impaired fertility or foetal harm in rats (2.5× RHD) and rabbits (4.8× RHD)
Evolocumab	Lipid-lowering drug (monoclonal antibody)	-	Yes (data in monkeys; no human data available)	Unknown	Inadequate human data • not recommended
					Animal data: • no adverse effects on foetal growth or development in monkeys • reduced T cell-dependent antibody response in monkeys immunized with KLH

Continued

Downloaded from https://academic.oup.com/eurheartj/article-abstract/39/34/3165/5078465 by guest on 13 September 2018

Ezetemibe	Lipid-lowering drug	-	Yes (data in rats and rabbits; no human data available)	Unknown (increased plasma concentration in nursing rat pups)	Inadequate human data • use only when benefit outweighs risk Animal data: • no evidence of embryolethal effects in rats and rabbits • increased incidence of common foetal skeletal findings in rats (at ~10× the human exposure at 10 mg/day) • increased incidence of extra thoracic ribs in rabbits (at 150× the human exposure at 10 mg/day) • combination with statins in rats and rabbits during organogenesis results in higher ezetimibe and statin exposure
Fenofibrate	Lipid-lowering drug	C	Yes	Yes	Inadequate human data • use only when benefit outweighs risk Animal data: • embryocidal and teratogenic in rats (7–10× MRHD) and embryocidal in rabbits (9× MRHD) • in rats (9× MRHD before and throughout gestation): delayed delivery, increased post-implantation loss, decreased litter size, decreased birth weight, 40% survival of pups at birth, 4% survival of pups as neonates, 0% survival of pups to weaning, increase in spina bifida • increase in foetal gross, visceral, and skeletal findings in rats (10× MRHD on day 6–15 of gestation) • delayed delivery, 40% decrease in live births, 75% decrease in neonatal survival, decreased pup weight in rats (7× MRHD from day 15 of gestation through weaning) • abortions in 10–25% of dams (9–18× MRHD), death in 7% of foetuses (18× MRHD).
Flecainide	Antiarrhythmic (Class IC)	C	Yes	Yes[b]	Inadequate human data Animal data: • teratogenic effects (e.g. club paws, sternebral and vertebral abnormalities, pale hearts with contracted ventricular septa) and an embryotoxic effect (e.g. increased resorptions) in one breed of rabbit (New Zealand White) but not in another (Dutch Belted) (4× MRHD) • no teratogenic effects in rats or mice (at 50 and 80 mg/kg/day, respectively), but delayed sternebral and vertebral ossification at high dose in rats

Continued

Downloaded from https://academic.oup.com/eurheartj/article-abstract/39/34/3165/5078465 by guest on 13 September 2018

Fondaparinux	Anticoagulant	-	Yes (maximum of 10%)	Yes (excreted in rat milk)	Inadequate human data • use only when benefit outweighs risk
					Animal data: • studies in rats/rabbits: subcutaneous doses up to 10 mg/kg/day in rats (about 32× RHD based on body surface area) and at subcutaneous doses up to 10 mg/kg/day in rabbits (about 65× RHD based on body surface area) revealed no evidence of impaired fertility or harm to the foetus • should not be prescribed to pregnant women unless clearly necessary (see also discussion in section 11)
Furosemide	Diuretic (loop)	C	Yes	Well tolerated; milk production can be reduced	Oligohydramnios • inadequate human data • use only when benefit outweighs risk • monitoring of foetal growth is recommended
					Animal data: • unexplained maternal deaths and abortions in rabbits (2, 4, and 8× MRHD) • increased incidence and severity of hydronephrosis in mice and rabbits
Gemfibrozil	Lipid-lowering drug	C	Yes	Unknown	Inadequate human data
					Animal data: • rats: increase in stillborns, slight reduction in pup weight, increased skeletal variations, and, rarely, anophthalmia (0.6 and 2× RHD) • rabbits: decreased litter size (1 and 3× RHD) and increased incidence of parietal bone variations (3× RHD)
Glyceryl trinitrate	Nitrate	C	Unknown	Unknown	Bradycardia, tocolytic
					Animal data: • rats and rabbits (with nitroglycerin ointment): no teratogenic effects
Heparin (low molecular weight)	Anticoagulant	B	No	No	• Long-term use: less osteoporosis and thrombocytopenia than UFH, increased risk of maternal bleeding (see discussion in section 3 for use during pregnancy) • Human data: retrospective cohort study with 693 live births: no increased risk of major developmental abnormalities
					Animal data: • rats/rabbits: no evidence of teratogenic effects or foetotoxicity
Heparin (unfractionated)	Anticoagulant	B	No	No	Long-term use: less osteoporosis and thrombocytopenia than UFH, increased risk of maternal bleeding (see further discussion in section 3 for use during pregnancy)

Continued

Downloaded from https://academic.oup.com/eurheartj/article-abstract/39/34/3165/5078465 by guest on 13 September 2018

Hydralazine	Vasodilator	C	Yes	Yes (1%)[b]	• maternal side effects: lupus-like symptoms, foetal tachyarrhythmia • see also section 10 on hypertensive disorders
					Animal data: • teratogenic in mice (20–30× MRHD) and rabbits (10–15× MRHD): cleft palate, malformations of facial and cranial bones • no teratogenicity in rats
Hydrochlorothiazide	Diuretic (thiazide)	B	Yes	Yes; milk production can be reduced	Oligohydramnios • impaired foetal–placental perfusion, foetal and neonatal effects like icterus, disturbance of electrolyte balance, and thrombocytopenia
Iloprost	Prostacyclin analogue	C	Unknown	Unknown	Inadequate human data • use only when benefit outweighs risk
					Animal data:- rats: shortened digits of the thoracic extremity in foetuses and pups at a dosage of 0.01 mg/kg/day in Han-Wistar rats (these alterations are considered to be haemodynamic alterations in the fetoplacental unit and not teratogenic)
					No such digital anomalies or other gross structural abnormalities in Sprague-Dawley rats or monkeys In Sprague-Dawley rats, iloprost clathrate (13% iloprost) significantly increased the number of non-viable foetuses at a maternally toxic oral dosage of 250 mg/kg/day, and in Han-Wistar rats it was found to be embryolethal in 15 of 44 litters at an i.v. dosage of 1 mg/kg/day
Indapamide	Diuretic (thiazide)	B	Yes	Unknown	Inadequate human data • use only when benefit outweighs risk
					Animal data: • no evidence of impaired fertility or foetal harm in rats, mice, or rabbits (6.25× RHD), and unaffected post-natal development in rats and mice
Isosorbide dinitrate	Nitrate	B	Unknown	Unknown	Bradycardia
					Animal data: • dose-related increase in embryotoxicity (excess mummified pups) in rabbits at 70 mg/kg (12× MRHD)
Isradipine	Calcium channel blocker	C	Yes	Unknown	Inadequate human data • potential synergism with magnesium sulfate may induce hypotension
					Animal data: • in rats and rabbits, significant reduction in maternal weight gain; no teratogenicity (up to 150× MRHD)

Continued

Downloaded from https://academic.oup.com/eurheartj/article-abstract/39/34/3165/5078465 by guest on 13 September 2018

Ivabradine	I_f-channel blocker	-	Yes (transferred to placenta in rats)	Yes (animal studies show excretion in breast milk; contraindicated in breastfeeding)	Inadequate human data • contraindicated Animal data: • exposure close to therapeutic doses showed a higher incidence of foetal cardiac defects in the rat and a small number of foetuses with ectrodactyly in the rabbit drug of choice for hypertension • intrauterine growth retardation (second and third trimesters), neonatal bradycardia and hypotension (used near term), hypoglycaemia
Labetalol	α/β-blocker	C	Yes	Yes[b]	Animal data: • rats and rabbits (4× or 6× MRHD): no foetal malformations
Levosimendan	Calcium sensitizer	-	Unknown	Yes (animal studies show excretion in breast milk)	Inadequate human data Animal data: • generalized reduction in the degree of ossification in rat and rabbit foetuses, with anomalous development of the supraoccipital bone in the rabbit • administration before and during early pregnancy decreased the number of corpora lutea, implantations, and pups per litter, and increased the number of early resorptions and post-implantation losses in the female rat (effects were seen at clinical exposure levels)
Lidocaine	Antiarrhythmic (Class IB)	C	Yes	Yes[b]	Foetal bradycardia, acidosis, central nervous system toxicity Animal data: • reproduction studies in rats (6× RHD): no evidence of harm to the foetus
Macitentan	Endothelin receptor antagonist	X	Unknown	Yes (animal studies show excretion in breast milk)	Contraindicated • no human data Animal data: • teratogenic in rabbits and rats at all doses tested, cardiovascular and mandibular arch fusion abnormalities • reduced pup survival and impairment of reproductive capability of offspring (6× RHD during late pregnancy/lactation)
Methyldopa	Central alpha-agonist	B	Yes	Yes[b]	Mild neonatal hypotension • no teratogenic effects in recently published prospective observational cohort study (first trimester exposure, *n* = 261), but higher risk of pre-term birth[389] Animal data • mice (16.6× MRHD), rats (1.7× MRHD), and rabbits (3.3× MRHD): no evidence of foetal harm

Continued

Downloaded from https://academic.oup.com/eurheartj/article-abstract/39/34/3165/5078465 by guest on 13 September 2018

Metolazone	Diuretic (thiazide)	B	Yes	Yes	Inadequate human data • use only if clearly needed
					Animal data: • treatment of male rats prior to mating with untreated females: birth weight of offspring was decreased and the pregnancy rate was reduced in dams mated with males from the 10 and 50 mg/kg groups
Metoprolol	Beta-blocker (Class II)	C	Yes	Yes[b]	Bradycardia and hypoglycaemia in foetus
					Animal data: • rats: no evidence of teratogenicity
Mexiletine	Antiarrhythmic (Class IB)	C	Yes	Yes[b]	Inadequate human data • foetal bradycardia • use only when benefit outweighs risk
					Animal data: • rats, mice, and rabbits (4× MRHD): no evidence of teratogenicity or impaired fertility, but increase in foetal resorption
Milrinone	Phosphodiesterase inhibitor	C	Unknown	Unknown	Inadequate human data
					Animal data • in rats/rabbits, no teratogenicity after oral or i.v. application
Nadolol	Beta-blocker (Class II)	C	Unknown	Yes	Foetal bradycardia and hypoglycaemia
					Animal data: • evidence of embryo- and foetotoxicity was found in rabbits, but not in rats or hamsters, at doses 5–10× MRHD; no teratogenic potential was observed in any of these species
Nesiritide	Recombinant B-type natriuretic peptide	C	Unknown	Unknown	Inadequate human data • use only when benefit outweighs risk
					Animal data:

Continued

Downloaded from https://academic.oup.com/eurheartj/article-abstract/39/34/3165/5078465 by guest on 13 September 2018

					• rabbits (70× RHD): no adverse effects on live births or foetal development
Nifedipine	Calcium channel blocker	C	Yes	Yes[b] (maximum of 1.8%)	Tocolytic; sublingual application and potential synergism with magnesium sulfate may induce hypotension (mother) and foetal hypoxia • clinical studies: first trimester: (n = 34 and n = 76): no teratogenic effects[433,434] • however, increased perinatal asphyxia, caesarean delivery, prematurity, and intrauterine growth retardation
					Animal data: • rodents, rabbits, and monkeys: embryotoxic, placentotoxic, teratogenic, and foetotoxic effects: stunted foetuses (rats, mice, and rabbits), digital anomalies (rats and rabbits), rib deformities (mice), cleft palate (mice), small placentas and underdeveloped chorionic villi (monkeys), embryonic and foetal deaths (rats, mice, and rabbits), prolonged pregnancy (rats; not evaluated in other species), and decreased neonatal survival (rats; not evaluated in other species)
Nitroprusside	Vasodilator	C	Yes (animal studies in ewes, crosses the placental barrier)	Unknown	Inadequate human data • use only if needed
					Animal data: • no adequate, well-controlled studies • foetal cyanide levels were shown to be dose-related to maternal levels of nitroprusside • in pregnant ewes, metabolic transformation led to fatal levels of cyanide in the foetuses; infusion of 25 μg/kg/min for 1 h in pregnant ewes resulted in the death of all foetuses, infusion with 1 μg/kg/min for 1 h delivered normal lambs • effects of administering sodium thiosulfate in pregnancy, either alone or in combination with sodium nitroprusside, are unknown
Phenprocoumon	Vitamin K antagonist	D	Yes	Yes (maximum of 10%), well tolerated as inactive metabolite	Coumarin embryopathy, bleeding (see discussions in sections 3 and 5)
Prasugrel	Antiplatelet drug	-	Unknown	Yes (studies in rats have shown excretion in breast milk)	Inadequate human data
					Animal data: • no malformations in rats and rabbits • at very high dose (>240× RHD), effects on maternal body weight and/or food consumption, and a slight decrease in offspring body weight (relative to controls), was documented • in pre- and post-natal rat studies (240× RHD), maternal treatment had no effect on the behavioural or reproductive development of the offspring

Continued

Downloaded from https://academic.oup.com/eurheartj/article-abstract/39/34/3165/5078465 by guest on 13 September 2018

Procainamide	Antiarrhythmic (Class IA)	C	Yes	Yes	• Unknown (limited experience) • No animal data
Propafenone	Antiarrhythmic (Class IC)	C	Yes	Unknown	Unknown (limited experience)
					Animal data: • rabbits (3× MRHD) and rats (6× MRHD): embryotoxic (decreased survival) • rats (1× MRHD): increases in maternal deaths, and reductions in neonatal survival, body weight gain, and physiological development at 4× MRHD
Propranolol	Beta-blocker (Class II)	C	Yes	Yes[b]	Bradycardia and hypoglycaemia in foetus
					Animal data: • rats (1× MRHD): embryotoxicity (reduced litter size, increased resorption rates) and toxicity (deaths) • rabbits (5× MRHD): no embryo or neonatal toxicity
Quinidine	Antiarrhythmic (Class IA)	C	Yes	Yes[b]	Thrombocytopenia, premature birth, eighth nerve toxicity
Ranolazine	I_{Na}-channel blocker	-	Unknown	Unknown	Inadequate human data
					Animal data: • signs of embryonal and maternal toxicity at doses <400 mg/kg/day (2–2.7× MRHD) in rats and 150 mg/kg/day (1.5–2× MRHD) in rabbits, misshapen sternebrae and reduced ossification in offspring; these doses in rats and rabbits were associated with an increased maternal mortality rate
Riociguat	Guanylate cyclase stimulator	-	Unknown	Yes (present in rat milk)	Contraindicated
					Animal data: • rats: teratogenic and embryotoxic, increased rate of cardiac ventricular septal defect at 8× MRHD, increased post-implantation loss at 2× MRHD; • rabbits: increased abortions (4× MRHD) and foetal toxicity (13× MRHD)
Rivaroxaban	Anticoagulant	-	Yes	Yes (data from animals indicate secretion in milk)	Inadequate human data • contraindicated
					Animal data: • in rats: embryofoetal toxicity (post-implantation loss, retarded/progressed ossification, and hepatic multiple light-coloured spots), increased incidence of common malformations, and placental changes observed at clinically relevant concentrations; maternal haemorrhagic complications

Continued

Downloaded from https://academic.oup.com/eurheartj/article-abstract/39/34/3165/5078465 by guest on 13 September 2018

					• in rabbits: increased incidence of post-implantation pregnancy loss, decreased number of live foetuses, and decreased foetal body weight (doses: 4× human exposure of unbound drug) • in pre-/post-natal rat studies, reduced viability of the offspring at doses toxic to the dams was documented • intrinsic risk of bleeding
Sacubitril/valsartan	Angiotensin receptor neprilysin inhibitor	-	Unknown	Yes (excreted in the milk of lactating rats)	Contraindicated • can cause foetal harm • sacubitril: inadequate human data
					Animal data: • rabbits: decreased foetal body weight and skeletal malformations (5.7× MRHD) • rats: no embryofoetal toxicity or teratogenicity at 2.2× MRHD • valsartan: renal or tubular dysplasia, oligohydramnion, growth retardation, ossification disorders of skull, lung hypoplasia, contractures, large joints, anaemia, and intrauterine foetal death • sacubitril/valsartan: rats/rabbits: increased embryofoetal toxicity, low incidence of foetal hydrocephaly with maternally toxic doses, cardiomegaly (rabbits) at maternally non-toxic doses, foetal skeletal variations (rabbits) • adverse embryofoetal effects are attributed to ARBs
Selexipag	IP-receptor agonist	-	Unknown	Unknown	Inadequate human data
					Animal data: • rats: no adverse developmental effects in the foetus up to 47× MRHD, slight reduction in foetal and maternal body weight at the high dose • rabbits: no adverse developmental effects in the foetus up to 50× MRHD
Sildenafil	Phosphodiesterase type 5 inhibitor	B	Unknown	Unknown	Inadequate human data
					Animal data: • no teratogenicity, embryotoxicity, or foetotoxicity in rats (20× MRHD) and rabbits (40× MRHD) during organogenesis
Sotalol	Antiarrhythmic (Class III)	B	Yes	Yes[b]	Bradycardia and hypoglycaemia
					Animal data: • no teratogenic potential in rats (9× MRHD) and rabbits (7× MRHD) • rabbits: a high dose of sotalol hydrochloride (6× MRHD) produced a slight increase in foetal death, likely due to maternal toxicity • rats (18× MRHD): increased number of early resorptions

Continued

Downloaded from https://academic.oup.com/eurheartj/article-abstract/39/34/3165/5078465 by guest on 13 September 2018

Spironolactone	Aldosterone antagonist	D	Yes	Yes (1.2%); milk production can be reduced	Antiandrogenic effects, oral clefts (first trimester) • inadequate human data
					Animal data: • mice (dose below the MRHD): no teratogenic or other embryotoxic effects • rabbits (dose approximately MRHD): increased rate of resorption and lower number of live foetuses • rats (200 mg/kg/day): feminization of male foetuses; exposure during late pregnancy (50/100 mg/kg/day) led to dose-dependent decreases in ventral prostate and seminal vesicle weights in males, and enlarged ovaries and uteri in females
Statins[f]	Lipid-lowering drugs	X	Yes	Unknown	Congenital anomalies
Tadalafil	Phosphodiesterase type 5 inhibitor	B	Yes (in rats)	Yes (in rats)	Inadequate human data
					Animal data: • rats and mice (up to 11× MRHD): no teratogenicity, embryotoxicity, or foetotoxicity. One of two studies in rats showed decreased post-natal pup survival (at doses >10× MRHD)
Ticagrelor	Antiplatelet drug	-	Unknown	Yes (excretion shown in rat milk)	Inadequate human data • not recommended during pregnancy
					Animal data: • rats: minor developmental anomalies at maternal toxic doses; rabbits: slight delay in hepatic maturity and skeletal development at maternal non-toxic doses • rats/rabbits: slightly reduced maternal body weight, reduced neonatal viability and birth weight with delayed growth
Ticlopidine	Antiplatelet	C	Unknown	Yes (in rats)	Inadequate human data
					Animal data: • mice (200 mg/kg/day), rats (400 mg/kg/day), and rabbits (up to 100 mg/kg/day): no teratogenic potential
Torasemide	Diuretic (loop)	B	Unknown	Unknown	Inadequate human data • contraindicated
					Animal data: • no foetotoxicity or teratogenicity in rats (at 15× human dose of 20 mg/day) or rabbits (at 5× human dose of 20 mg/day); decrease in average body weight, increase in foetal resorption, delayed foetal ossification at 4× (rabbits) and 5× (rats) higher doses

Continued

Downloaded from https://academic.oup.com/eurheartj/article-abstract/39/34/3165/5078465 by guest on 13 September 2018

Treprostinil	Prostacyclin analogue	B	Unknown	Unknown	Inadequate human data • use only if needed
					Animal data: • rabbits (subcutaneous) at dose higher than RHD: increased incidence of foetal skeletal variations
Triamterene	Diuretic (potassium-sparing)	C	Yes	Yes (excretion shown in animal milk)	Inadequate human data
					Animal data • no foetal harm in rats (at 6× MRHD)
Urapidil	Αλπηα-1-blocker/5-HT_{1A} agonist	-	Unknown	Unknown	Inadequate human data
Vardenafil	Phosphodiesterase type 5 inhibitor	B	Unknown	Yes (in rats)	Inadequate human data
					Animal data: • rats (100× MRHD) and rabbits (20× MRHD): no teratogenicity, embryotoxicity, or foetotoxicity; retarded physical development of pups in rats at 1 (= MRHD) and 8 mg/kg/day
Verapamil oral	Calcium channel blocker (Class IV)	C	Yes	Yes[b]	Well tolerated
					Animal data:- rabbits (oral, 1.5× RHD): no teratogenicity; rats (oral, 6× RHD): no teratogenicity, but embryocidal, retarded foetal growth and development, and hypotension
Verapamil i.v.	Calcium channel blocker (Class IV)	C	Yes	Yes[b]	i.v. use is associated with a greater risk of hypotension and subsequent foetal hypoperfusion • see verapamil oral
Vernakalant	Antiarrhythmic	-	Unknown	Unknown	Inadequate human data
					Animal data: • rats: malformations (misshapen/absent/fused skull bones including cleft palates, bent radius, bent/misshapen scapula, constricted trachea, absent thyroid, and undescended testes) and increased embryofoetal lethality at exposure levels higher than the single i.v. dose in humans

Continued

Downloaded from https://academic.oup.com/eurheartj/article-abstract/39/34/3165/5078465 by guest on 13 September 2018

					• rabbits: increased number of fused and/or additional sternebrae (at the highest tested dose)
Vorapaxar	Antiplatelet drug	-	Unknown	Yes (excretion shown in rat milk)	Inadequate human data
					Animal data: • rats/rabbits: no defects in embryofoetal development (rats: 56× RHD; rabbits 26× RHD) • transient effects on sensory function and neurobehavioural development in pups at 67× RHD • decreased memory in female pups at 31× RHD • pre- and post-natal studies: rat pups had decreased survival and body weight gain (at 67× RHD)
Warfarin	Vitamin K antagonist	D	Yes	Yes (maximum of 10%), well tolerated as inactive metabolite	Coumarin embryopathy, bleeding (see discussion in sections 3 and 5 for use during pregnancy)

For older substances, the former FDA classification is given wherever available; for newer substances released after 30 June 2015, the FDA classification has been replaced with detailed information from www.ema.europa.eu/, www.accessdata.fda.gov, http://www.embryotox.de, or from prescription labels provided by manufacturers.

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; AUC = area under the curve; FDA = US Food and Drug Administration; 5-HT_{1A} = 5-hydroxytryptamine (serotonin); i.v. = intravenous; KLH = keyhole limpet haemocyanin; MRHD = maximum recommended human dose; RAAS = renin–angiotensin–aldosterone system; RHD = recommended human dose; UFH = unfractionated heparin; VTE = venous thrombo-embolism.

[a]The available data on first trimester use do not strongly support teratogenic potential.[435,436] Because ACE inhibitors, ARBs, aldosterone antagonists, and renin inhibitors should be avoided during pregnancy and breastfeeding the risk category is D. Positive outcomes with ACE inhibitors have been described and pregnancy does not have to be terminated if the patient was exposed to these medications, but should be followed-up closely.

[b]Breastfeeding is possible if the mother is treated with the drug.[437]

[c]Adenosine: Most experiences with this drug are in the second and third trimesters. Its short half-life may prevent it from reaching the foetus.

[d]Atenolol is classified D by the FDA,[438] although some authors classify it as C.[439]

[e]Digoxin: The experience with digoxin is extensive, and it is considered to be the safest antiarrhythmic drug during pregnancy. A prophylactic antiarrhythmic efficacy has never been demonstrated.

[f]Statins: These should not be prescribed in pregnancy and during breastfeeding since their harmlessness is not proven. There are no expected disadvantages to the mother from a temporary interruption of the therapy during pregnancy.

Downloaded from https://academic.oup.com/eurheartj/article-abstract/39/34/3165/5078465 by guest on 13 September 2018

13. Gaps in evidence

Epidemiological data

European epidemiological (e.g. registers such as ROPAC) data on women with CVDs and their outcomes, and the foetal risk during pregnancy and in the peripartum period, are important sources of information. However, there is also a clear need for randomized controlled trials. In women with specific aortic diseases, the outcome is not well studied and the impact of treatment with beta-blockers during pregnancy is lacking.

The impact of pregnancy in a woman with congenital or aortic disease on the long-term maternal and foetal outcome is not well studied.

The impact of fertility treatment on pregnancy complications and maternal outcomes remains unknown.

Mechanical valve prostheses

In women with mechanical valve prostheses, no prospective studies are available that compare different anticoagulation regimens. There are unresolved questions concerning LMWH, including optimal anti-Xa levels, the importance of peak vs. pre-dose levels, the best time intervals for anti-Xa monitoring, and the duration of use (first trimester or throughout pregnancy).

Coronary artery disease

In women with CAD, the required delay of a subsequent pregnancy following MI is unknown. Furthermore, optimal management and follow-up of patients with P-SCAD is a burning clinical problem. This includes the decision for interventional therapy as well as counselling on the recurrence risk for repeated pregnancies.

Drugs

The safety of antiplatelet agents used after PCI in pregnancy is not well known.

There is a lack of randomized trials on the use of antiarrhythmic drugs and interventions during pregnancy.

Data based on prospective randomized clinical trials in pregnant women to assess drug efficacy and safety are very limited. They will stay limited in some areas due to accepted ethical limitations. However, greater efforts can be made by prospective registries to answer burning treatment questions.

Studies investigating the pharmacokinetic changes during pregnancy that modify clinical drug efficacy are required.

Cardiomyopathies

The pathophysiology of PPCM has still to be explored in more detail. PPCM includes LV dysfunction due to several different causes and thus PPCM is not a well-described entity. The potential for recovery is often unclear and the risks of subsequent pregnancies are not well defined. For acute HF in the context of pregnancy there are almost no evidence-based treatments. More research is clearly needed.

Cardiac transplantation

Evidence is also limited for pregnancies in patients post-cardiac transplantation.

Delivery

Trials evaluating the level of surveillance at delivery and the warranted monitoring level after delivery are needed. Furthermore, the optimal mode of delivery is not clear for high-risk situations.

Hypertension

It is still unclear whether mild–moderate hypertension in pregnancy should be pharmacologically treated. The current guidelines are based on expert consensus regarding thresholds to initiate antihypertensive medication. Prospective studies, even observational, in this area are needed.

Diagnostic pathways

More data are needed on diagnostic pathways, specifically the place of D-dimers, in VTE. The value of monitoring anti-Xa values in patients with VTE (treatment) is unknown. Studies are needed on the benefit of using the combination of peak and trough levels. The lack of data regarding the length of anticoagulation after delivery is an unmet need.

14. Key messages

- Risk estimation should be individualized depending on the underlying cardiac diagnosis, ventricular and valvular function, functional class, presence of cyanosis, PAPs, and other factors.
- Indications for intervention (surgical or catheter) in the majority of patients do not differ in women who consider pregnancy compared with other patients. There are a few exceptions, such as some degree of aortic dilatation and severe asymptomatic MS.
- In women with a moderate or high-risk of complications during pregnancy (mWHO II–III, III, and IV), pre-pregnancy counselling and management during pregnancy and around delivery should be performed in an expert centre by a multidisciplinary team: the pregnancy heart team.
- All women with congenital or other possibly genetic heart disease should be offered foetal echocardiography in weeks 19–22 of pregnancy.
- A delivery plan should be made between 20–30 weeks of pregnancy detailing induction, management of labour, delivery, and post-partum surveillance.
- Induction of labour should be considered at 40 weeks of gestation in all women with cardiac disease.
- Vaginal delivery is the first choice for the majority of patients.
- Indications for caesarean section are:
  - pre-term labour in patients on OACs
  - aggressive aortic pathology
  - acute intractable HF
  - severe forms of PH (including Eisenmenger's syndrome)
- Pregnancy termination should be discussed if there is a high-risk of maternal morbidity or mortality, and/or of foetal abnormality.
- Pregnancy, and consequently fertility treatment, is contraindicated in women with mWHO class IV.
- All patients with known cardiac or aortic disease need investigations and counselling about the risks of pregnancy pre-pregnancy or before assisted reproductive therapy.
- The following patients should be counselled against pregnancy:
  - with a Fontan operation and additional comorbidities (ventricular dysfunction, arrhythmias, or valve regurgitation)

Downloaded from https://academic.oup.com/eurheartj/article-abstract/39/34/3165/5078465 by guest on 13 September 2018

  - with PAH
  - severe systemic ventricular dysfunction (EF <30% or NYHA class III–IV).
  - severe (re-)coarctation
  - systemic right ventricle with moderate or severely decreased ventricular function
  - with vascular Ehlers-Danlos
  - with severe aortic dilatation or (history of) aortic dissection
  - with severe MS (even when asymptomatic)
  - Patients with severe AS who are symptomatic, or asymptomatic patients with impaired LV function or a pathological exercise test
  - if LVEF does not normalize in women with previous PPCM.
- Women with a mechanical valve prosthesis are at high-risk of maternal morbidity (especially valve thrombosis and bleeding) and even mortality, and should be managed by a pregnancy heart team in expert centres.
- LMWH should only be used when weekly monitoring of anti-Xa levels with dose adjustment is available.
- Women with HF during pregnancy should be treated according to current guidelines for non-pregnant patients, respecting contraindications for some drugs in pregnancy (see table 'Recommendations for drug use in pregnancy'). When inotropes or more advanced treatment is necessary, transport to an expert centre is recommended.
- It is recommended to inform women with DCM and HFrEF about the risk of deterioration of the condition during gestation and peripartum.
- In women with PPCM and DCM, subsequent pregnancy is not recommended if LVEF does not normalize.
- Patients with congenital LQTS and catecholaminergic polymorphic VT are recommended beta-blockers during pregnancy and post-partum.
- Initiation of antihypertensive drug treatment is recommended in all women with persistent elevation of BP ≥150/95 mmHg and at values >140/90 mmHg in women with:
  - gestational hypertension (with or without proteinuria)
  - pre-existing hypertension with the superimposition of gestational hypertension
  - hypertension with subclinical organ damage or symptoms at any time during pregnancy.
- Women at high or moderate risk of pre-eclampsia should be advised to take 100–150 mg of acetylsalicylic acid daily from week 12 to week 36–37 in addition to their hypertension treatment.
- Methyldopa, labetalol, and calcium antagonists are recommended for the treatment of hypertension in pregnancy.
- LMWH is the agent of choice for VTE prophylaxis and treatment.
- Thrombolytics to treat thrombo-embolism should only be used in patients with severe hypotension or shock.
- In the case of an emergency, drugs that are not recommended by the pharmaceutical industry during pregnancy and breastfeeding should not be withheld from the mother. The potential risk of a drug and the possible benefit of the therapy must be weighed against each other.

Downloaded from https://academic.oup.com/eurheartj/article-abstract/39/34/3165/5078465 by guest on 13 September 2018

15. 'What to do' and 'what not to do' messages from the Guidelines

Recommendations		
General recommendations	**Class[a]**	**Level[b]**
Pre-pregnancy risk assessment and counselling is indicated in all women with known or suspected congenital or acquired cardiovascular and aortic disease.[39]	I	C
It is recommended to treat high risk patients in specialized centres by a multidisciplinary team: the pregnancy heart team.[39]	I	C
Echocardiography is recommended in any pregnant patient with unexplained or new cardiovascular signs or symptoms	I	C
Vaginal delivery is recommended as first choice in most patients; for most important exceptions see below.[96]	I	C
Prophylactic antibiotic therapy to prevent endocarditis during delivery is not recommended.[112]	III	C
Recommendations for pregnancy and pulmonary hypertension or congenital heart disease		
Right heart catheterization is recommended to confirm the diagnosis of PAH (group 1). This can be performed during pregnancy but with very strict indications, optimal timing, and shielding of the foetus.[10]	I	C
Pregnancy is not recommended in patients with PAH.[119]	III	B
Pregnancy is not recommended in patients after Fontan operation and any associated complication.	III	C
Recommendations for the management of aortic disease		
All aortic diseases		
Imaging of the entire aorta (CT/MRI) is recommended before pregnancy in patients with a genetically proven aortic syndrome or known aortic disease.[53]	I	C
When a woman with known aortic dilatation, (history of) dissection, or genetic predisposition for dissection becomes pregnant, strict blood pressure control is recommended.[185]	I	C
Repeated echocardiographic imaging every 4–12 weeks (depending on the diagnosis and severity of dilatation) is recommended during pregnancy and 6 months post-partum in patients with ascending aorta dilatation.[194]	I	C
It is recommended to deliver all women with aortic dilatation or (history of) aortic dissection in an experienced centre with a pregnancy heart team, where cardiothoracic surgery is available.	I	C
In patients with an ascending aorta <40 mm, vaginal delivery is recommended.[96]	I	C
Specific syndromes		
Pregnancy is not recommended in patients with vascular Ehlers–Danlos syndrome.[26]	III	C
Recommendations for the management of native valvular heart disease		
Mitral stenosis		
In patients with symptoms or pulmonary hypertension, restricted activities and beta-1-selective blockers are recommended.[5,204]	I	B
Diuretics are recommended when congestive symptoms persist despite beta-blockers.[5]	I	B

Continued

Downloaded from https://academic.oup.com/eurheartj/article-abstract/39/34/3165/5078465 by guest on 13 September 2018

Intervention is recommended before pregnancy in patients with MS and valve area <1.0 cm^2.	I	C
Therapeutic anticoagulation using heparins or VKA is recommended in case of AF, left atrial thrombosis, or prior embolism.	I	C
Aortic stenosis		
Intervention is recommended before pregnancy in patients with severe AS if they are symptomatic.	I	B
Intervention is recommended before pregnancy in patients with severe AS if LV dysfunction (LVEF <50%) is present.[204]	I	C
Intervention is recommended before pregnancy in patients with severe AS when they develop symptoms during exercise testing.	I	C
Chronic regurgitant lesions		
Surgical treatment is recommended before pregnancy in patients with severe aortic or mitral regurgitation and symptoms, impaired ventricular function, or ventricular dilatation.[204]	I	C
Medical therapy is recommended in pregnant women with regurgitant lesions when symptoms occur.	I	C
Recommendations for the management of prosthetic heart valves		
It is recommended to choose the valve prosthesis in women contemplating pregnancy in consultation with a pregnancy heart team.	I	C
It is recommended to manage pregnancy in women with mechanical valves in a centre with a pregnancy heart team.	I	C
If delivery starts while on VKA or in less than 2 weeks after discontinuation of a VKA, caesarean section is indicated.	I	C
It is recommended to discontinue VKA and start adjusted-dose intravenous UFH (aPTT ≥2× control) or adjusted-dose LMWH (see separate recommendations) at the 36th week of gestation.	I	C
It is recommended to anticipate the timing of delivery to ensure safe and effective peripartum anticoagulation.	I	C
Immediate echocardiography is indicated in women with mechanical valves presenting with dyspnoea and/or an embolic event.	I	C
During the second and third trimesters until the 36th week, VKAs are recommended in women needing a low dose.[a]	I	C
Recommendations for the management of coronary artery disease		
ECG and measurement of troponin levels is recommended when a pregnant woman has chest pain.[238]	I	C
Primary coronary angioplasty is recommended as the preferred reperfusion therapy for STEMI during pregnancy.[237]	I	C
Breastfeeding is not recommended in mothers who take antiplatelet agents other than low-dose aspirin due to a lack of data (see section 12).	III	C
Recommendations for the management of cardiomyopathies and heart failure		
Anticoagulation is recommended in patients with intracardiac thrombus detected by imaging or with evidence of systemic embolism.[286]	I	A
It is recommended to treat women with heart failure during pregnancy according to current guidelines for non-pregnant patients, respecting contraindications for some drugs in pregnancy[130] (see *Table 7*).	I	B
It is recommended to inform women with HFrEF about the risk of deterioration of the condition during gestation and peripartum.[29]	I	C
Therapeutic anticoagulation with LMWH or VKAs according to stage of pregnancy is recommended for patients with AF.	I	C
In HFrEF, it is recommended that beta-blockers are continued in women who used them before pregnancy, or that they are installed with caution if symptoms persist.	I	C
In patients with PPCM and DCM, counselling for recurrence risk during subsequent pregnancy is recommended in all cases, even after recovery of LV function.	I	C

Continued

Downloaded from https://academic.oup.com/eurheartj/article-abstract/39/34/3165/5078465 by guest on 13 September 2018

HCM		
In patients with HCM, it is recommended that beta-blockers are continued in women who used them before pregnancy.[313]	I	C
Recommendations for the management of arrhythmias		
Acute management (intravenous administration of drugs) of SVT and AF		
Immediate electrical cardioversion is recommended for any tachycardia with haemodynamic instability and for pre-excited AF.[12,306]	I	C
Long-term management (oral administration of drugs) of SVT and AF		
Beta-1-selective blockers or verapamil[b] are recommended for the prevention of SVT in patients without pre-excitation on resting ECG.[12,327]	I	C
Flecainide[c] or propafenone[c] are recommended for the prevention of SVT in patients with WPW syndrome.[12]	I	C
Beta-1-selective blockers are recommended for rate control of AT or AF.[12]	I	C
Acute management (intravenous administration of drugs) of ventricular tachyarrhythmias		
Immediate electrical cardioversion is recommended for both sustained unstable and stable VT.[72]	I	C
Long-term management (oral administration of drugs) of ventricular tachyarrhythmias		
Beta-blocking agents are recommended during pregnancy and post-partum in patients with long QT syndrome or catecholaminergic polymorphic ventricular tachycardia.[72]	I	C
Recommendations for the management of hypertension		
Low-dose aspirin (100–150 mg daily) is recommended in women at high or moderate risk of pre-eclampsia from week 12 to week 36 - 37.[347,348]	I	A
In women with gestational hypertension or pre-existing hypertension superimposed by gestational hypertension, or with hypertension and subclinical organ damage or symptoms, initiation of drug treatment is recommended at SBP >140 mmHg or DBP >90 mmHg.[99] In all other cases, initiation of drug treatment is recommended at SBP ≥150 mmHg or DBP ≥95 mmHg.[348,375]	I	C
SBP ≥170 mmHg or DBP ≥110 mmHg in a pregnant woman is an emergency, and hospitalization is recommended.	I	C
Methyldopa, labetalol, and calcium antagonists are the drugs of choice for the treatment of hypertension in pregnancy.[51,379,389]	I	C
It is recommended to expedite delivery in pre-eclampsia, and with adverse conditions such as visual disturbances or haemostatic disorders.	I	C
In severe hypertension, drug treatment with intravenous labetalol, oral methyldopa, or nifedipine is recommended.[51]	I	C
Recommendations for the management of venous thrombo-embolism		
LMWH is recommended for the prevention and treatment of VTE in pregnant patients.[13]	I	B
For high-risk women, it is recommended to give a weight-related prophylactic dose of LMWH (e.g. enoxaparin 0.5 mg/kg once daily).[13]	I	B
It is recommended that the therapeutic dose of LMWH is based on body weight.[14]	I	C
Thrombolytics to manage patients with pulmonary embolism are only recommended in patients with severe hypotension or shock.[21]	I	C
In high-risk women, it is recommended to convert LMWH to UFH at least 36 h prior to delivery and to stop the UFH infusion 4 - 6 h prior to anticipated delivery. aPTT should be normal before regional anaesthesia.[22]	I	C

Continued

Downloaded from https://academic.oup.com/eurheartj/article-abstract/39/34/3165/5078465 by guest on 13 September 2018

Recommendations for drug use in pregnancy		
Before pharmacological treatment in pregnancy is started, it is recommended to check drugs and safety data (see *Table 7*)	I	C
In the absence of clinical safety data, it is recommended to check the Supplementary Data and www.safefetus.com for pre-clinical safety data.	I	C
Decision making based on former FDA categories alone is no longer recommended.	III	C

©ESC 2018

Class III drugs should not be used in prolonged QTc. Cardioversion of AF and atrial flutter should generally be preceded by anticoagulation (see below).[146]
AF = atrial fibrillation; aPTT = activated partial thromboplastin time; AS = aortic stenosis; AT = atrial tachycardia; CT = computed tomography; DBP = diastolic blood pressure; DCM = dilated cardiomyopathy; ECG = electrocardiogram; FDA = US Food and Drug Administration; HCM = hypertrophic cardiomyopathy; HFrEF = heart failure with reduced ejection fraction; LMWH = low molecular weight heparin; LV = left ventricular; LVEF = left ventricular ejection fraction; MRI = magnetic resonance imaging; MS = mitral stenosis; PAH = pulmonary arterial hypertension; PPCM = peripartum cardiomyopathy; SBP = systolic blood pressure; STEMI = ST-elevation myocardial infarction; SVT = supraventricular tachycardia; UFH = unfractionated heparin; VKA= vitamin K antagonist; VT = ventricular tachycardia; VTE = venous thrombo-embolism; WPW = Wolff–Parkinson–White.
[a]Low-dose VKA: warfarin <5 mg/day, phenprocoumon <3 mg/day, or acenocoumarol <2 mg/day. High-dose VKA: warfarin >5 mg/day, phenprocoumon >3 mg/day, or acenocoumarol >2 mg/day.
[b]AV nodal blocking agents should not be used in patients with pre-excitation on resting ECG or pre-excited AF.
[c]Flecainide and propafenone should be combined with AV nodal blocking agents for certain atrial tachycardias, but structural heart disease, reduced left ventricular function, and bundle branch block should be excluded.

16. Appendix

ESC Committee for Practice Guidelines (CPG): Stephan Windecker (Chairperson) (Switzerland), Victor Aboyans (France), Stefan Agewall (Norway), Emanuele Barbato (Italy), Héctor Bueno (Spain), Antonio Coca (Spain), Jean-Philippe Collet (France), Ioan Mircea Coman (Romania), Veronica Dean (France), Victoria Delgado (The Netherlands), Donna Fitzsimons (UK), Oliver Gaemperli (Switzerland), Gerhard Hindricks (Germany), Bernard Iung (France), Peter Jüni (Canada), Hugo A. Katus (Germany), Juhani Knuuti (Finland), Patrizio Lancellotti (Belgium), Christophe Leclercq (France), Theresa A. McDonagh (UK), Massimo Francesco Piepoli (Italy), Piotr Ponikowski (Poland), Dimitrios J. Richter (Greece), Marco Roffi (Switzerland), Evgeny Shlyakhto (Russia), Iain A. Simpson (UK), Miguel Sousa-Uva (Portugal), Jose Luis Zamorano (Spain).

ESC National Cardiac Societies actively involved in the review process of the 2018 ESC Guidelines for the management of cardiovascular diseases during pregnancy: **Algeria**: Algerian Society of Cardiology, Naima Hammoudi; **Armenia**: Armenian Cardiologists Association, Armen Piruzyan; **Austria**: Austrian Society of Cardiology, Julia Mascherbauer; **Azerbaijan**: Azerbaijan Society of Cardiology, Fuad Samadov; **Belarus**: Belorussian Scientific Society of Cardiologists, Andrei Prystrom; **Belgium**: Belgian Society of Cardiology, Agnes Pasquet; **Bosnia and Herzegovina**: Association of Cardiologists of Bosnia and Herzegovina, Jasmin Caluk; **Bulgaria**: Bulgarian Society of Cardiology, Nina Gotcheva; **Croatia**: Croatian Cardiac Society, Bosko Skoric; **Cyprus**: Cyprus Society of Cardiology, Hera Heracleous; **Denmark**: Danish Society of Cardiology, Niels Vejlstrup; **Estonia**: Estonian Society of Cardiology, Maarja Maser; **Finland**: Finnish Cardiac Society, Risto Juhani Kaaja; **The Former Yugoslav Republic of Macedonia:** Macedonian FYR Society of Cardiology, Elizabeta Srbinovska-Kostovska; **France**: French Society of Cardiology, Claire Mounier-Vehier; **Georgia**: Georgian Society of Cardiology, Tamar Vakhtangadze; **Germany**: German Cardiac Society, Karin Rybak; **Greece**: Hellenic Society of Cardiology, George Giannakoulas; **Hungary**: Hungarian Society of Cardiology, Robert Gabor Kiss; **Iceland**: Icelandic Society of Cardiology, Inga S. Thrainsdottir; **Ireland**: Irish Cardiac Society, R John Erwin; **Israel**: Israel Heart Society, Avital Porter; **Italy**: Italian Federation of Cardiology, Giovanna Geraci; **Kosovo**: Kosovo Society of Cardiology, Pranvera Ibrahimi; **Kyrgyzstan**: Kyrgyz Society of Cardiology, Olga Lunegova; **Latvia**: Latvian Society of Cardiology, Iveta Mintale; **Lebanon**: Lebanese Society of Cardiology, Zeina Kadri; **Libya**: Libyan Cardiac Society, Hisham Benlamin; **Lithuania**: Lithuanian Society of Cardiology, Jurate Barysiene; **Luxembourg**: Luxembourg Society of Cardiology, Cristiana A. Banu; **Malta**: Maltese Cardiac Society, Maryanne Caruana; **Moldova**: Moldavian Society of Cardiology, Cristina Gratii; **Morocco**: Moroccan Society of Cardiology, Laila Haddour; **The Netherlands**: Netherlands Society of Cardiology, Berto J. Bouma; **Norway**: Norwegian Society of Cardiology, Mette-Elise Estensen; **Poland**: Polish Cardiac Society, Piotr Hoffman; **Romania**: Romanian Society of Cardiology, Antoniu Octavian Petris; **Russian Federation**: Russian Society of Cardiology, Olga Moiseeva; **San Marino**: San Marino Society of Cardiology, Luca Bertelli; **Serbia**: Cardiology Society of Serbia, Bosiljka Vujisic Tesic; **Slovakia**: Slovak Society of Cardiology, Juraj Dubrava; **Slovenia**: Slovenian Society of Cardiology, Mirta Koželj; **Spain**: Spanish Society of Cardiology, Raquel Prieto-Arévalo; **Sweden**: Swedish Society of Cardiology, Eva Furenäs; **Switzerland**: Swiss Society of Cardiology, Markus Schwerzmann; **Tunisia**: Tunisian Society of Cardiology and Cardio-Vascular Surgery, Mohamed Sami Mourali; **Turkey**: Turkish Society of Cardiology, Necla Ozer; **Ukraine**: Ukrainian Association of Cardiology, Olena Mitchenko; **United Kingdom**: British Cardiovascular Society, Catherine Nelson-Piercy.

Downloaded from https://academic.oup.com/eurheartj/article-abstract/39/34/3165/5078465 by guest on 13 September 2018

References

1. Bouvier-Colle MH, Mohangoo AD, Gissler M, Novak-Antolic Z, Vutuc C, Szamotulska K, Zeitlin J. What about the mothers? An analysis of maternal mortality and morbidity in perinatal health surveillance systems in europe. *BJOG* 2012;**119**:880–889; discussion 890.
2. Cantwell R, Clutton-Brock T, Cooper G, Dawson A, Drife J, Garrod D, Harper A, Hulbert D, Lucas S, McClure J, Millward-Sadler H, Neilson J, Nelson-Piercy C, Norman J, O'Herlihy C, Oates M, Shakespeare J, de Swiet M, Williamson C, Beale V, Knight M, Lennox C, Miller A, Parmar D, Rogers J, Springett A. Saving mothers' lives: Reviewing maternal deaths to make motherhood safer: 2006-2008. The eighth report of the confidential enquiries into maternal deaths in the United Kingdom. *BJOG* 2011;**118**:1–203.
3. Knight M, Nair M, Tuffnell D, Kenyon S, Shakespeare J, Brocklehurst P, Kurinczuk JJ, (Eds.) on behalf of MBRRACE-UK. *Saving lives, improving mothers' care - surveillance of maternal deaths in the UK 2012–14 and lessons learned to inform maternity care from the uk and ireland confidential enquiries into maternal deaths and morbidity 2009–14*. Oxford: National Perinatal Epidemiology Unit, University of Oxford; 2016.
4. van Hagen IM, Boersma E, Johnson MR, Thorne SA, Parsonage WA, Escribano Subias P, Lesniak-Sobelga A, Irtyuga O, Sorour KA, Taha N, Maggioni AP, Hall R, Roos-Hesselink JW. Global cardiac risk assessment in the registry of pregnancy and cardiac disease: Results of a registry from the European Society of Cardiology. *Eur J Heart Fail* 2016;**18**:523–533.
5. Elkayam U, Goland S, Pieper PG, Silverside CK. High-risk cardiac disease in pregnancy: Part *i*. *J Am Coll Cardiol* 2016;**68**:396–410.
6. Farr A, Lenz-Gebhart A, Einig S, Ortner C, Holzer I, Elhenicky M, Husslein PW, Lehner R. Outcomes and trends of peripartum maternal admission to the intensive care unit. *Wien Klin Wochenschr* 2017;**129**:605–611.
7. Hermus MA, Wiegers TA, Hitzert MF, Boesveld IC, van den Akker-van Marle ME, Akkermans HA, Bruijnzeels MA, Franx A, de Graaf JP, Rijnders ME, Steegers EA, van der Pal-de Bruin KM. The Dutch Birth Centre Study: Study design of a programmatic evaluation of the effect of birth centre care in the netherlands. *BMC Pregnancy Childbirth* 2015;**15**:148.
8. de Jonge L, Garne E, Gini R, Jordan SE, Klungsoyr K, Loane M, Neville AJ, Pierini A, Puccini A, Thayer DS, Tucker D, Vinkel Hansen A, Bakker MK. Improving information on maternal medication use by linking prescription data to congenital anomaly registers: A EUROmediCAT study. *Drug Saf* 2015;**38**:1083–1093.
9. Regitz-Zagrosek V, Blomstrom Lundqvist C, Borghi C, Cifkova R, Ferreira R, Foidart JM, Gibbs JS, Gohlke-Baerwolf C, Gorenek B, Iung B, Kirby M, Maas AH, Morais J, Nihoyannopoulos P, Pieper PG, Presbitero P, Roos-Hesselink JW, Schaufelberger M, Seeland U, Torracca L. ESC guidelines on the management of cardiovascular diseases during pregnancy. *Eur Heart J* 2011;**32**:3147–3197.
10. Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP III, Guyton RA, O'Gara PT, Ruiz CE, Skubas NJ, Sorajja P, Sundt TM III, Thomas JD. 2014 AHA/ACC guideline for the management of patients with valvular heart disease. *J Am Coll Cardiol* 2014;**63**:e57–e185.
11. Pijuan-Domenech A, Galian L, Goya M, Casellas M, Merced C, Ferreira-Gonzalez I, Marsal-Mora JR, Dos-Subira L, Subirana-Domenech MT, Pedrosa V, Baro-Marine F, Manrique S, Casaldaliga-Ferrer J, Tornos P, Cabero L, Garcia-Dorado D. Cardiac complications during pregnancy are better predicted with the modified who risk score. *Int J Cardiol* 2015;**195**:149–154.
12. Katritsis DG, Boriani G, Cosio FG, Hindricks G, Jais P, Josephson ME, Keegan R, Kim YH, Knight BP, Kuck KH, Lane DA, Lip GY, Malmborg H, Oral H, Pappone C, Themistoclakis S, Wood KA, Blomstrom-Lundqvist C. European Heart Rhythm Association (EHRA) consensus document on the management of supraventricular arrhythmias, endorsed by Heart Rhythm Society (HRS), Asia-Pacific Heart Rhythm Society (APHRS), and Sociedad Latinoamericana de Estimulación Cardiaca y Electrofisiologia (SOLAECE). *Europace* 2017;**19**:465–511.
13. Greer IA, Nelson-Piercy C. Low-molecular-weight heparins for thromboprophylaxis and treatment of venous thromboembolism in pregnancy: A systematic review of safety and efficacy. *Blood* 2005;**106**:401–407.
14. McDonnell BP, Glennon K, McTiernan A, O'Connor HD, Kirkham C, Kevane B, Donnelly JC, Ni Ainle F. Adjustment of therapeutic LMWH to achieve specific target anti-FXa activity does not affect outcomes in pregnant patients with venous thromboembolism. *J Thromb Thrombolysis* 2017;**43**:105–111.
15. Driver K, Chisholm CA, Darby AE, Malhotra R, Dimarco JP, Ferguson JD. Catheter ablation of arrhythmia during pregnancy. *J Cardiovasc Electrophysiol* 2015;**26**:698–702.
16. Chen G, Sun G, Xu R, Chen X, Yang L, Bai Y, Yang S, Guo P, Zhang Y, Zhao C, Wang DW, Wang Y. Zero-fluoroscopy catheter ablation of severe drug-resistant arrhythmia guided by Ensite NavX system during pregnancy: Two case reports and literature review. *Medicine (Baltimore)* 2016;**95**:e4487.
17. Szumowski L, Szufladowicz E, Orczykowski M, Bodalski R, Derejko P, Przybylski A, Urbanek P, Kusmierczyk M, Kozluk E, Sacher F, Sanders P, Dangel J, Haissaguerre M, Walczak F. Ablation of severe drug-resistant tachyarrhythmia during pregnancy. *J Cardiovasc Electrophysiol* 2010;**21**:877–882.
18. Dronkers CE, Sramek A, Huisman MV, Klok FA. Accurate diagnosis of iliac vein thrombosis in pregnancy with magnetic resonance direct thrombus imaging (MRDTI). *BMJ Case Rep* 2016;**2016**:bcr2016218091.
19. Curry RA, Gelson E, Swan L, Dob D, Babu-Narayan SV, Gatzoulis MA, Steer PJ, Johnson MR. Marfan syndrome and pregnancy: Maternal and neonatal outcomes. *BJOG* 2014;**121**:610–617.
20. Carlson M, Airhart N, Lopez L, Silberbach M. Moderate aortic enlargement and bicuspid aortic valve are associated with aortic dissection in turner syndrome: Report of the international Turner syndrome aortic dissection registry. *Circulation* 2012;**126**:2220–2226.
21. Heavner MS, Zhang M, Bast CE, Parker L, Eyler RF. Thrombolysis for massive pulmonary embolism in pregnancy. *Pharmacotherapy* 2017;**37**:1449–1457.
22. Leffert L, Butwick A, Carvalho B, Arendt K, Bates SM, Friedman A, Horlocker T, Houle T, Landau R, Dubois H, Fernando R, Houle T, Kopp S, Montgomery D, Pellegrini J, Smiley R, Toledo P. The society for obstetric anesthesia and perinatology consensus statement on the anesthetic management of pregnant and postpartum women receiving thromboprophylaxis or higher dose anticoagulants. *Anesth Analg* 2018;**126**:928–944.
23. Galie N, Humbert M, Vachiery JL, Gibbs S, Lang I, Torbicki A, Simonneau G, Peacock A, Vonk Noordegraaf A, Beghetti M, Ghofrani A, Gomez Sanchez MA, Hansmann G, Klepetko W, Lancellotti P, Matucci M, McDonagh T, Pierard LA, Trindade PT, Zompatori M, Hoeper M, Aboyans V, Vaz Carneiro A, Achenbach S, Agewall S, Allanore Y, Asteggiano R, Paolo Badano L, Albert Barbera J, Bouvaist H, Bueno H, Byrne RA, Carerj S, Castro G, Erol C, Falk V, Funck-Brentano C, Gorenflo M, Granton J, Iung B, Kiely DG, Kirchhof P, Kjellstrom B, Landmesser U, Lekakis J, Lionis C, Lip GY, Orfanos SE, Park MH, Piepoli MF, Ponikowski P, Revel MP, Rigau D, Rosenkranz S, Voller H, Luis Zamorano J. 2015 ESC/ERS guidelines for the diagnosis and treatment of pulmonary hypertension. *Eur Heart J* 2016;**37**:67–119.
24. Sliwa K, Blauwet L, Tibazarwa K, Libhaber E, Smedema JP, Becker A, McMurray J, Yamac H, Labidi S, Struman I, Hilfiker-Kleiner D. Evaluation of bromocriptine in the treatment of acute severe peripartum cardiomyopathy: A proof-of-concept pilot study. *Circulation* 2010;**121**:1465–1473.
25. Hilfiker-Kleiner D, Haghikia A, Berliner D, Vogel-Claussen J, Schwab J, Franke A, Schwarzkopf M, Ehlermann P, Pfister R, Michels G, Westenfeld R, Stangl V, Kindermann I, Kuhl U, Angermann CE, Schlitt A, Fischer D, Podewski E, Bohm M, Sliwa K, Bauersachs J. Bromocriptine for the treatment of peripartum cardiomyopathy: A multicentre randomized study. *Eur Heart J* 2017;**38**:2671–2679.
26. Pepin M, Schwarze U, Superti-Furga A, Byers PH. Clinical and genetic features of Ehlers-Danlos syndrome type IV, the vascular type. *N Engl J Med* 2000;**342**:673–680.
27. Worldatlas. Countries with the oldest average mother's age at first birth. https://www.worldatlas.com/articles/countries-with-the-highest-mother-s-mean-age-at-first-birth.html **(**25 April 2017**).**
28. Khan KS, Wojdyla D, Say L, Gulmezoglu AM, Van Look PF. WHO analysis of causes of maternal death: A systematic review. *Lancet* 2006;**367**:1066–1074.
29. Siu SC, Sermer M, Colman JM, Alvarez AN, Mercier LA, Morton BC, Kells CM, Bergin ML, Kiess MC, Marcotte F, Taylor DA, Gordon EP, Spears JC, Tam JW, Amankwah KS, Smallhorn JF, Farine D, Sorensen S. Prospective multicenter study of pregnancy outcomes in women with heart disease. *Circulation* 2001;**104**:515–521.
30. Swan L. Congenital heart disease in pregnancy. *Best Pract Res Clin Obstet Gynaecol* 2014;**28**:495–506.
31. Rutherford JD. Heart failure in pregnancy. *Curr Heart Fail Rep* 2012;**9**:277–281.
32. Hilfiker-Kleiner D, Sliwa K. Pathophysiology and epidemiology of peripartum cardiomyopathy. *Nat Rev Cardiol* 2014;**11**:364–370.
33. Kampman MA, Valente MA, van Melle JP, Balci A, Roos-Hesselink JW, Mulder BJ, van Dijk AP, Oudijk MA, Jongbloed MR, van Veldhuisen DJ, Pieper PG. Cardiac adaption during pregnancy in women with congenital heart disease and healthy women. *Heart* 2016;**102**:1302–1308.
34. Cornette J, Ruys TP, Rossi A, Rizopoulos D, Takkenberg JJ, Karamermer Y, Opic P, Van den Bosch AE, Geleijnse ML, Duvekot JJ, Steegers EA, Roos-Hesselink JW. Hemodynamic adaptation to pregnancy in women with structural heart disease. *Int J Cardiol* 2013;**168**:825–831.
35. Wald RM, Silversides CK, Kingdom J, Toi A, Lau CS, Mason J, Colman JM, Sermer M, Siu SC. Maternal cardiac output and fetal doppler predict adverse neonatal outcomes in pregnant women with heart disease. *J Am Heart Assoc* 2015;**4**:e002414.
36. Pieper PG. Use of medication for cardiovascular disease during pregnancy. *Nat Rev Cardiol* 2015;**12**:718–729.
37. Pieper PG, Balci A, Aarnoudse JG, Kampman MA, Sollie KM, Groen H, Mulder BJ, Oudijk MA, Roos-Hesselink JW, Cornette J, van Dijk AP, Spaanderman ME, Drenthen W, van Veldhuisen DJ. Uteroplacental blood flow, cardiac function, and pregnancy outcome in women with congenital heart disease. *Circulation* 2013;**128**:2478–2487.
38. Anderson GD. Pregnancy-induced changes in pharmacokinetics: A mechanistic-based approach. *Clin Pharmacokinet* 2005;**44**:989–1008.

Downloaded from https://academic.oup.com/eurheartj/article-abstract/39/34/3165/5078465 by guest on 13 September 2018

39. Roos-Hesselink JW, Budts W, Walker F, De Backer JFA, Swan L, Stones W, Kranke P, Sliwa-Hahnle K, Johnson MR. Organisation of care for pregnancy in patients with congenital heart disease. *Heart* 2017;**103**:1854–1859.
40. Ohuchi H, Tanabe Y, Kamiya C, Noritake K, Yasuda K, Miyazaki A, Ikeda T, Yamada O. Cardiopulmonary variables during exercise predict pregnancy outcome in women with congenital heart disease. *Circ J* 2013;**77**:470–476.
41. Drenthen W, Pieper PG, Roos-Hesselink JW, van Lottum WA, Voors AA, Mulder BJ, van Dijk AP, Vliegen HW, Yap SC, Moons P, Ebels T, van Veldhuisen DJ. Outcome of pregnancy in women with congenital heart disease: A literature review. *J Am Coll Cardiol* 2007;**49**:2303–2311.
42. Drenthen W, Boersma E, Balci A, Moons P, Roos-Hesselink JW, Mulder BJ, Vliegen HW, van Dijk AP, Voors AA, Yap SC, van Veldhuisen DJ, Pieper PG. Predictors of pregnancy complications in women with congenital heart disease. *Eur Heart J* 2010;**31**:2124–2132.
43. Ruys TP, Roos-Hesselink JW, Hall R, Subirana-Domenech MT, Grando-Ting J, Estensen M, Crepaz R, Fesslova V, Gurvitz M, De Backer J, Johnson MR, Pieper PG. Heart failure in pregnant women with cardiac disease: Data from the ropac. *Heart* 2014;**100**:231–238.
44. Balci A, Sollie-Szarynska KM, van der Bijl AG, Ruys TP, Mulder BJ, Roos-Hesselink JW, van Dijk AP, Wajon EM, Vliegen HW, Drenthen W, Hillege HL, Aarnoudse JG, van Veldhuisen DJ, Pieper PG. Prospective validation and assessment of cardiovascular and offspring risk models for pregnant women with congenital heart disease. *Heart* 2014;**100**:1373–1381.
45. Cauldwell M, Patel RR, Steer PJ, Swan L, Norman-Taylor J, Gatzoulis M, Johnson MR. Managing subfertility in patients with heart disease: What are the choices? *Am Heart J* 2017;**187**:29–36.
46. Tanous D, Siu SC, Mason J, Greutmann M, Wald RM, Parker JD, Sermer M, Colman JM, Silversides CK. B-type natriuretic peptide in pregnant women with heart disease. *J Am Coll Cardiol* 2010;**56**:1247–1253.
47. Kampman MA, Balci A, van Veldhuisen DJ, van Dijk AP, Roos-Hesselink JW, Sollie-Szarynska KM, Ludwig-Ruitenberg M, van Melle JP, Mulder BJ, Pieper PG. N-terminal pro-b-type natriuretic peptide predicts cardiovascular complications in pregnant women with congenital heart disease. *Eur Heart J* 2014;**35**:708–715.
48. Song YB, Park SW, Kim JH, Shin DH, Cho SW, Choi JO, Lee SC, Moon JR, Huh J, Kang IS, Lee HJ. Outcomes of pregnancy in women with congenital heart disease: A single center experience in Korea. *J Korean Med Sci* 2008;**23**:808–813.
49. Liu H, Huang TT, Lin JH. Risk factors and risk index of cardiac events in pregnant women with heart disease. *Chin Med J (Engl)* 2012;**125**:3410–3415.
50. Khairy P, Ouyang DW, Fernandes SM, Lee-Parritz A, Economy KE, Landzberg MJ. Pregnancy outcomes in women with congenital heart disease. *Circulation* 2006;**113**:517–524.
51. Lindheimer MD, Taler SJ, Cunningham FG. ASH position paper: Hypertension in pregnancy. *J Clin Hypertens (Greenwich)* 2009;**11**:214–225.
52. Cornette J, Ruys TP, Roos-Hesselink JW. Assessment of the right ventricle in pregnant women with and without structural heart disease. *Int J Cardiol* 2013;**168**:3087.
53. American College of Obstetricians Gynecologists' Committee on Obstetric Practice. Committee opinion no. 656: Guidelines for diagnostic imaging during pregnancy and lactation. *Obstet Gynecol* 2016;**127**:e75–e80.
54. Buys R, Cornelissen V, Van De Bruaene A, Stevens A, Coeckelberghs E, Onkelinx S, Thomaes T, Delecluse C, Budts W, Vanhees L. Measures of exercise capacity in adults with congenital heart disease. *Int J Cardiol* 2011;**153**:26–30.
55. Ray JG, Vermeulen MJ, Bharatha A, Montanera WJ, Park AL. Association between MRI exposure during pregnancy and fetal and childhood outcomes. *JAMA* 2016;**316**:952–961.
56. ACOG Committee on Obstetric Practice. ACOG committee opinion. Number 299, September 2004 (replaces no. 158, September 1995). Guidelines for diagnostic imaging during pregnancy. *Obstet Gynecol* 2004;**104**:647–651.
57. International Commission on Radiological Protection. Pregnancy and medical radiation. ICRP publication 84. *Ann ICRP* 2000;**30**:iii–viii, 1–43.
58. Yang B, Ren BX, Tang FR. Prenatal irradiation-induced brain neuropathology and cognitive impairment. *Brain Dev* 2017;**39**:10–22.
59. Boice JD Jr, Miller RW. Childhood and adult cancer after intrauterine exposure to ionizing radiation. *Teratology* 1999;**59**:227–233.
60. Kelaranta A, Kaasalainen T, Seuri R, Toroi P, Kortesniemi M. Fetal radiation dose in computed tomography. *Radiat Prot Dosimetry* 2015;**165**:226–230.
61. Schrale RG, Ormerod J, Ormerod OJ. Percutaneous device closure of the patent foramen ovale during pregnancy. *Catheter Cardiovasc Interv* 2007;**69**:579–583.
62. Sachs HC. The transfer of drugs and therapeutics into human breast milk: An update on selected topics. *Pediatrics* 2013;**132**:e796–e809.
63. van der Linde D, Konings EE, Slager MA, Witsenburg M, Helbing WA, Takkenberg JJ, Roos-Hesselink JW. Birth prevalence of congenital heart disease worldwide: A systematic review and meta-analysis. *J Am Coll Cardiol* 2011;**58**:2241–2247.
64. Gill HK, Splitt M, Sharland GK, Simpson JM. Patterns of recurrence of congenital heart disease: An analysis of 6,640 consecutive pregnancies evaluated by detailed fetal echocardiography. *J Am Coll Cardiol* 2003;**42**:923–929.
65. Elliott PM, Anastasakis A, Borger MA, Borggrefe M, Cecchi F, Charron P, Hagege AA, Lafont A, Limongelli G, Mahrholdt H, McKenna WJ, Mogensen J, Nihoyannopoulos P, Nistri S, Pieper PG, Pieske B, Rapezzi C, Rutten FH, Tillmanns C, Watkins H. 2014 ESC guidelines on diagnosis and management of hypertrophic cardiomyopathy. *Eur Heart J* 2014;**35**:2733–2779.
66. Charron P, Arad M, Arbustini E, Basso C, Bilinska Z, Elliott P, Helio T, Keren A, McKenna WJ, Monserrat L, Pankuweit S, Perrot A, Rapezzi C, Ristic A, Seggewiss H, van Langen I, Tavazzi L. Genetic counselling and testing in cardiomyopathies: A position statement of the European Society of Cardiology Working Group on Myocardial and Pericardial Diseases. *Eur Heart J* 2010;**31**:2715–2726.
67. De Stefano V, Rossi E. Testing for inherited thrombophilia and consequences for antithrombotic prophylaxis in patients with venous thromboembolism and their relatives. *Thromb Haemost* 2013;**110**:697–705.
68. Pierpont ME, Basson CT, Benson DW Jr, Gelb BD, Giglia TM, Goldmuntz E, McGee G, Sable CA, Srivastava D, Webb CL. Genetic basis for congenital heart defects: Current knowledge. *Circulation* 2007;**115**:3015–3038.
69. Burchill L, Greenway S, Silversides CK, Mital S. Genetic counseling in the adult with congenital heart disease: What is the role? *Curr Cardiol Rep* 2011;**13**:347–355.
70. Cowan JR, Ware SM. Genetics and genetic testing in congenital heart disease. *Clin Perinatol* 2015;**42**:373–393, ix.
71. Girerd B, Lau E, Montani D, Humbert M. Genetics of pulmonary hypertension in the clinic. *Curr Opin Pulm Med* 2017;**23**:386–391.
72. Priori SG, Blomstrom-Lundqvist C, Mazzanti A, Blom N, Borggrefe M, Camm J, Elliott PM, Fitzsimons D, Hatala R, Hindricks G, Kirchhof P, Kjeldsen K, Kuck KH, Hernandez-Madrid A, Nikolaou N, Norekval TM, Spaulding C, Van Veldhuisen DJ. 2015 ESC guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death. *Eur Heart J* 2015;**36**:2793–2867.
73. Skirton H, Goldsmith L, Jackson L, Lewis C, Chitty L. Offering prenatal diagnostic tests: European guidelines for clinical practice [corrected]. *Eur J Hum Genet* 2014;**22**:580–586.
74. Alanen J, Leskinen M, Sairanen M, Korpimaki T, Kouru H, Gissler M, Ryynanen M, Nevalainen J. Fetal nuchal translucency in severe congenital heart defects: Experiences in Northern Finland. *J Matern Fetal Neonatal Med* 2017:1–7.
75. Hyett J, Perdu M, Sharland G, Snijders R, Nicolaides KH. Using fetal nuchal translucency to screen for major congenital cardiac defects at 10-14 weeks of gestation: Population based cohort study. *BMJ* 1999;**318**:81–85.
76. Rasiah SV, Publicover M, Ewer AK, Khan KS, Kilby MD, Zamora J. A systematic review of the accuracy of first-trimester ultrasound examination for detecting major congenital heart disease. *Ultrasound Obstet Gynecol* 2006;**28**:110–116.
77. Eleftheriades M, Tsapakis E, Sotiriadis A, Manolakos E, Hassiakos D, Botsis D. Detection of congenital heart defects throughout pregnancy; impact of first trimester ultrasound screening for cardiac abnormalities. *J Matern Fetal Neonatal Med* 2012;**25**:2546–2550.
78. Thaman R, Varnava A, Hamid MS, Firoozi S, Sachdev B, Condon M, Gimeno JR, Murphy R, Elliott PM, McKenna WJ. Pregnancy related complications in women with hypertrophic cardiomyopathy. *Heart* 2003;**89**:752–756.
79. Rychik J, Ayres N, Cuneo B, Gotteiner N, Hornberger L, Spevak PJ, Van Der Veld M. American Society of Echocardiography guidelines and standards for performance of the fetal echocardiogram. *J Am Soc Echocardiogr* 2004;**17**:803–810.
80. Fetal Echocardiography Task Force, American Institute of Ultrasound in Medicine Clinical Standards Committee, American College of Obstetricians and Gynecologists, Society for Maternal-Fetal Medicine. AIUM practice guideline for the performance of fetal echocardiography. *J Ultrasound Med* 2011;**30**:127–136.
81. Neilson JP, Alfirevic Z. Doppler ultrasound for fetal assessment in high-risk pregnancies. *Cochrane Database Syst Rev* 2000;**2**:CD000073.
82. Manning FA. Fetal biophysical profile. *Obstet Gynecol Clin North Am* 1999;**26**:557–577.
83. Lees CC, Marlow N, van Wassenaer-Leemhuis A, Arabin B, Bilardo CM, Brezinka C, Calvert S, Derks JB, Diemert A, Duvekot JJ, Ferrazzi E, Frusca T, Ganzevoort W, Hecher K, Martinelli P, Ostermayer E, Papageorghiou AT, Schlembach D, Schneider KT, Thilaganathan B, Todros T, Valcamonico A, Visser GH, Wolf H. 2 year neurodevelopmental and intermediate perinatal outcomes in infants with very preterm fetal growth restriction (TRUFFLE): A randomised trial. *Lancet* 2015;**385**:2162–2172.
84. Wieseler KM, Bhargava P, Kanal KM, Vaidya S, Stewart BK, Dighe MK. Imaging in pregnant patients: Examination appropriateness. *Radiographics* 2010;**30**:1215–1229; discussion 1230–1213.
85. Ntusi NA, Samuels P, Moosa S, Mocumbi AO. Diagnosing cardiac disease during pregnancy: Imaging modalities. *Cardiovasc J Afr* 2016;**27**:95–103.
86. Kapoor MC. Cardiopulmonary bypass in pregnancy. *Ann Card Anaesth* 2014;**17**:33–39.
87. Baschat AA, Cosmi E, Bilardo CM, Wolf H, Berg C, Rigano S, Germer U, Moyano D, Turan S, Hartung J, Bhide A, Muller T, Bower S, Nicolaides KH, Thilaganathan B, Gembruch U, Ferrazzi E, Hecher K, Galan HL, Harman CR. Predictors of neonatal outcome in early-onset placental dysfunction. *Obstet Gynecol* 2007;**109**:253–261.

Downloaded from https://academic.oup.com/eurheartj/article-abstract/39/34/3165/5078465 by guest on 13 September 2018

88. John AS, Gurley F, Schaff HV, Warnes CA, Phillips SD, Arendt KW, Abel MD, Rose CH, Connolly HM. Cardiopulmonary bypass during pregnancy. *Ann Thorac Surg* 2011;**91**:1191–1196.
89. Chandrasekhar S, Cook CR, Collard CD. Cardiac surgery in the parturient. *Anesth Analg* 2009;**108**:777–785.
90. Hosseini S, Kashfi F, Samiei N, Khamoushi A, Ghavidel AA, Yazdanian F, Mirmesdagh Y, Mestres CA. Feto-maternal outcomes of urgent open-heart surgery during pregnancy. *J Heart Valve Dis* 2015;**24**:253–259.
91. Mishanina E, Rogozinska E, Thatthi T, Uddin-Khan R, Khan KS, Meads C. Use of labour induction and risk of cesarean delivery: A systematic review and meta-analysis. *CMAJ* 2014;**186**:665–673.
92. Roos-Hesselink JW, Ruys TP, Stein JI, Thilen U, Webb GD, Niwa K, Kaemmerer H, Baumgartner H, Budts W, Maggioni AP, Tavazzi L, Taha N, Johnson MR, Hall R. Outcome of pregnancy in patients with structural or ischaemic heart disease: Results of a registry of the European Society of Cardiology. *Eur Heart J* 2013;**34**:657–665.
93. Ramsey PS, Hogg BB, Savage KG, Winkler DD, Owen J. Cardiovascular effects of intravaginal misoprostol in the mid trimester of pregnancy. *Am J Obstet Gynecol* 2000;**183**:1100–1102.
94. Kilpatrick AW, Thorburn J. Severe hypotension due to intramyometrial injection of prostaglandin E2. *Anaesthesia* 1990;**45**:848–849.
95. Perloff JK, Child J. *Congenital heart disease in adults.* 2nd ed. Philadelphia: WB Saunders; 1998.
96. Ruys TP, Roos-Hesselink JW, Pijuan-Domenech A, Vasario E, Gaisin IR, Iung B, Freeman LJ, Gordon EP, Pieper PG, Hall R, Boersma E, Johnson MR. Is a planned caesarean section in women with cardiac disease beneficial? *Heart* 2015;**101**:530–536.
97. van Veen JJ, Maclean RM, Hampton KK, Laidlaw S, Kitchen S, Toth P, Makris M. Protamine reversal of low molecular weight heparin: Clinically effective? *Blood Coagul Fibrinolysis* 2011;**22**:565–570.
98. van Aart L, Eijkhout HW, Kamphuis JS, Dam M, Schattenkerk ME, Schouten TJ, Ploeger B, Strengers PF. Individualized dosing regimen for prothrombin complex concentrate more effective than standard treatment in the reversal of oral anticoagulant therapy: An open, prospective randomized controlled trial. *Thromb Res* 2006;**118**:313–320.
99. Chai-Adisaksopha C, Hillis C, Siegal DM, Movilla R, Heddle N, Iorio A, Crowther M. Prothrombin complex concentrates versus fresh frozen plasma for warfarin reversal. A systematic review and meta-analysis. *Thromb Haemost* 2016;**116**:879–890.
100. Devitt JH, Noble WH, Byrick RJ. A Swan-Ganz catheter related complication in a patient with Eisenmenger's syndrome. *Anesthesiology* 1982;**57**:335–337.
101. Dob DP, Yentis SM. Practical management of the parturient with congenital heart disease. *Int J Obstet Anesth* 2006;**15**:137–144.
102. Rossi A, Cornette J, Johnson MR, Karamermer Y, Springeling T, Opic P, Moelker A, Krestin GP, Steegers E, Roos-Hesselink J, van Geuns RJ. Quantitative cardiovascular magnetic resonance in pregnant women: Cross-sectional analysis of physiological parameters throughout pregnancy and the impact of the supine position. *J Cardiovasc Magn Reson* 2011;**13**:31.
103. Blake MJ, Martin A, Manktelow BN, Armstrong C, Halligan AW, Panerai RB, Potter JF. Changes in baroreceptor sensitivity for heart rate during normotensive pregnancy and the puerperium. *Clin Sci (Lond)* 2000;**98**:259–268.
104. Foley M, Lockwood C, Gersh B, Barss V. Maternal cardiovascular and hemodynamic adaptation to pregnancy. https://www.scribd.com/document/269648347/Maternal-Cardiovascular-and-Hemodynamic-Adaptations-to-Pregnancy 2010.
105. Cauldwell M, Steer PJ, Swan L, Uebing A, Gatzoulis MA, Johnson MR. The management of the third stage of labour in women with heart disease. *Heart* 2017;**103**:945–951.
106. Hofmeyr GJ, Gulmezoglu AM, Novikova N, Linder V, Ferreira S, Piaggio G. Misoprostol to prevent and treat postpartum haemorrhage: A systematic review and meta-analysis of maternal deaths and dose-related effects. *Bull World Health Organ* 2009;**87**:666–677.
107. de Labriolle A, Genee O, Heggs LM, Fauchier L. Acute myocardial infarction following oral methyl-ergometrine intake. *Cardiovasc Toxicol* 2009;**9**:46–48.
108. Svanstrom MC, Biber B, Hanes M, Johansson G, Naslund U, Balfors EM. Signs of myocardial ischaemia after injection of oxytocin: A randomized double-blind comparison of oxytocin and methylergometrine during caesarean section. *Br J Anaesth* 2008;**100**:683–689.
109. Bateman BT, Patorno E, Desai RJ, Seely EW, Mogun H, Maeda A, Fischer MA, Hernandez-Diaz S, Huybrechts KF. Late pregnancy β blocker exposure and risks of neonatal hypoglycemia and bradycardia. *Pediatrics* 2016;**138**:e20160731.
110. Kuijpers JM, Koolbergen DR, Groenink M, Peels KCH, Reichert CLA, Post MC, Bosker HA, Wajon E, Zwinderman AH, Mulder BJM, Bouma BJ. Incidence, risk factors, and predictors of infective endocarditis in adult congenital heart disease: Focus on the use of prosthetic material. *Eur Heart J* 2017;**38**: 2048–2056.
111. Kebed KY, Bishu K, Al Adham RI, Baddour LM, Connolly HM, Sohail MR, Steckelberg JM, Wilson WR, Murad MH, Anavekar NS. Pregnancy and postpartum infective endocarditis: A systematic review. *Mayo Clin Proc* 2014;**89**:1143–1152.
112. Habib G, Lancellotti P, Antunes MJ, Bongiorni MG, Casalta JP, Del Zotti F, Dulgheru R, El Khoury G, Erba PA, Iung B, Miro JM, Mulder BJ, Plonska-Gosciniak E, Price S, Roos-Hesselink J, Snygg-Martin U, Thuny F, Tornos Mas P, Vilacosta I, Zamorano JL. 2015 ESC guidelines for the management of infective endocarditis. *Eur Heart J* 2015;**36**:3075–3128.
113. Montoya ME, Karnath BM, Ahmad M. Endocarditis during pregnancy. *South Med J* 2003;**96**:1156–1157.
114. Campuzano K, Roque H, Bolnick A, Leo MV, Campbell WA. Bacterial endocarditis complicating pregnancy: Case report and systematic review of the literature. *Arch Gynecol Obstet* 2003;**268**:251–255.
115. Drugs.com. FDA Pregnancy Categories. https://www.drugs.com/pregnancy/.
116. Thorne S, Nelson-Piercy C, MacGregor A, Gibbs S, Crowhurst J, Panay N, Rosenthal E, Walker F, Williams D, de Swiet M, Guillebaud J. Pregnancy and contraception in heart disease and pulmonary arterial hypertension. *J Fam Plann Reprod Health Care* 2006;**32**:75–81.
117. World Health Organization. *Medical eligibility criteria for contraceptive use.* 5th ed. Geneva: WHO Press; 2015. p.267.
118. Mercer CH, Tanton C, Prah P, Erens B, Sonnenberg P, Clifton S, Macdowall W, Lewis R, Field N, Datta J, Copas AJ, Phelps A, Wellings K, Johnson AM. Changes in sexual attitudes and lifestyles in Britain through the life course and over time: Findings from the National Surveys of Sexual Attitudes and Lifestyles (NATSAL). *Lancet* 2013;**382**:1781–1794.
119. Vigl M, Kaemmerer M, Niggemeyer E, Nagdyman N, Seifert-Klauss V, Trigas V, Bauer U, Schneider KT, Berger F, Hess J, Kaemmerer H. Sexuality and reproductive health in women with congenital heart disease. *Am J Cardiol* 2010;**105**:538–541.
120. Roos-Hesselink JW, Cornette J, Sliwa K, Pieper PG, Veldtman GR, Johnson MR. Contraception and cardiovascular disease. *Eur Heart J* 2015;**36**:1728–1734, 1734a–1734b.
121. Lidegaard O, Lokkegaard E, Svendsen AL, Agger C. Hormonal contraception and risk of venous thromboembolism: National follow-up study. *BMJ* 2009;**339**:b2890.
122. Lidegaard O, Lokkegaard E, Jensen A, Skovlund CW, Keiding N. Thrombotic stroke and myocardial infarction with hormonal contraception. *N Engl J Med* 2012;**366**:2257–2266.
123. Vieira CS, Ferriani RA, Garcia AA, Pintao MC, Azevedo GD, Gomes MK, Silva-de-Sa MF. Use of the etonogestrel-releasing implant is associated with hypoactivation of the coagulation cascade. *Hum Reprod* 2007;**22**:2196–2201.
124. Cheng L, Che Y, Gulmezoglu AM. Interventions for emergency contraception. *Cochrane Database Syst Rev* 2012;**8**:CD001324.
125. Vasilakis C, Jick SS, Jick H. The risk of venous thromboembolism in users of postcoital contraceptive pills. *Contraception* 1999;**59**:79–83.
126. Gemzell-Danielsson K, Rabe T, Cheng L. Emergency contraception. *Gynecol Endocrinol* 2013;**29**:1–14.
127. Jesam C, Cochon L, Salvatierra AM, Williams A, Kapp N, Levy-Gompel D, Brache V. A prospective, open-label, multicenter study to assess the pharmacodynamics and safety of repeated use of 30 mg ulipristal acetate. *Contraception* 2016;**93**:310–316.
128. Valle RF, Carignan CS, Wright TC. Tissue response to the stop microcoil transcervical permanent contraceptive device: Results from a prehysterectomy study. *Fertil Steril* 2001;**76**:974–980.
129. Ireland LD, Gatter M, Chen AY. Medical compared with surgical abortion for effective pregnancy termination in the first trimester. *Obstet Gynecol* 2015;**126**:22–28.
130. Dhalwani NN, Fiaschi L, West J, Tata LJ. Occurrence of fertility problems presenting to primary care: Population-level estimates of clinical burden and socioeconomic inequalities across the UK. *Hum Reprod* 2013;**28**:960–968.
131. Humaidan P, Nelson SM, Devroey P, Coddington CC, Schwartz LB, Gordon K, Frattarelli JL, Tarlatzis BC, Fatemi HM, Lutjen P, Stegmann BJ. Ovarian hyperstimulation syndrome: Review and new classification criteria for reporting in clinical trials. *Hum Reprod* 2016;**31**:1997–2004.
132. Kametas NA, McAuliffe F, Krampl E, Chambers J, Nicolaides KH. Maternal cardiac function in twin pregnancy. *Obstet Gynecol* 2003;**102**:806–815.
133. Ombelet W, Martens G, De Sutter P, Gerris J, Bosmans E, Ruyssinck G, Defoort P, Molenberghs G, Gyselaers W. Perinatal outcome of 12,021 singleton and 3108 twin births after non-IVF-assisted reproduction: A cohort study. *Hum Reprod* 2006;**21**:1025–1032.
134. Royal College of Obstetricians and Gynaecologists. *Antenatal corticosteroids to reduce neonatal morbidity and mortality. Royal College of Obstetricians and Gynaecologists Green-Top Guideline No. 7. October 2010*. London: Royal College of Obstetricians and Gynaecologists; 2015.

Downloaded from https://academic.oup.com/eurheartj/article-abstract/39/34/3165/5078465 by guest on 13 September 2018

135. Lees C, Marlow N, Arabin B, Bilardo CM, Brezinka C, Derks JB, Duvekot J, Frusca T, Diemert A, Ferrazzi E, Ganzevoort W, Hecher K, Martinelli P, Ostermayer E, Papageorghiou AT, Schlembach D, Schneider KT, Thilaganathan B, Todros T, van Wassenaer-Leemhuis A, Valcamonico A, Visser GH, Wolf H. Perinatal morbidity and mortality in early-onset fetal growth restriction: Cohort outcomes of the trial of randomized umbilical and fetal flow in Europe (TRUFFLE). *Ultrasound Obstet Gynecol* 2013;**42**:400–408.
136. Marelli AJ, Ionescu-Ittu R, Mackie AS, Guo L, Dendukuri N, Kaouache M. Lifetime prevalence of congenital heart disease in the general population from 2000 to 2010. *Circulation* 2014;**130**:749–756.
137. Mandalenakis Z, Rosengren A, Skoglund K, Lappas G, Eriksson P, Dellborg M. Survivorship in children and young adults with congenital heart disease in Sweden. *JAMA Intern Med* 2017;**177**:224–230.
138. Sliwa K, van Hagen IM, Budts W, Swan L, Sinagra G, Caruana M, Blanco MV, Wagenaar LJ, Johnson MR, Webb G, Hall R, Roos-Hesselink JW. Pulmonary hypertension and pregnancy outcomes: Data from the Registry of Pregnancy and Cardiac Disease (ROPAC) of the European Society of Cardiology. *Eur J Heart Fail* 2016;**18**:1119–1128.
139. Balint OH, Siu SC, Mason J, Grewal J, Wald R, Oechslin EN, Kovacs B, Sermer M, Colman JM, Silversides CK. Cardiac outcomes after pregnancy in women with congenital heart disease. *Heart* 2010;**96**:1656–1661.
140. Peacock AJ, Murphy NF, McMurray JJ, Caballero L, Stewart S. An epidemiological study of pulmonary arterial hypertension. *Eur Respir J* 2007;**30**:104–109.
141. Bendayan D, Hod M, Oron G, Sagie A, Eidelman L, Shitrit D, Kramer MR. Pregnancy outcome in patients with pulmonary arterial hypertension receiving prostacyclin therapy. *Obstet Gynecol* 2005;**106**:1206–1210.
142. Jais X, Olsson KM, Barbera JA, Blanco I, Torbicki A, Peacock A, Vizza CD, Macdonald P, Humbert M, Hoeper MM. Pregnancy outcomes in pulmonary arterial hypertension in the modern management era. *Eur Respir J* 2012;**40**:881–885.
143. Duarte AG, Thomas S, Safdar Z, Torres F, Pacheco LD, Feldman J, DeBoisblanc B. Management of pulmonary arterial hypertension during pregnancy: A retrospective, multicenter experience. *Chest* 2013;**143**:1330–1336.
144. Bedard E, Dimopoulos K, Gatzoulis MA. Has there been any progress made on pregnancy outcomes among women with pulmonary arterial hypertension? *Eur Heart J* 2009;**30**:256–265.
145. Hemnes AR, Kiely DG, Cockrill BA, Safdar Z, Wilson VJ, Al Hazmi M, Preston IR, MacLean MR, Lahm T. Statement on pregnancy in pulmonary hypertension from the pulmonary vascular research institute. *Pulm Circ* 2015;**5**:435–465.
146. Duan R, Xu X, Wang X, Yu H, You Y, Liu X, Xing A, Zhou R, Xi M. Pregnancy outcome in women with Eisenmenger's syndrome: A case series from west china. *BMC Pregnancy Childbirth* 2016;**16**:356.
147. Cha KS, Cho KI, Seo JS, Choi JH, Park YH, Yang DH, Hong GR, Kim DS. Effects of inhaled iloprost on exercise capacity, quality of life, and cardiac function in patients with pulmonary arterial hypertension secondary to congenital heart disease (the Eisenmenger syndrome) (from the EIGER Study). *Am J Cardiol* 2013;**112**:1834–1839.
148. Ladouceur M, Benoit L, Basquin A, Radojevic J, Hauet Q, Hascoet S, Moceri P, Le Gloan L, Amedro P, Lucron H, Richard A, Gouton M, Nizard J. How pregnancy impacts adult cyanotic congenital heart disease: A multicenter observational study. *Circulation* 2017;**135**:2444–2447.
149. Presbitero P, Somerville J, Stone S, Aruta E, Spiegelhalter D, Rabajoli F. Pregnancy in cyanotic congenital heart disease. Outcome of mother and fetus. *Circulation* 1994;**89**:2673–2676.
150. Yap SC, Drenthen W, Meijboom FJ, Moons P, Mulder BJ, Vliegen HW, van Dijk AP, Jaddoe VW, Steegers EA, Roos-Hesselink JW, Pieper PG. Comparison of pregnancy outcomes in women with repaired versus unrepaired atrial septal defect. *BJOG* 2009;**116**:1593–1601.
151. Balci A, Drenthen W, Mulder BJ, Roos-Hesselink JW, Voors AA, Vliegen HW, Moons P, Sollie KM, van Dijk AP, van Veldhuisen DJ, Pieper PG. Pregnancy in women with corrected tetralogy of fallot: Occurrence and predictors of adverse events. *Am Heart J* 2011;**161**:307–313.
152. Kampman MA, Siegmund AS, Bilardo CM, van Veldhuisen DJ, Balci A, Oudijk MA, Groen H, Mulder BJ, Roos-Hesselink JW, Sieswerda G, de Laat MW, Sollie-Szarynska KM, Pieper PG. Uteroplacental doppler flow and pregnancy outcome in women with tetralogy of fallot. *Ultrasound Obstet Gynecol* 2017;**49**:231–239.
153. Lima FV, Koutrolou-Sotiropoulou P, Yen TY, Stergiopoulos K. Clinical characteristics and outcomes in pregnant women with Ebstein anomaly at the time of delivery in the USA: 2003-2012. *Arch Cardiovasc Dis* 2016;**109**:390–398.
154. Bowater SE, Selman TJ, Hudsmith LE, Clift PF, Thompson PJ, Thorne SA. Long-term outcome following pregnancy in women with a systemic right ventricle: Is the deterioration due to pregnancy or a consequence of time? *Congenit Heart Dis* 2013;**8**:302–307.
155. Cataldo S, Doohan M, Rice K, Trinder J, Stuart AG, Curtis SL. Pregnancy following Mustard or Senning correction of transposition of the great arteries: A retrospective study. *BJOG* 2016;**123**:807–813.
156. Hornung TS, Bernard EJ, Celermajer DS, Jaeggi E, Howman-Giles RB, Chard RB, Hawker RE. Right ventricular dysfunction in congenitally corrected transposition of the great arteries. *Am J Cardiol* 1999;**84**:1116–1119, A1110.
157. Gouton M, Nizard J, Patel M, Sassolas F, Jimenez M, Radojevic J, Mathiron A, Amedro P, Barre E, Labombarda F, Vaksmann G, Chantepie A, Le Gloan L, Ladouceur M. Maternal and fetal outcomes of pregnancy with Fontan circulation: A multicentric observational study. *Int J Cardiol* 2015;**187**:84–89.
158. Cauldwell M, Von Klemperer K, Uebing A, Swan L, Steer PJ, Gatzoulis M, Johnson MR. Why is post-partum haemorrhage more common in women with congenital heart disease? *Int J Cardiol* 2016;**218**:285–290.
159. Zentner D, Kotevski A, King I, Grigg L, d'Udekem Y. Fertility and pregnancy in the Fontan population. *Int J Cardiol* 2016;**208**:97–101.
160. Niwa K, Siu SC, Webb GD, Gatzoulis MA. Progressive aortic root dilatation in adults late after repair of tetralogy of fallot. *Circulation* 2002;**106**:1374–1378.
161. Sawlani N, Shroff A, Vidovich MI. Aortic dissection and mortality associated with pregnancy in the United States. *J Am Coll Cardiol* 2015;**65**:1600–1601.
162. Thalmann M, Sodeck GH, Domanovits H, Grassberger M, Loewe C, Grimm M, Czerny M. Acute type a aortic dissection and pregnancy: A population-based study. *Eur J Cardiothorac Surg* 2011;**39**:e159–e163.
163. Hiratzka LF, Bakris GL, Beckman JA, Bersin RM, Carr VF, Casey DE Jr, Eagle KA, Hermann LK, Isselbacher EM, Kazerooni EA, Kouchoukos NT, Lytle BW, Milewicz DM, Reich DL, Sen S, Shinn JA, Svensson LG, Williams DM; American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines; American Association for Thoracic Surgery; American College of Radiology; American Stroke Association; Society of Cardiovascular Anesthesiologists; Society for Cardiovascular Angiography and Interventions; Society of Interventional Radiology; Society of Thoracic Surgeons; Society for Vascular Medicine. 2010 ACCF/AHA/AATS/ACR/ASA/SCA/SCAI/SIR/STS/SVM guidelines for the diagnosis and management of patients with thoracic aortic disease: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, American Association for Thoracic Surgery, American College of Radiology, American Stroke Association,Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, Society of Interventional Radiology, Society of Thoracic Surgeones, and Society for Vascular Medicine. *Circulation* 2010;**121**:e266–e369.
164. Erbel R, Aboyans V, Boileau C, Bossone E, Bartolomeo RD, Eggebrecht H, Evangelista A, Falk V, Frank H, Gaemperli O, Grabenwoger M, Haverich A, Iung B, Manolis AJ, Meijboom F, Nienaber CA, Roffi M, Rousseau H, Sechtem U, Sirnes PA, Allmen RS, Vrints CJ. 2014 ESC guidelines on the diagnosis and treatment of aortic diseases. *Eur Heart J* 2014;**35**:2873–2926.
165. Manalo-Estrella P, Barker AE. Histopathologic findings in human aortic media associated with pregnancy. *Arch Pathol* 1967;**83**:336–341.
166. Gutin LS, Merz AE, Bakalov VK, Gharib AM, Bondy CA. Parity and aortic dimensions in healthy women. *Int J Cardiol* 2013;**165**:383–384.
167. Meijboom LJ, Vos FE, Timmermans J, Boers GH, Zwinderman AH, Mulder BJ. Pregnancy and aortic root growth in the Marfan syndrome: A prospective study. *Eur Heart J* 2005;**26**:914–920.
168. Donnelly RT, Pinto NM, Kocolas I, Yetman AT. The immediate and long-term impact of pregnancy on aortic growth rate and mortality in women with Marfan syndrome. *J Am Coll Cardiol* 2012;**60**:224–229.
169. Januzzi JL, Isselbacher EM, Fattori R, Cooper JV, Smith DE, Fang J, Eagle KA, Mehta RH, Nienaber CA, Pape LA. Characterizing the young patient with aortic dissection: Results from the International Registry of Aortic Dissection (IRAD). *J Am Coll Cardiol* 2004;**43**:665–669.
170. Smith K, Gros B. Pregnancy-related acute aortic dissection in Marfan syndrome: A review of the literature. *Congenit Heart Dis* 2017;**12**:251–260.
171. Pyeritz RE. Maternal and fetal complications of pregnancy in the Marfan syndrome. *Am J Med* 1981;**71**:784–790.
172. Sayama S, Takeda N, Iriyama T, Inuzuka R, Maemura S, Fujita D, Yamauchi H, Nawata K, Bougaki M, Hyodo H, Shitara R, Nakayama T, Komatsu A, Nagamatsu T, Osuga Y, Fujii T. Peripartum type B aortic dissection in patients with Marfan syndrome who underwent aortic root replacement: A case series study. *BJOG* 2017;**125**:487–493.
173. Rossiter JP, Repke JT, Morales AJ, Murphy EA, Pyeritz RE. A prospective longitudinal evaluation of pregnancy in the Marfan syndrome. *Am J Obstet Gynecol* 1995;**173**:1599–1606.
174. Loeys BL, Dietz HC, Braverman AC, Callewaert BL, De Backer J, Devereux RB, Hilhorst-Hofstee Y, Jondeau G, Faivre L, Milewicz DM, Pyeritz RE, Sponseller PD, Wordsworth P, De Paepe AM. The revised Ghent nosology for the Marfan syndrome. *J Med Genet* 2010;**47**:476–485.
175. Goland S, Elkayam U. Cardiovascular problems in pregnant women with Marfan syndrome. *Circulation* 2009;**119**:619–623.
176. McKellar SH, MacDonald RJ, Michelena HI, Connolly HM, Sundt TM III. Frequency of cardiovascular events in women with a congenitally bicuspid

Downloaded from https://academic.oup.com/eurheartj/article-abstract/39/34/3165/5078465 by guest on 13 September 2018

aortic valve in a single community and effect of pregnancy on events. *Am J Cardiol* 2011;**107**:96–99.
177. Murray ML, Pepin M, Peterson S, Byers PH. Pregnancy-related deaths and complications in women with vascular Ehlers-Danlos syndrome. *Genet Med* 2014;**16**:874–880.
178. Gravholt CH, Andersen NH, Conway GS, Dekkers OM, Geffner ME, Klein KO, Lin AE, Mauras N, Quigley CA, Rubin K, Sandberg DE, Sas TCJ, Silberbach M, Soderstrom-Anttila V, Stochholm K, van Alfen-van derVelden JA, Woelfle J, Backeljauw PF. Clinical practice guidelines for the care of girls and women with Turner syndrome: Proceedings from the 2016 Cincinnati International Turner Syndrome Meeting. *Eur J Endocrinol* 2017;**177**:G1–G70.
179. Carlson M, Silberbach M. Dissection of the aorta in Turner syndrome: Two cases and review of 85 cases in the literature. *J Med Genet* 2007;**44**:745–749.
180. Gravholt CH, Landin-Wilhelmsen K, Stochholm K, Hjerrild BE, Ledet T, Djurhuus CB, Sylven L, Baandrup U, Kristensen BO, Christiansen JS. Clinical and epidemiological description of aortic dissection in Turner's syndrome. *Cardiol Young* 2006;**16**:430–436.
181. Regalado ES, Guo DC, Estrera AL, Buja LM, Milewicz DM. Acute aortic dissections with pregnancy in women with ACTA2 mutations. *Am J Med Genet A* 2014;**164A**:106–112.
182. van Hagen IM, van der Linde D, van de Laar IM, Muino Mosquera L, De Backer J, Roos-Hesselink JW. Pregnancy in women with SMAD3 mutation. *J Am Coll Cardiol* 2017;**69**:1356–1358.
183. Braverman AC, Moon MR, Geraghty P, Willing M, Bach C, Kouchoukos NT. Pregnancy after aortic root replacement in Loeys-Dietz syndrome: High risk of aortic dissection. *Am J Med Genet A* 2016;**170**:2177–2180.
184. Jondeau G, Ropers J, Regalado E, Braverman A, Evangelista A, Teixedo G, De Backer J, Muino-Mosquera L, Naudion S, Zordan C, Morisaki T, Morisaki H, Von Kodolitsch Y, Dupuis-Girod S, Morris SA, Jeremy R, Odent S, Ades LC, Bakshi M, Holman K, LeMaire S, Milleron O, Langeois M, Spentchian M, Aubart M, Boileau C, Pyeritz R, Milewicz DM, Montalcino Aortic C. International registry of patients carrying TGFBR1 or TGFBR2 mutations: Results of the MAC (Montalcino Aortic Consortium). *Circ Cardiovasc Genet* 2016;**9**:548–558.
185. Whelton PK, Carey RM, Aronow WS, Casey DE Jr, Collins KJ, Dennison Himmelfarb C, DePalma SM, Gidding S, Jamerson KA, Jones DW, MacLaughlin EJ, Muntner P, Ovbiagele B, Smith SC, Jr., Spencer CC, Stafford RS, Taler SJ, Thomas RJ, Williams KA, Sr., Williamson JD, Wright JT Jr. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APHA/aASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: A report of the American College of Cardiology/American Heart Association Task Force on Cinical Practice Guidelines. *Hypertension* 2018;**71**:e13–e115.
186. Ong KT, Perdu J, De Backer J, Bozec E, Collignon P, Emmerich J, Fauret AL, Fiessinger JN, Germain DP, Georgesco G, Hulot JS, De Paepe A, Plauchu H, Jeunemaitre X, Laurent S, Boutouyrie P. Effect of celiprolol on prevention of cardiovascular events in vascular Ehlers-Danlos syndrome: A prospective randomised, open, blinded-endpoints trial. *Lancet* 2010;**376**:1476–1484.
187. Yates MT, Soppa G, Smelt J, Fletcher N, van Besouw JP, Thilaganathan B, Jahangiri M. Perioperative management and outcomes of aortic surgery during pregnancy. *J Thorac Cardiovasc Surg* 2015;**149**:607–610.
188. Suzuki T, Isselbacher EM, Nienaber CA, Pyeritz RE, Eagle KA, Tsai TT, Cooper JV, Januzzi JL Jr, Braverman AC, Montgomery DG, Fattori R, Pape L, Harris KM, Booher A, Oh JK, Peterson M, Ramanath VS, Froehlich JB. Type-selective benefits of medications in treatment of acute aortic dissection (from the international registry of acute aortic dissection [IRAD]). *Am J Cardiol* 2012;**109**(1):122–127.
189. Fattori R, Montgomery D, Lovato L, Kische S, Di Eusanio M, Ince H, Eagle KA, Isselbacher EM, Nienaber CA. Survival after endovascular therapy in patients with type b aortic dissection: A report from the International Registry of Acute Aortic Dissection (irad). *JACC Cardiovasc Interv* 2013;**6**:876–882.
190. Brener MI, Keramati AR. Type B dissection in a pregnant woman managed with peripartum thoracic endovascular aortic repair. *Circulation* 2016;**133**:e369–e373.
191. De Martino RR, Johnstone J, Baldwin EA, Brost BC, Connolly HM, Pochettino A. Endograft as bridge to open repair for ruptured thoracic aneurysm in a pregnant Marfan patient. *Ann Thorac Surg* 2015;**100**:304–307.
192. Liu H, Shu C, Li X, Wang T, Li M, Li QM, Fang K, Wang S. Endovascular aortic repair combined with chimney technique in the treatment of stanford type B aortic dissection involving aortic arch. *Ann Vasc Surg* 2015;**29**:758–763.
193. Chahwala V, Tashiro J, Baqai A, Gologorsky E, Rey J, Robinson HR. Endovascular repair of a thoracic aortic aneurysm in pregnancy at 22 weeks of gestation. *J Vasc Surg* 2015;**62**:1323–1325.
194. Lesniak-Sobelga A, Tracz W, KostKiewicz M, Podolec P, Pasowicz M. Clinical and echocardiographic assessment of pregnant women with valvular heart diseases–maternal and fetal outcome. *Int J Cardiol* 2004;**94**:15–23.
195. Zuhlke L, Engel ME, Karthikeyan G, Rangarajan S, Mackie P, Cupido B, Mauff K, Islam S, Joachim A, Daniels R, Francis V, Ogendo S, Gitura B, Mondo C, Okello E, Lwabi P, Al-Kebsi MM, Hugo-Hamman C, Sheta SS, Haileamlak A, Daniel W, Goshu DY, Abdissa SG, Desta AG, Shasho BA, Begna DM, ElSayed A, Ibrahim AS, Musuku J, Bode-Thomas F, Okeahialam BN, Ige O, Sutton C, Misra R, Abul Fadl A, Kennedy N, Damasceno A, Sani M, Ogah OS, Olunuga T, Elhassan HH, Mocumbi AO, Adeoye AM, Mntla P, Ojji D, Mucumbitsi J, Teo K, Yusuf S, Mayosi BM. Characteristics, complications, and gaps in evidence-based interventions in rheumatic heart disease: The Global Rheumatic Heart Disease Registry (the REMEDY study). *Eur Heart J* 2015;**36**:1115–1122a.
196. van Hagen IM, Roos-Hesselink JW, Ruys TP, Merz WM, Goland S, Gabriel H, Lelonek M, Trojnarska O, Al Mahmeed WA, Balint HO, Ashour Z, Baumgartner H, Boersma E, Johnson MR, Hall R. Pregnancy in women with a mechanical heart valve: Data of the European Society of Cardiology Registry of Pregnancy and Cardiac Disease (ROPAC). *Circulation* 2015;**132**:132–142.
197. Samiei N, Amirsardari M, Rezaei Y, Parsaee M, Kashfi F, Hantoosh Zadeh S, Beikmohamadi S, Fouladi M, Hosseini S, Peighambari MM, Mohebbi A. Echocardiographic evaluation of hemodynamic changes in left-sided heart valves in pregnant women with valvular heart disease. *Am J Cardiol* 2016;**118**:1046–1052.
198. Hameed A, Karaalp IS, Tummala PP, Wani OR, Canetti M, Akhter MW, Goodwin I, Zapadinsky N, Elkayam U. The effect of valvular heart disease on maternal and fetal outcome of pregnancy. *J Am Coll Cardiol* 2001;**37**:893–899.
199. van Hagen IM, Thorne SA, Taha N, Youssef G, Elnagar A, Gabriel H, ElRakshy Y, Iung B, Johnson MR, Hall R, Roos-Hesselink JW; ROPAC Investigators and EORP Team. Pregnancy outcomes in women with rheumatic mitral valve disease: Results from the Registry of Pregnancy and Cardiac Disease. *Circulation* 2018;**137**:806–816.
200. Silversides CK, Colman JM, Sermer M, Siu SC. Cardiac risk in pregnant women with rheumatic mitral stenosis. *Am J Cardiol* 2003;**91**:1382–1385.
201. Avila WS, Rossi EG, Ramires JA, Grinberg M, Bortolotto MR, Zugaib M, da Luz PL. Pregnancy in patients with heart disease: Experience with 1,000 cases. *Clin Cardiol* 2003;**26**:135–142.
202. Diao M, Kane A, Ndiaye MB, Mbaye A, Bodian M, Dia MM, Sarr M, Kane A, Monsuez JJ, Ba SA. Pregnancy in women with heart disease in sub-Saharan Africa. *Arch Cardiovasc Dis* 2011;**104**:370–374.
203. Ahmed N, Kausar H, Ali L, Rakhshinda. Fetomaternal outcome of pregnancy with mitral stenosis. *Pak J Med Sci* 2015;**31**:643–647.
204. Baumgartner H, Falk V, Bax JJ, De Bonis M, Hamm C, Holm PJ, Iung B, Lancellotti P, Lansac E, Rodriguez Munoz D, Rosenhek R, Sjogren J, Tornos Mas P, Vahanian A, Walther T, Wendler O, Windecker S, Zamorano JL. 2017 ESC/EACTS guidelines for the management of valvular heart disease. *Eur Heart J* 2017;**38**:2739–2791.
205. Baumgartner H, Hung J, Bermejo J, Chambers JB, Evangelista A, Griffin BP, Iung B, Otto CM, Pellikka PA, Quinones M. Echocardiographic assessment of valve stenosis: EAE/ASE recommendations for clinical practice. *Eur J Echocardiogr* 2009;**10**:1–25.
206. Elassy SM, Elmidany AA, Elbawab HY. Urgent cardiac surgery during pregnancy: A continuous challenge. *Ann Thorac Surg* 2014;**97**:1624–1629.
207. Orwat S, Diller GP, van Hagen IM, Schmidt R, Tobler D, Greutmann M, Jonkaitiene R, Elnagar A, Johnson MR, Hall R, Roos-Hesselink JW, Baumgartner H. Risk of pregnancy in moderate and severe aortic stenosis: From the multinational ROPAC registry. *J Am Coll Cardiol* 2016;**68**:1727–1737.
208. Silversides CK, Colman JM, Sermer M, Farine D, Siu SC. Early and intermediate-term outcomes of pregnancy with congenital aortic stenosis. *Am J Cardiol* 2003;**91**:1386–1389.
209. Yap SC, Drenthen W, Pieper PG, Moons P, Mulder BJ, Mostert B, Vliegen HW, van Dijk AP, Meijboom FJ, Steegers EA, Roos-Hesselink JW. Risk of complications during pregnancy in women with congenital aortic stenosis. *Int J Cardiol* 2008;**126**:240–246.
210. Tzemos N, Silversides CK, Colman JM, Therrien J, Webb GD, Mason J, Cocoara E, Sermer M, Siu SC. Late cardiac outcomes after pregnancy in women with congenital aortic stenosis. *Am Heart J* 2009;**157**:474–480.
211. Heuvelman HJ, Arabkhani B, Cornette JM, Pieper PG, Bogers AJ, Takkenberg JJ, Roos-Hesselink JW. Pregnancy outcomes in women with aortic valve substitutes. *Am J Cardiol* 2013;**111**:382–387.
212. Lawley CM, Lain SJ, Algert CS, Ford JB, Figtree GA, Roberts CL. Prosthetic heart valves in pregnancy, outcomes for women and their babies: A systematic review and meta-analysis. *BJOG* 2015;**122**:1446–1455.
213. Yap SC, Drenthen W, Pieper PG, Moons P, Mulder BJ, Klieverik LM, Vliegen HW, van Dijk AP, Meijboom FJ, Roos-Hesselink JW. Outcome of pregnancy in women after pulmonary autograft valve replacement for congenital aortic valve disease. *J Heart Valve Dis* 2007;**16**:398–403.
214. Vause S, Clarke B, Tower CL, Hay C, Knight M. Pregnancy outcomes in women with mechanical prosthetic heart valves: A prospective descriptive population

Downloaded from https://academic.oup.com/eurheartj/article-abstract/39/34/3165/5078465 by guest on 13 September 2018

based study using the United Kingdom Obstetric Surveillance System (UKOSS) data collection system. *BJOG* 2017;**124**:1411–1419.
215. Abildgaard U, Sandset PM, Hammerstrom J, Gjestvang FT, Tveit A. Management of pregnant women with mechanical heart valve prosthesis: Thromboprophylaxis with low molecular weight heparin. *Thromb Res* 2009;**124**:262–267.
216. Sillesen M, Hjortdal V, Vejlstrup N, Sorensen K. Pregnancy with prosthetic heart valves - 30 years' nationwide experience in Denmark. *Eur J Cardiothorac Surg* 2011;**40**:448–454.
217. 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.
218. 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.
219. Xu Z, Fan J, Luo X, Zhang WB, Ma J, Lin YB, Ma SH, Chen X, Wang ZP, Ou JS, Zhang X. Anticoagulation regimens during pregnancy in patients with mechanical heart valves: A systematic review and meta-analysis. *Can J Cardiol* 2016;**32**:1248.e1–1248.e9.
220. Yinon Y, Siu SC, Warshafsky C, Maxwell C, McLeod A, Colman JM, Sermer M, Silversides CK. Use of low molecular weight heparin in pregnant women with mechanical heart valves. *Am J Cardiol* 2009;**104**:1259–1263.
221. Quinn J, Von Klemperer K, Brooks R, Peebles D, Walker F, Cohen H. Use of high intensity adjusted dose low molecular weight heparin in women with mechanical heart valves during pregnancy: A single-center experience. *Haematologica* 2009;**94**:1608–1612.
222. Basude S, Hein C, Curtis SL, Clark A, Trinder J. Low-molecular-weight heparin or warfarin for anticoagulation in pregnant women with mechanical heart valves: What are the risks? A retrospective observational study. *BJOG* 2012;**119**:1008–1013; discussion 1012–1003.
223. D'Souza R, Ostro J, Shah PS, Silversides CK, Malinowski A, Murphy KE, Sermer M, Shehata N. Anticoagulation for pregnant women with mechanical heart valves: A systematic review and meta-analysis. *Eur Heart J* 2017;**214**:S351–S351.
224. 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.
225. Goland S, Schwartzenberg S, Fan J, Kozak N, Khatri N, Elkayam U. Monitoring of anti-Xa in pregnant patients with mechanical prosthetic valves receiving low-molecular-weight heparin: Peak or trough levels? *J Cardiovasc Pharmacol Ther* 2014;**19**:451–456.
226. Vijayan V, Rachel T. Pregnancy outcomes compared in women with mechanical heart valve replacements anticoagulated with warfarin and enoxaparin in pregnancy. *Med J Malaysia* 2012;**67**:591–594.
227. McLintock C. Thromboembolism in pregnancy: Challenges and controversies in the prevention of pregnancy-associated venous thromboembolism and management of anticoagulation in women with mechanical prosthetic heart valves. *Best Pract Res Clin Obstet Gynaecol* 2014;**28**:519–536.
228. 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.
229. Wesseling J, Van Driel D, Heymans HS, Rosendaal FR, Geven-Boere LM, Smrkovsky M, Touwen BC, Sauer PJ, Van der Veer E. Coumarins during pregnancy: Long-term effects on growth and development of school-age children. *Thromb Haemost* 2001;**85**:609–613.
230. van Driel D, Wesseling J, Sauer PJ, van Der Veer E, Touwen BC, Smrkovsky M. In utero exposure to coumarins and cognition at 8 to 14 years old. *Pediatrics* 2001;**107**:123–129.
231. Ozkan M, Cakal B, Karakoyun S, Gursoy OM, Cevik C, Kalcik M, Oguz AE, Gunduz S, Astarcioglu MA, Aykan AC, Bayram Z, Biteker M, Kaynak E, Kahveci G, Duran NE, Yildiz M. Thrombolytic therapy for the treatment of prosthetic heart valve thrombosis in pregnancy with low-dose, slow infusion of tissue-type plasminogen activator. *Circulation* 2013;**128**:532–540.
232. Petitti DB, Sidney S, Quesenberry CP Jr, Bernstein A. Incidence of stroke and myocardial infarction in women of reproductive age. *Stroke* 1997;**28**:280–283.
233. Ladner HE, Danielsen B, Gilbert WM. Acute myocardial infarction in pregnancy and the puerperium: A population-based study. *Obstet Gynecol* 2005;**105**:480–484.
234. James AH, Jamison MG, Biswas MS, Brancazio LR, Swamy GK, Myers ER. Acute myocardial infarction in pregnancy: A United States population-based study. *Circulation* 2006;**113**:1564–1571.
235. Bush N, Nelson-Piercy C, Spark P, Kurinczuk JJ, Brocklehurst P, Knight M. Myocardial infarction in pregnancy and postpartum in the UK. *Eur J Prev Cardiol* 2013;**20**:12–20.
236. Berg CJ, Callaghan WM, Syverson C, Henderson Z. Pregnancy-related mortality in the United States, 1998 to 2005. *Obstet Gynecol* 2010;**116**:1302–1309.
237. Roth A, Elkayam U. Acute myocardial infarction associated with pregnancy. *J Am Coll Cardiol* 2008;**52**:171–180.
238. Lameijer H, Kampman MA, Oudijk MA, Pieper PG. Ischaemic heart disease during pregnancy or post-partum: Systematic review and case series. *Neth Heart J* 2015;**23**:249–257.
239. Elkayam U, Jalnapurkar S, Barakkat MN, Khatri N, Kealey AJ, Mehra A, Roth A. Pregnancy-associated acute myocardial infarction: A review of contemporary experience in 150 cases between 2006 and 2011. *Circulation* 2014;**129**:1695–1702.
240. Roos-Hesselink JW, Duvekot JJ, Thorne SA. Pregnancy in high-risk cardiac conditions. *Heart* 2009;**95**:680–686.
241. Tweet MS, Hayes SN, Codsi E, Gulati R, Rose CH, Best PJM. Spontaneous coronary artery dissection associated with pregnancy. *J Am Coll Cardiol* 2017;**70**:426–435.
242. Vijayaraghavan R, Verma S, Gupta N, Saw J. Pregnancy-related spontaneous coronary artery dissection. *Circulation* 2014;**130**:1915–1920.
243. Saw J, Ricci D, Starovoytov A, Fox R, Buller CE. Spontaneous coronary artery dissection: Prevalence of predisposing conditions including fibromuscular dysplasia in *a tertiary center cohort. JACC Cardiovasc Interv* 2013;**6**:44–52.
244. Saw J, Aymong E, Sedlak T, Buller CE, Starovoytov A, Ricci D, Robinson S, Vuurmans T, Gao M, Humphries K, Mancini GB. Spontaneous coronary artery dissection: Association with predisposing arteriopathies and precipitating stressors and cardiovascular outcomes. *Circ Cardiovasc Interv* 2014;**7**:645–655.
245. Agewall S, Beltrame JF, Reynolds HR, Niessner A, Rosano G, Caforio AL, De Caterina R, Zimarino M, Roffi M, Kjeldsen K, Atar D, Kaski JC, Sechtem U, Tornvall P. ESC working group position paper on myocardial infarction with non-obstructive coronary arteries. *Eur Heart J* 2017;**38**:143–153.
246. Alfonso F, Paulo M, Lennie V, Dutary J, Bernardo E, Jimenez-Quevedo P, Gonzalo N, Escaned J, Banuelos C, Perez-Vizcayno MJ, Hernandez R, Macaya C. Spontaneous coronary artery dissection: Long-term follow-up of a large series of patients prospectively managed with a "conservative" therapeutic strategy. *JACC Cardiovasc Interv* 2012;**5**:1062–1070.
247. Tweet MS, Gulati R, Williamson EE, Vrtiska TJ, Hayes SN. Multimodality imaging for spontaneous coronary artery dissection in women. *JACC Cardiovasc Imaging* 2016;**9**:436–450.
248. Goland S, Elkayam U. Anticoagulation in pregnancy. *Cardiol Clin* 2012;**30**:395–405.
249. Gordon CT, Jimenez-Fernandez S, Daniels LB, Kahn AM, Tarsa M, Matsubara T, Shimizu C, Burns JC, Gordon JB. Pregnancy in women with a history of Kawasaki disease: Management and outcomes. *BJOG* 2014;**121**:1431–1438.
250. Thygesen K, Alpert JS, Jaffe AS, Simoons ML, Chaitman BR, White HD. Third universal definition of myocardial infarction. *Eur Heart J* 2012;**33**:2551–2567.
251. Ibanez B, James S, Agewall S, Antunes MJ, Bucciarelli-Ducci C, Bueno H, Caforio ALP, Crea F, Goudevenos JA, Halvorsen S, Hindricks G, Kastrati A, Lenzen MJ, Prescott E, Roffi M, Valgimigli M, Varenhorst C, Vranckx P, Widimsky P; ESC Scientific Document Group. 2017 ESC guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: The Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the *European Society of Cardiology (ESC). Eur Heart J* 2018;**39**:119–177.
252. Shade GH Jr, Ross G, Bever FN, Uddin Z, Devireddy L, Gardin JM. Troponin I in the diagnosis of acute myocardial infarction in pregnancy, labor, and post partum. *Am J Obstet Gynecol* 2002;**187**:1719–1720.
253. Joyal D, Leya F, Koh M, Besinger R, Ramana R, Kahn S, Jeske W, Lewis B, Steen L, Mestril R, Arab D. Troponin I levels in patients with preeclampsia. *Am J Med* 2007;**120**:819.e13–819.e14.
254. Lancellotti P, Price S, Edvardsen T, Cosyns B, Neskovic AN, Dulgheru R, Flachskampf FA, Hassager C, Pasquet A, Gargani L, Galderisi M, Cardim N, Haugaa KH, Ancion A, Zamorano JL, Donal E, Bueno H, Habib G. The use of echocardiography in acute cardiovascular care: Recommendations of the European Association of Cardiovascular Imaging and the Acute Cardiovascular Care Association. *Eur Heart J Acute Cardiovasc Care* 2015;**4**:3–5.
255. Mahmoud AN, Taduru SS, Mentias A, Mahtta D, Barakat AF, Saad M, Elgendy AY, Mojadidi MK, Omer M, Abuzaid A, Agarwal N, Elgendy IY, Anderson RD, Saw J. Trends of incidence, clinical presentation, and in-hospital mortality among women with acute myocardial infarction with or without spontaneous coronary artery dissection: A population-based analysis. *JACC Cardiovasc Interv* 2018;**11**:80–90.
256. Jeejeebhoy FM, Zelop CM, Lipman S, Carvalho B, Joglar J, Mhyre JM, Katz VL, Lapinsky SE, Einav S, Warnes CA, Page RL, Griffin RE, Jain A, Dainty KN, Arafeh J, Windrim R, Koren G, Callaway CW. Cardiac arrest in pregnancy: A scientific statement from the American Heart Association. *Circulation* 2015;**132**:1747–1773.
257. Frishman WH, Elkayam U, Aronow WS. Cardiovascular drugs in pregnancy. *Cardiol Clin* 2012;**30**:463–491.

Downloaded from https://academic.oup.com/eurheartj/article-abstract/39/34/3165/5078465 by guest on 13 September 2018

258. Tweet MS, Hayes SN, Gulati R, Rose CH, Best PJ. Pregnancy after spontaneous coronary artery dissection: A case series. *Ann Intern Med* 2015;**162**:598–600.
259. Colletti PM, Lee KH, Elkayam U. Cardiovascular imaging of the pregnant patient. *AJR Am J Roentgenol* 2013;**200**:515–521.
260. Burchill LJ, Lameijer H, Roos-Hesselink JW, Grewal J, Ruys TP, Kulikowski JD, Burchill LA, Oudijk MA, Wald RM, Colman JM, Siu SC, Pieper PG, Silversides CK. Pregnancy risks in women with pre-existing coronary artery disease, or following acute coronary syndrome. *Heart* 2015;**101**:525–529.
261. Dufour PH, Occelli B, Puech F. Pregnancy after myocardial infarction. *Int J Gynaecol Obstet* 1997;**59**:251–253.
262. Bagg W, Henley PG, Macpherson P, Cundy TF. Pregnancy in women with diabetes and ischaemic heart disease. *Aust N Z J Obstet Gynaecol* 1999;**39**:99–102.
263. Sliwa K, Hilfiker-Kleiner D, Petrie MC, Mebazaa A, Pieske B, Buchmann E, Regitz-Zagrosek V, Schaufelberger M, Tavazzi L, van Veldhuisen DJ, Watkins H, Shah AJ, Seferovic PM, Elkayam U, Pankuweit S, Papp Z, Mouquet F, McMurray JJ. Current state of knowledge on aetiology, diagnosis, management, and therapy of peripartum cardiomyopathy. *Eur J Heart Fail* 2010;**12**:767–778.
264. Hilfiker-Kleiner D, Haghikia A, Nonhoff J, Bauersachs J. Peripartum cardiomyopathy: Current management and future perspectives. *Eur Heart J* 2015;**36**:1090–1097.
265. Sliwa K, Hilfiker-Kleiner D, Mebazaa A, Petrie MC, Maggioni AP, Regitz-Zagrosek V, Schaufelberger M, Tavazzi L, van Veldhuisen DJ, Roos-Hesslink JW, Shah AJ, Seferovic PM, Elkayam U, van Spaendonck-Zwarts K, Bachelier-Walenta K, Mouquet F, Kraigher-Krainer E, Hall R, Ponikowski P, McMurray JJ, Pieske B. EURObservational Research Programme: A worldwide registry on peripartum cardiomyopathy (PPCM) in conjunction with the Heart Failure Association of the European Society of Cardiology Working Group on PPCM. *Eur J Heart Fail* 2014;**16**:583–591.
266. Sliwa K, Mebazaa A, Hilfiker-Kleiner D, Petrie MC, Maggioni AP, Laroche C, Regitz-Zagrosek V, Schaufelberger M, Tavazzi L, van der Meer P, Roos-Hesselink JW, Seferovic P, van Spandonck-Zwarts K, Mbakwem A, Bohm M, Mouquet F, Pieske B, Hall R, Ponikowski P, Bauersachs J. Clinical characteristics of patients from the worldwide registry on peripartum cardiomyopathy (PPCM): EURObservational Research Programme in conjunction with the Heart Failure Association of the European Society of Cardiology Study Group on PPCM. *Eur J Heart Fail* 2017;**19**:1131–1141.
267. Sliwa K, Forster O, Libhaber E, Fett JD, Sundstrom JB, Hilfiker-Kleiner D, Ansari AA. Peripartum cardiomyopathy: Inflammatory markers as predictors of outcome in 100 prospectively studied patients. *Eur Heart J* 2006;**27**:441–446.
268. Halkein J, Tabruyn SP, Ricke-Hoch M, Haghikia A, Nguyen NQ, Scherr M, Castermans K, Malvaux L, Lambert V, Thiry M, Sliwa K, Noel A, Martial JA, Hilfiker-Kleiner D, Struman I. MicroRNA-146a is a therapeutic target and biomarker for peripartum cardiomyopathy. *J Clin Invest* 2013;**123**:2143–2154.
269. Patten IS, Rana S, Shahul S, Rowe GC, Jang C, Liu L, Hacker MR, Rhee JS, Mitchell J, Mahmood F, Hess P, Farrell C, Koulisis N, Khankin EV, Burke SD, Tudorache I, Bauersachs J, del Monte F, Hilfiker-Kleiner D, Karumanchi SA, Arany Z. Cardiac angiogenic imbalance leads to peripartum cardiomyopathy. *Nature* 2012;**485**:333–338.
270. Haghikia A, Kaya Z, Schwab J, Westenfeld R, Ehlermann P, Bachelier K, Oettl R, von Kaisenberg CS, Katus HA, Bauersachs J, Hilfiker-Kleiner D. Evidence of autoantibodies against cardiac troponin I and sarcomeric myosin in peripartum cardiomyopathy. *Basic Res Cardiol* 2015;**110**:60.
271. Hilfiker-Kleiner D, Kaminski K, Podewski E, Bonda T, Schaefer A, Sliwa K, Forster O, Quint A, Landmesser U, Doerries C, Luchtefeld M, Poli V, Schneider MD, Balligand JL, Desjardins F, Ansari A, Struman I, Nguyen NQ, Zschemisch NH, Klein G, Heusch G, Schulz R, Hilfiker A, Drexler H. A cathepsin D-cleaved 16 kDa form of prolactin mediates postpartum cardiomyopathy. *Cell* 2007;**128**:589–600.
272. Walenta K, Schwarz V, Schirmer SH, Kindermann I, Friedrich EB, Solomayer EF, Sliwa K, Labidi S, Hilfiker-Kleiner D, Bohm M. Circulating microparticles as indicators of peripartum cardiomyopathy. *Eur Heart J* 2012;**33**:1469–1479.
273. Morales A, Painter T, Li R, Siegfried JD, Li D, Norton N, Hershberger RE. Rare variant mutations in pregnancy-associated or peripartum cardiomyopathy. *Circulation* 2010;**121**:2176–2182.
274. van Spaendonck-Zwarts KY, van Tintelen JP, van Veldhuisen DJ, van der Werf R, Jongbloed JD, Paulus WJ, Dooijes D, van den Berg MP. Peripartum cardiomyopathy as a part of familial dilated cardiomyopathy. *Circulation* 2010;**121**:2169–2175.
275. van Spaendonck-Zwarts KY, Posafalvi A, van den Berg MP, Hilfiker-Kleiner D, Bollen IA, Sliwa K, Alders M, Almomani R, van Langen IM, van der Meer P, Sinke RJ, van der Velden J, Van Veldhuisen DJ, van Tintelen JP, Jongbloed JD. Titin gene mutations are common in families with both peripartum cardiomyopathy and dilated cardiomyopathy. *Eur Heart J* 2014;**35**:2165–2173.
276. Ware JS, Li J, Mazaika E, Yasso CM, DeSouza T, Cappola TP, Tsai EJ, Hilfiker-Kleiner D, Kamiya CA, Mazzarotto F, Cook SA, Halder I, Prasad SK, Pisarcik J, Hanley-Yanez K, Alharethi R, Damp J, Hsich E, Elkayam U, Sheppard R, Kealey A, Alexis J, Ramani G, Safirstein J, Boehmer J, Pauly DF, Wittstein IS, Thohan V, Zucker MJ, Liu P, Gorcsan J III, McNamara DM, Seidman CE, Seidman JG, Arany Z. Shared genetic predisposition in peripartum and dilated cardiomyopathies. *N Engl J Med* 2016;**374**:233–241.
277. Haghikia A, Podewski E, Libhaber E, Labidi S, Fischer D, Roentgen P, Tsikas D, Jordan J, Lichtinghagen R, von Kaisenberg CS, Struman I, Bovy N, Sliwa K, Bauersachs J, Hilfiker-Kleiner D. Phenotyping and outcome on contemporary management in a German cohort of patients with peripartum cardiomyopathy. *Basic Res Cardiol* 2013;**108**:366.
278. McNamara DM, Elkayam U, Alharethi R, Damp J, Hsich E, Ewald G, Modi K, Alexis JD, Ramani GV, Semigran MJ, Haythe J, Markham DW, Marek J, Gorcsan J III, Wu WC, Lin Y, Halder I, Pisarcik J, Cooper LT, Fett JD. Clinical outcomes for peripartum cardiomyopathy in North America: Results of the IPAC study (Investigations of Pregnancy-Associated Cardiomyopathy). *J Am Coll Cardiol* 2015;**66**:905–914.
279. Bauersachs J, Arrigo M, Hilfiker-Kleiner D, Veltmann C, Coats AJ, Crespo-Leiro MG, De Boer RA, van der Meer P, Maack C, Mouquet F, Petrie MC, Piepoli MF, Regitz-Zagrosek V, Schaufelberger M, Seferovic P, Tavazzi L, Ruschitzka F, Mebazaa A, Sliwa K. Current management of patients with severe acute peripartum cardiomyopathy: Practical guidance from the Heart Failure Association of the European Society of Cardiology Study Group on peripartum cardiomyopathy. *Eur J Heart Fail* 2016;**18**:1096–1105.
280. Honigberg MC, Givertz MM. Arrhythmias in peripartum cardiomyopathy. *Card Electrophysiol Clin* 2015;**7**:309–317.
281. Haghikia A, Rontgen P, Vogel-Claussen J, Schwab J, Westenfeld R, Ehlermann P, Berliner D, Podewski E, Hilfiker-Kleiner D, Bauersachs J. Prognostic implication of right ventricular involvement in peripartum cardiomyopathy: A cardiovascular magnetic resonance study. *ESC Heart Fail* 2015;**2**:139–149.
282. Blauwet LA, Delgado-Montero A, Ryo K, Marek JJ, Alharethi R, Mather PJ, Modi K, Sheppard R, Thohan V, Pisarcik J, McNamara DM, Gorcsan J, III. Right ventricular function in peripartum cardiomyopathy at presentation is associated with subsequent left ventricular recovery and clinical outcomes. *Circ Heart Fail* 2016;**9**:e002756.
283. Libhaber E, Sliwa K, Bachelier K, Lamont K, Bohm M. Low systolic blood pressure and high resting heart rate as predictors of outcome in patients with peripartum cardiomyopathy. *Int J Cardiol* 2015;**190**:376–382.
284. Biteker M, Ilhan E, Biteker G, Duman D, Bozkurt B. Delayed recovery in peripartum cardiomyopathy: An indication for long-term follow-up and sustained therapy. *Eur J Heart Fail* 2012;**14**:895–901.
285. Hilfiker-Kleiner D, Haghikia A, Masuko D, Nonhoff J, Held D, Libhaber E, Petrie MC, Walker NL, Podewski E, Berliner D, Bauersachs J, Sliwa K. Outcome of subsequent pregnancies in patients with a history of peripartum cardiomyopathy. *Eur J Heart Fail* 2017;**19**:1723–1728.
286. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JG, Coats AJ, Falk V, Gonzalez-Juanatey JR, Harjola VP, Jankowska EA, Jessup M, Linde C, Nihoyannopoulos P, Parissis JT, Pieske B, Riley JP, Rosano GM, Ruilope LM, Ruschitzka F, Rutten FH, van der Meer P. 2016 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J* 2016;**37**:2129–2200.
287. Hershberger RE, Hedges DJ, Morales A. Dilated cardiomyopathy: The complexity of a diverse genetic architecture. *Nat Rev Cardiol* 2013;**10**:531–547.
288. Grewal J, Siu SC, Ross HJ, Mason J, Balint OH, Sermer M, Colman JM, Silversides CK. Pregnancy outcomes in women with dilated cardiomyopathy. *J Am Coll Cardiol* 2009;**55**:45–52.
289. Mebazaa A, Yilmaz MB, Levy P, Ponikowski P, Peacock WF, Laribi S, Ristic AD, Lambrinou E, Masip J, Riley JP, McDonagh T, Mueller C, deFilippi C, Harjola VP, Thiele H, Piepoli MF, Metra M, Maggioni A, McMurray J, Dickstein K, Damman K, Seferovic PM, Ruschitzka F, Leite-Moreira AF, Bellou A, Anker SD, Filippatos G. Recommendations on pre-hospital & early hospital management of acute heart failure: A consensus paper from the Heart Failure Association of the European Society of Cardiology, the European Society of Emergency Medicine and the Society of Academic Emergency Medicine. *Eur J Heart Fail* 2015;**17**:544–558.
290. Hilfiker-Kleiner D, Westhoff-Bleck M, Gunter HH, von Kaisenberg CS, Bohnhorst B, Hoeltje M, Kuehn C. A management algorithm for acute heart failure in pregnancy. The Hannover experience. *Eur Heart J* 2015;**36**:769–770.
291. Stapel B, Kohlhaas M, Ricke-Hoch M, Haghikia A, Erschow S, Knuuti J, Silvola JM, Roivainen A, Saraste A, Nickel AG, Saar JA, Sieve I, Pietzsch S, Muller M, Bogeski I, Kappl R, Jauhiainen M, Thackeray JT, Scherr M, Bengel FM, Hagl C, Tudorache I, Bauersachs J, Maack C, Hilfiker-Kleiner D. Low STAT3 expression sensitizes to toxic effects of β-adrenergic receptor stimulation in peripartum cardiomyopathy. *Eur Heart J* 2017;**38**:349–361.
292. Labbene I, Arrigo M, Tavares M, Hajjej Z, Brandao JL, Tolppanen H, Feliot E, Gayat E, Ferjani M, Mebazaa A. Decongestive effects of levosimendan in cardiogenic shock induced by postpartum cardiomyopathy. *Anaesth Crit Care Pain Med* 2017;**36**:39–42.

Downloaded from https://academic.oup.com/eurheartj/article-abstract/39/34/3165/5078465 by guest on 13 September 2018

293. Haghikia A, Tongers J, Berliner D, Konig T, Schafer A, Brehm M, Bohm M, Hilfiker-Kleiner D, Bauersachs J. Early ivabradine treatment in patients with acute peripartum cardiomyopathy: Subanalysis of the German PPCM registry. *Int J Cardiol* 2016;**216**:165–167.
294. Haghikia A, Podewski E, Berliner D, Sonnenschein K, Fischer D, Angermann CE, Bohm M, Rontgen P, Bauersachs J, Hilfiker-Kleiner D. Rationale and design of a randomized, controlled multicentre clinical trial to evaluate the effect of bromocriptine on left ventricular function in women with peripartum cardiomyopathy. *Clin Res Cardiol* 2015;**104**:911–917.
295. Desplantie O, Tremblay-Gravel M, Avram R, Marquis-Gravel G, Ducharme A, Jolicoeur EM. The medical treatment of new-onset peripartum cardiomyopathy: A systematic review of prospective studies. *Can J Cardiol* 2015;**31**:1421–1426.
296. Arrigo M, Blet A, Mebazaa A. Bromocriptine for the treatment of peripartum cardiomyopathy: Welcome on board. *Eur Heart J* 2017;**38**:2680–2682.
297. Duncker D, Haghikia A, Konig T, Hohmann S, Gutleben KJ, Westenfeld R, Oswald H, Klein H, Bauersachs J, Hilfiker-Kleiner D, Veltmann C. Risk for ventricular fibrillation in peripartum cardiomyopathy with severely reduced left ventricular function-value of the wearable cardioverter/defibrillator. *Eur J Heart Fail* 2014;**16**:1331–1336.
298. Duncker D, Konig T, Hohmann S, Bauersachs J, Veltmann C. Avoiding untimely implantable cardioverter/defibrillator implantation by intensified heart failure therapy optimization supported by the wearable cardioverter/defibrillator-the PROLONG study. *J Am Heart Assoc* 2017;**6**:e004512.
299. Kober L, Thune JJ, Nielsen JC, Haarbo J, Videbaek L, Korup E, Jensen G, Hildebrandt P, Steffensen FH, Bruun NE, Eiskjaer H, Brandes A, Thogersen AM, Gustafsson F, Egstrup K, Videbaek R, Hassager C, Svendsen JH, Hofsten DE, Torp-Pedersen C, Pehrson S. Defibrillator implantation in patients with nonischemic systolic heart failure. *N Engl J Med* 2016;**375**:1221–1230.
300. Rasmusson K, Brunisholz K, Budge D, Horne BD, Alharethi R, Folsom J, Connolly JJ, Stehlik J, Kfoury A. Peripartum cardiomyopathy: Post-transplant outcomes from the United Network for Organ Sharing Database. *J Heart Lung Transplant* 2012;**31**:180–186.
301. Abdalla M, Mancini DM. Management of pregnancy in the post-cardiac transplant patient. *Semin Perinatol* 2014;**38**:318–325.
302. O'Boyle PJ, Smith JD, Danskine AJ, Lyster HS, Burke MM, Banner NR. De novo HLA sensitization and antibody mediated rejection following pregnancy in a heart transplant recipient. *Am J Transplant* 2010;**10**(1):180–183.
303. Costanzo MR, Dipchand A, Starling R, Anderson A, Chan M, Desai S, Fedson S, Fisher P, Gonzales-Stawinski G, Martinelli L, McGiffin D, Smith J, Taylor D, Meiser B, Webber S, Baran D, Carboni M, Dengler T, Feldman D, Frigerio M, Kfoury A, Kim D, Kobashigawa J, Shullo M, Stehlik J, Teuteberg J, Uber P, Zuckermann A, Hunt S, Burch M, Bhat G, Canter C, Chinnock R, Crespo-Leiro M, Delgado R, Dobbels F, Grady K, Kao W, Lamour J, Parry G, Patel J, Pini D, Towbin J, Wolfel G, Delgado D, Eisen H, Goldberg L, Hosenpud J, Johnson M, Keogh A, Lewis C, O'Connell J, Rogers J, Ross H, Russell S, Vanhaecke J. The International Society of Heart and Lung Transplantation Guidelines for the care of heart transplant recipients. *J Heart Lung Transplant* 2010;**29**:914–956.
304. McKay DB, Josephson MA, Armenti VT, August P, Coscia LA, Davis CL, Davison JM, Easterling T, Friedman JE, Hou S, Karlix J, Lake KD, Lindheimer M, Matas AJ, Moritz MJ, Riely CA, Ross LF, Scott JR, Wagoner LE, Wrenshall L, Adams PL, Bumgardner GL, Fine RN, Goral S, Krams SM, Martinez OM, Tolkoff-Rubin N, Pavlakis M, Scantlebury V. Reproduction and transplantation: Report on the AST Consensus Conference on Reproductive Issues and Transplantation. *Am J Transplant* 2005;**5**:1592–1599.
305. Bhagra CJ, Bhagra SK, Donado A, Butt T, Forrest L, MacGowan GA, Parry G. Pregnancy in cardiac transplant recipients. *Clin Transplant* 2016;**30**:1059–1065.
306. Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B, Castella M, Diener HC, Heidbuchel H, Hendriks J, Hindricks G, Manolis AS, Oldgren J, Popescu BA, Schotten U, Van Putte B, Vardas P. 2016 ESC guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *Eur Heart J* 2016;**37**:2893–2962.
307. Metra M. September 2016 at a glance: Pregnancy, hypertrophic cardiomyopathy, epidemiology, medical treatment. *Eur J Heart Fail* 2016;**18**:1091–1092.
308. Schinkel AF. Pregnancy in women with hypertrophic cardiomyopathy. *Cardiol Rev* 2014;**22**:217–222.
309. Van Tintelen JP, Pieper PG, Van Spaendonck-Zwarts KY, Van Den Berg MP. Pregnancy, cardiomyopathies, and genetics. *Cardiovasc Res* 2014;**101**:571–578.
310. Spirito P, Autore C. Management of hypertrophic cardiomyopathy. *BMJ* 2006;**332**:1251–1255.
311. Autore C, Conte MR, Piccininno M, Bernabo P, Bonfiglio G, Bruzzi P, Spirito P. Risk associated with pregnancy in hypertrophic cardiomyopathy. *J Am Coll Cardiol* 2002;**40**:1864–1869.
312. Tanaka H, Kamiya C, Katsuragi S, Tanaka K, Miyoshi T, Tsuritani M, Yoshida M, Iwanaga N, Neki R, Yoshimatsu J, Ikeda T. Cardiovascular events in pregnancy with hypertrophic cardiomyopathy. *Circ J* 2014;**78**:2501–2506.
313. Pieper PG, Walker F. Pregnancy in women with hypertrophic cardiomyopathy. *Neth Heart J* 2013;**21**:14–18.
314. Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B, Castella M, Diener HC, Heidbuchel H, Hendriks J, Hindricks G, Manolis AS, Oldgren J, Popescu BA, Schotten U, Van Putte B, Vardas P; ESC Scientific Document Group. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *Eur Heart J* 2016;**37**:2893–2962.
315. Sideris S, Kasiakogias A, Aggeli C, Manakos K, Trantalis G, Gatzoulis K, Tousoulis D, Kallikazaros I. Implantation of a defibrillator in a pregnant woman with hypertrophic cardiomyopathy under echocardiographic guidance: A case report. *Int J Cardiol* 2015;**179**:323–324.
316. Luscher TF. Device therapy in cardiac disease: A success story. *Eur Heart J* 2015;**36**:2473–2475.
317. Ashikhmina E, Farber MK, Mizuguchi KA. Parturients with hypertrophic cardiomyopathy: Case series and review of pregnancy outcomes and anesthetic management of labor and delivery. *Int J Obstet Anesth* 2015;**24**:344–355.
318. Vaidya VR, Arora S, Patel N, Badheka AO, Patel N, Agnihotri K, Billimoria Z, Turakhia MP, Friedman PA, Madhavan M, Kapa S, Noseworthy PA, Cha YM, Gersh B, Asirvatham SJ, Deshmukh AJ. Burden of arrhythmia in pregnancy. *Circulation* 2017;**135**:619–621.
319. Li JM, Nguyen C, Joglar JA, Hamdan MH, Page RL. Frequency and outcome of arrhythmias complicating admission during pregnancy: Experience from a high-volume and ethnically-diverse obstetric service. *Clin Cardiol* 2008;**31**:538–541.
320. Lee MS, Chen W, Zhang Z, Duan L, Ng A, Spencer HT, Kwan DM, Shen AY. Atrial fibrillation and atrial flutter in pregnant women-a population-based study. *J Am Heart Assoc* 2016;**5**:e003182.
321. Opotowsky AR, Siddiqi OK, D'Souza B, Webb GD, Fernandes SM, Landzberg MJ. Maternal cardiovascular events during childbirth among women with congenital heart disease. *Heart* 2012;**98**:145–151.
322. Silversides CK, Harris L, Haberer K, Sermer M, Colman JM, Siu SC. Recurrence rates of arrhythmias during pregnancy in women with previous tachyarrhythmia and impact on fetal and neonatal outcomes. *Am J Cardiol* 2006;**97**:1206–1212.
323. Rashba EJ, Zareba W, Moss AJ, Hall WJ, Robinson J, Locati EH, Schwartz PJ, Andrews M. Influence of pregnancy on the risk for cardiac events in patients with hereditary long QT syndrome. LQTS investigators. *Circulation* 1998;**97**:451–456.
324. Hodes AR, Tichnell C, Te Riele AS, Murray B, Groeneweg JA, Sawant AC, Russell SD, van Spaendonck-Zwarts KY, van den Berg MP, Wilde AA, Tandri H, Judge DP, Hauer RN, Calkins H, van Tintelen JP, James CA. Pregnancy course and outcomes in women with arrhythmogenic right ventricular cardiomyopathy. *Heart* 2016;**102**:303–312.
325. Chang SH, Kuo CF, Chou IJ, See LC, Yu KH, Luo SF, Chiou MJ, Zhang W, Doherty M, Wen MS, Chen WJ, Yeh YH. Outcomes associated with paroxysmal supraventricular tachycardia during pregnancy. *Circulation* 2017;**135**:616–618.
326. Elkayam U, Goodwin TM. Adenosine therapy for supraventricular tachycardia during pregnancy. *Am J Cardiol* 1995;**75**:521–523.
327. Blomstrom-Lundqvist C, Scheinman MM, Aliot EM, Alpert JS, Calkins H, Camm AJ, Campbell WB, Haines DE, Kuck KH, Lerman BB, Miller DD, Shaeffer CW, Stevenson WG, Tomaselli GF, Antman EM, Smith SC Jr, Alpert JS, Faxon DP, Fuster V, Gibbons RJ, Gregoratos G, Hiratzka LF, Hunt SA, Jacobs AK, Russell RO Jr, Priori SG, Blanc JJ, Budaj A, Burgos EF, Cowie M, Deckers JW, Garcia MA, Klein WW, Lekakis J, Lindahl B, Mazzotta G, Morais JC, Oto A, Smiseth O, Trappe HJ; European Society of Cardiology Committee, NASPE-Heart Rhythm Society. ACC/AHA/ESC guidelines for the management of patients with supraventricular arrhythmias–executive summary. a report of the American college of cardiology/American heart association task force on practice guidelines and the European society of cardiology committee for practice guidelines (writing committee to develop guidelines for the management of patients with supraventricular arrhythmias) developed in collaboration with NASPE-Heart Rhythm Society. *J Am Coll Cardiol* 2003;**42**:1493–1531.
328. Page RL, Joglar JA, Caldwell MA, Calkins H, Conti JB, Deal BJ, Estes NAM III, Field ME, Goldberger ZD, Hammill SC, Indik JH, Lindsay BD, Olshansky B, Russo AM, Shen WK, Tracy CM, Al-Khatib SM. 2015 ACC/AHA/HRS guideline for the management of adult patients with supraventricular tachycardia: Executive summary: A report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. *J Am Coll Cardiol* 2016;**67**:1575–1623.
329. Kockova R, Kocka V, Kiernan T, Fahy GJ. Ibutilide-induced cardioversion of atrial fibrillation during pregnancy. *J Cardiovasc Electrophysiol* 2007;**18**:545–547.
330. Miyoshi T, Kamiya CA, Katsuragi S, Ueda H, Kobayashi Y, Horiuchi C, Yamanaka K, Neki R, Yoshimatsu J, Ikeda T, Yamada Y, Okamura H, Noda T, Shimizu W. Safety and efficacy of implantable cardioverter-defibrillator during pregnancy and after delivery. *Circ J* 2013;**77**:1166–1170.

Downloaded from https://academic.oup.com/eurheartj/article-abstract/39/34/3165/5078465 by guest on 13 September 2018

331. Nakagawa M, Katou S, Ichinose M, Nobe S, Yonemochi H, Miyakawa I, Saikawa T. Characteristics of new-onset ventricular arrhythmias in pregnancy. *J Electrocardiol* 2004;**37**:47–53.
332. Ishibashi K, Aiba T, Kamiya C, Miyazaki A, Sakaguchi H, Wada M, Nakajima I, Miyamoto K, Okamura H, Noda T, Yamauchi T, Itoh H, Ohno S, Motomura H, Ogawa Y, Goto H, Minami T, Yagihara N, Watanabe H, Hasegawa K, Terasawa A, Mikami H, Ogino K, Nakano Y, Imashiro S, Fukushima Y, Tsuzuki Y, Asakura K, Yoshimatsu J, Shiraishi I, Kamakura S, Miyamoto Y, Yasuda S, Akasaka T, Horie M, Shimizu W, Kusano K. Arrhythmia risk and β-blocker therapy in pregnant women with long QT syndrome. *Heart* 2017;**103**:1374–1379.
333. Friday KP, Moak JP, Fries MH, Iqbal SN. Catecholaminergic ventricular tachycardia, pregnancy and teenager: Are they compatible? *Pediatr Cardiol* 2015;**36**:1542–1547.
334. Hidaka N, Chiba Y, Fukushima K, Wake N. Pregnant women with complete atrioventricular block: Perinatal risks and review of management. *Pacing Clin Electrophysiol* 2011;**34**:1161–1176.
335. Suri V, Keepanasseril A, Aggarwal N, Vijayvergiya R, Chopra S, Rohilla M. Maternal complete heart block in pregnancy: Analysis of four cases and review of management. *J Obstet Gynaecol Res* 2009;**35**:434–437.
336. Wang YC, Chen CH, Su HY, Yu MH. The impact of maternal cardioversion on fetal haemodynamics. *Eur J Obstet Gynecol Reprod Biol* 2006;**126**:268–269.
337. Page RL. Treatment of arrhythmias during pregnancy. *Am Heart J* 1995;**130**:871–876.
338. Moore JS, Teefey P, Rao K, Berlowitz MS, Chae SH, Yankowitz J. Maternal arrhythmia: A case report and review of the literature. *Obstet Gynecol Surv* 2012;**67**:298–312.
339. Barnes EJ, Eben F, Patterson D. Direct current cardioversion during pregnancy should be performed with facilities available for fetal monitoring and emergency caesarean section. *BJOG* 2002;**109**:1406–1407.
340. Natale A, Davidson T, Geiger MJ, Newby K. Implantable cardioverter-defibrillators and pregnancy: A safe combination? *Circulation* 1997;**96**:2808–2812.
341. Burke MC, Gold MR, Knight BP, Barr CS, Theuns DA, Boersma LV, Knops RE, Weiss R, Leon AR, Herre JM, Husby M, Stein KM, Lambiase PD. Safety and efficacy of the totally subcutaneous implantable defibrillator: 2-year results from a pooled analysis of the ide study and effortless registry. *J Am Coll Cardiol* 2015;**65**:1605–1615.
342. Strewe C, Fichtner S. [completely subcutaneous implantable cardioverter defibrillator: Care of S-ICD wearers during childbirth]. *Anaesthesist* 2015;**64**:843–845.
343. Saltzberg MT, Szymkiewicz S, Bianco NR. Characteristics and outcomes of peripartum versus nonperipartum cardiomyopathy in women using a wearable cardiac defibrillator. *J Card Fail* 2012;**18**:21–27.
344. Hartz J, Clark BC, Ito S, Sherwin ED, Berul CI. Transvenous nonfluoroscopic pacemaker implantation during pregnancy guided by 3-dimensional electroanatomic mapping. *HeartRhythm Case Rep* 2017;**3**:490–492.
345. Villar J, Carroli G, Wojdyla D, Abalos E, Giordano D, Ba'aqeel H, Farnot U, Bergsjo P, Bakketeig L, Lumbiganon P, Campodonico L, Al-Mazrou Y, Lindheimer M, Kramer M. Preeclampsia, gestational hypertension and intrauterine growth restriction, related or independent conditions? *Am J Obstet Gynecol* 2006;**194**:921–931.
346. National high blood pressure education program working group report on high blood pressure in pregnancy. *Am J Obstet Gynecol* 1990;**163**:1691–1712.
347. Levine RJ, Ewell MG, Hauth JC, Curet LB, Catalano PM, Morris CD, Choudhary G, Sibai BM. Should the definition of preeclampsia include a rise in diastolic blood pressure of >/=15 mm Hg to a level <90 mm Hg in association with proteinuria? *Am J Obstet Gynecol* 2000;**183**:787–792.
348. Mancia G, Fagard R, Narkiewicz K, Redon J, Zanchetti A, Bohm M, Christiaens T, Cifkova R, De Backer G, Dominiczak A, Galderisi M, Grobbee DE, Jaarsma T, Kirchhof P, Kjeldsen SE, Laurent S, Manolis AJ, Nilsson PM, Ruilope LM, Schmieder RE, Sirnes PA, Sleight P, Viigimaa M, Waeber B, Zannad F; Task Force Members. 2013 ESH/ESC Guidelines for the management of arterial hypertension: the Task Force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology. *J Hypertens* 2013; **31**:1281–1357.
349. dabl®Educational Trust. www.dableducation.org.
350. Blood Pressure UK. http://www.bloodpressureuk.org.
351. Penny JA, Halligan AW, Shennan AH, Lambert PC, Jones DR, de Swiet M, Taylor DJ. Automated, ambulatory, or conventional blood pressure measurement in pregnancy: Which is the better predictor of severe hypertension? *Am J Obstet Gynecol* 1998;**178**:521–526.
352. Magee LA, Ramsay G, von Dadelszen P. What is the role of out-of-office BP measurement in hypertensive pregnancy? *Hypertens Pregnancy* 2008;**27**:95–101.
353. Schmella MJ, Clifton RG, Althouse AD, Roberts JM. Uric acid determination in gestational hypertension: Is it as effective a delineator of risk as proteinuria in high-risk women? *Reprod Sci* 2015;**22**:1212–1219.
354. Cade TJ, de Crespigny PC, Nguyen T, Cade JR, Umstad MP. Should the spot albumin-to-creatinine ratio replace the spot protein-to-creatinine ratio as the primary screening tool for proteinuria in pregnancy? *Pregnancy Hypertens* 2015;**5**:298–302.
355. Chappell LC, Shennan AH. Assessment of proteinuria in pregnancy. *BMJ* 2008;**336**:968–969.
356. Cote AM, Firoz T, Mattman A, Lam EM, von Dadelszen P, Magee LA. The 24-hour urine collection: Gold standard or historical practice? *Am J Obstet Gynecol* 2008;**199**:625 e621–626.
357. Cnossen JS, Morris RK, ter Riet G, Mol BW, van der Post JA, Coomarasamy A, Zwinderman AH, Robson SC, Bindels PJ, Kleijnen J, Khan KS. Use of uterine artery Doppler ultrasonography to predict pre-eclampsia and intrauterine growth restriction: A systematic review and bivariable meta-analysis. *CMAJ* 2008;**178**:701–711.
358. Zeisler H, Llurba E, Chantraine F, Vatish M, Staff AC, Sennstrom M, Olovsson M, Brennecke SP, Stepan H, Allegranza D, Dilba P, Schoedl M, Hund M, Verlohren S. Predictive value of the sFlt-1:PlGF ratio in women with suspected preeclampsia. *N Engl J Med* 2016;**374**:13–22.
359. Leanos-Miranda A, Campos-Galicia I, Isordia-Salas I, Rivera-Leanos R, Romero-Arauz JF, Ayala-Mendez JA, Ulloa-Aguirre A. Changes in circulating concentrations of soluble fms-like tyrosine kinase-1 and placental growth factor measured by automated electrochemiluminescence immunoassays methods are predictors of preeclampsia. *J Hypertens* 2012;**30**:2173–2181.
360. American College of Obstetricians and Gynecologists; Task Force on Hypertension in Pregnancy. Hypertension in pregnancy. Report of the American College of Obstetricians and Gynecologists' Task Force on Hypertension in Pregnancy. *Obstet Gynecol* 2013;**122**:1122–1131.
361. Magee LA, Pels A, Helewa M, Rey E, von Dadelszen P. Diagnosis, evaluation, and management of the hypertensive disorders of pregnancy. *Pregnancy Hypertens* 2014;**4**:105–145.
362. Lowe SA, Bowyer L, Lust K, McMahon LP, Morton MR, North RA, Paech MJ, Said JM. The somanz guidelines for the management of hypertensive disorders of pregnancy 2014. *Aust N Z J Obstet Gynaecol* 2015;**55**:11–16.
363. Bartsch E, Medcalf KE, Park AL, Ray JG; High Risk of Pre-eclampsia Identification Group. Clinical risk factors for pre-eclampsia determined in early pregnancy: Systematic review and meta-analysis of large cohort studies. *BMJ* 2016;**353**:i1753.
364. National Collaborating Centre for Women's and Children's Health (UK). *Hypertension in pregnancy: The management of hypertensive disorders during pregnancy*. London: RCOG Press; 2010.
365. Rolnik DL, Wright D, Poon LC, O'Gorman N, Syngelaki A, de Paco Matallana C, Akolekar R, Cicero S, Janga D, Singh M, Molina FS, Persico N, Jani JC, Plasencia W, Papaioannou G, Tenenbaum-Gavish K, Meiri H, Gizurarson S, Maclagan K, Nicolaides KH. Aspirin versus placebo in pregnancies at high-risk for preterm preeclampsia. *N Engl J Med* 2017;**377**:613–622.
366. Hofmeyr GJ, Lawrie TA, Atallah AN, Duley L, Torloni MR. Calcium supplementation during pregnancy for preventing hypertensive disorders and related problems. *Cochrane Database Syst Rev* 2014;**6**:CD001059.
367. Xu H, Perez-Cuevas R, Xiong X, Reyes H, Roy C, Julien P, Smith G, von Dadelszen P, Leduc L, Audibert F, Moutquin JM, Piedboeuf B, Shatenstein B, Parra-Cabrera S, Choquette P, Winsor S, Wood S, Benjamin A, Walker M, Helewa M, Dube J, Tawagi G, Seaward G, Ohlsson A, Magee LA, Olatunbosun F, Gratton R, Shear R, Demianczuk N, Collet JP, Wei S, Fraser WD. An international trial of antioxidants in the prevention of preeclampsia (INTAPP). *Am J Obstet Gynecol* 2010;**202**:239.e1–239.e10.
368. Villar J, Purwar M, Merialdi M, Zavaleta N, Thi Nhu Ngoc N, Anthony J, De Greeff A, Poston L, Shennan A. World Health Organisation multicentre randomised trial of supplementation with vitamins C and E among pregnant women at high-risk for pre-eclampsia in populations of low nutritional status from developing countries. *BJOG* 2009;**116**:780–788.
369. Spinnato JA II, Freire S, Pinto, ESJL, Cunha Rudge MV, Martins-Costa S, Koch MA, Goco N, Santos Cde B, Cecatti JG, Costa R, Ramos JG, Moss N, Sibai BM. Antioxidant therapy to prevent preeclampsia: A randomized controlled trial. *Obstet Gynecol* 2007;**110**:1311–1318.
370. Poston L, Briley AL, Seed PT, Kelly FJ, Shennan AH. Vitamin C and vitamin E in pregnant women at risk for pre-eclampsia (VIP trial): Randomised placebo-controlled trial. *Lancet* 2006;**367**:1145–1154.
371. Redman CW. Fetal outcome in trial of antihypertensive treatment in pregnancy. *Lancet* 1976;**2**:753–756.
372. Cockburn J, Moar VA, Ounsted M, Redman CW. Final report of study on hypertension during pregnancy: The effects of specific treatment on the growth and development of the children. *Lancet* 1982;**1**:647–649.
373. Magee LA, von Dadelszen P, Rey E, Ross S, Asztalos E, Murphy KE, Menzies J, Sanchez J, Singer J, Gafni A, Gruslin A, Helewa M, Hutton E, Lee SK, Lee T, Logan AG, Ganzevoort W, Welch R, Thornton JG, Moutquin JM. Less-tight versus tight control of hypertension in pregnancy. *N Engl J Med* 2015;**372**:407–417.

Downloaded from https://academic.oup.com/eurheartj/article-abstract/39/34/3165/5078465 by guest on 13 September 2018

374. Magee LA, von Dadelszen P, Singer J, Lee T, Rey E, Ross S, Asztalos E, Murphy KE, Menzies J, Sanchez J, Gafni A, Helewa M, Hutton E, Koren G, Lee SK, Logan AG, Ganzevoort W, Welch R, Thornton JG, Moutquin JM. The CHIPS randomized controlled trial (Control of Hypertension in Pregnancy Study): Is severe hypertension just an elevated blood pressure? *Hypertension* 2016;**68**:1153–1159.
375. Abalos E, Duley L, Steyn DW. Antihypertensive drug therapy for mild to moderate hypertension during pregnancy. *Cochrane Database Syst Rev* 2014;**2**:CD002252.
376. Dodd JM, Turnbull D, McPhee AJ, Deussen AR, Grivell RM, Yelland LN, Crowther CA, Wittert G, Owens JA, Robinson JS. Antenatal lifestyle advice for women who are overweight or obese: LIMIT randomised trial. *BMJ* 2014;**348**:g1285.
377. Leddy MA, Power ML, Schulkin J. The impact of maternal obesity on maternal and fetal health. *Rev Obstet Gynecol* 2008;**1**:170–178.
378. Magee LA, Cham C, Waterman EJ, Ohlsson A, von Dadelszen P. Hydralazine for treatment of severe hypertension in pregnancy: Meta-analysis. *BMJ* 2003;**327**:955–960.
379. Vigil-De Gracia P, Lasso M, Ruiz E, Vega-Malek JC, de Mena FT, Lopez JC. Severe hypertension in pregnancy: Hydralazine or labetalol. A randomized clinical trial. *Eur J Obstet Gynecol Reprod Biol* 2006;**128**:157–162.
380. Shekhar S, Gupta N, Kirubakaran R, Pareek P. Oral nifedipine versus intravenous labetalol for severe hypertension during pregnancy: A systematic review and meta-analysis. *BJOG* 2016;**123**:40–47.
381. Clark SM, Dunn HE, Hankins GD. A review of oral labetalol and nifedipine in mild to moderate hypertension in pregnancy. *Semin Perinatol* 2015;**39**:548–555.
382. Altman D, Carroli G, Duley L, Farrell B, Moodley J, Neilson J, Smith D. Do women with pre-eclampsia, and their babies, benefit from magnesium sulphate? The Magpie Trial: A randomised placebo-controlled trial. *Lancet* 2002;**359**:1877–1890.
383. Koopmans CM, Bijlenga D, Groen H, Vijgen SM, Aarnoudse JG, Bekedam DJ, van den Berg PP, de Boer K, Burggraaff JM, Bloemenkamp KW, Drogtrop AP, Franx A, de Groot CJ, Huisjes AJ, Kwee A, van Loon AJ, Lub A, Papatsonis DN, van der Post JA, Roumen FJ, Scheepers HC, Willekes C, Mol BW, van Pampus MG; HYPITAT study group. Induction of labour versus expectant monitoring for gestational hypertension or mild pre-eclampsia after 36 weeks' gestation (HYPITAT): A multicentre, open-label randomised controlled trial. *Lancet* 2009;**374**:979–988.
384. Podymow T, August P. Postpartum course of gestational hypertension and pre-eclampsia. *Hypertens Pregnancy* 2010;**29**:294–300.
385. Beardmore KS, Morris JM, Gallery ED. Excretion of antihypertensive medication into human breast milk: A systematic review. *Hypertens Pregnancy* 2002;**21**:85–95.
386. Ray JG, Vermeulen MJ, Schull MJ, Redelmeier DA. Cardiovascular health after maternal placental syndromes (CHAMPS): Population-based retrospective cohort study. *Lancet* 2005;**366**:1797–1803.
387. Black MH, Zhou H, Sacks DA, Dublin S, Lawrence JM, Harrison TN, Reynolds K. Hypertensive disorders first identified in pregnancy increase risk for incident prehypertension and hypertension in the year after delivery. *J Hypertens* 2016;**34**:728–735.
388. Wang YA, Chughtai AA, Farquhar CM, Pollock W, Lui K, Sullivan EA. Increased incidence of gestational hypertension and preeclampsia after assisted reproductive technology treatment. *Fertil Steril* 2016;**105**:920–926 e922.
389. Hoeltzenbein M, Beck E, Fietz AK, Wernicke J, Zinke S, Kayser A, Padberg S, Weber-Schoendorfer C, Meister R, Schaefer C. Pregnancy outcome after first trimester use of methyldopa: A prospective cohort study. *Hypertension* 2017;**70**:201–208.
390. Liu S, Rouleau J, Joseph KS, Sauve R, Liston RM, Young D, Kramer MS. Epidemiology of pregnancy-associated venous thromboembolism: A population-based study in Canada. *J Obstet Gynaecol Can* 2009;**31**:611–620.
391. O'Connor DJ, Scher LA, Gargiulo NJ III, Jang J, Suggs WD, Lipsitz EC. Incidence and characteristics of venous thromboembolic disease during pregnancy and the postnatal period: A contemporary series. *Ann Vasc Surg* 2011;**25**:9–14.
392. Rutherford SE, Phelan JP. Deep venous thrombosis and pulmonary embolism in pregnancy. *Obstet Gynecol Clin North Am* 1991;**18**:345–370.
393. Sullivan EA, Ford JB, Chambers G, Slaytor EK. Maternal mortality in Australia, 1973-1996. *Aust N Z J Obstet Gynaecol* 2004;**44**:452–457; discussion 377.
394. Heit JA, Kobbervig CE, James AH, Petterson TM, Bailey KR, Melton LJ III. Trends in the incidence of venous thromboembolism during pregnancy or postpartum: A 30-year population-based study. *Ann Intern Med* 2005;**143**:697–706.
395. Meng K, Hu X, Peng X, Zhang Z. Incidence of venous thromboembolism during pregnancy and the puerperium: A systematic review and meta-analysis. *J Matern Fetal Neonatal Med* 2015;**28**:245–253.
396. Knight M; UKOSS. Antenatal pulmonary embolism: Risk factors, management and outcomes. *BJOG* 2008;**115**:453–461.
397. Sultan AA, West J, Tata LJ, Fleming KM, Nelson-Piercy C, Grainge MJ. Risk of first venous thromboembolism in and around pregnancy: A population-based cohort study. *Br J Haematol* 2012;**156**:366–373.
398. Galambosi PJ, Ulander VM, Kaaja RJ. The incidence and risk factors of recurrent venous thromboembolism during pregnancy. *Thromb Res* 2014;**134**:240–245.
399. Roeters van Lennep JE, Meijer E, Klumper FJ, Middeldorp JM, Bloemenkamp KW, Middeldorp S. Prophylaxis with low-dose low-molecular-weight heparin during pregnancy and postpartum: Is it effective? *J Thromb Haemost* 2011;**9**:473–480.
400. Sultan AA, Tata LJ, West J, Fiaschi L, Fleming KM, Nelson-Piercy C, Grainge MJ. Risk factors for first venous thromboembolism around pregnancy: A population-based cohort study from the United Kingdom. *Blood* 2013;**121**:3953–3961.
401. Royal College of Obstetricians and Gynaecologists. *Reducing the risk of thrombosis and embolism during pregnancy and the puerperium. Royal College of Obstetricians and Gynaecologists Green-Top Guideline No. 37a*. London: Royal College of Obstetricians and Gynaecologists; 2009.
402. Bauersachs RM, Dudenhausen J, Faridi A, Fischer T, Fung S, Geisen U, Harenberg J, Herchenhan E, Keller F, Kemkes-Matthes B, Schinzel H, Spannagl M, Thaler CJ. Risk stratification and heparin prophylaxis to prevent venous thromboembolism in pregnant women. *Thromb Haemost* 2007;**98**:1237–1245.
403. Stephenson ML, Serra AE, Neeper JM, Caballero DC, McNulty J. A randomized controlled trial of differing doses of postcesarean enoxaparin thromboprophylaxis in obese women. *J Perinatol* 2016;**36**:95–99.
404. Overcash RT, Somers AT, LaCoursiere DY. Enoxaparin dosing after cesarean delivery in morbidly obese women. *Obstet Gynecol* 2015;**125**:1371–1376.
405. Konstantinides SV, Torbicki A, Agnelli G, Danchin N, Fitzmaurice D, Galie N, Gibbs JS, Huisman MV, Humbert M, Kucher N, Lang I, Lankeit M, Lekakis J, Maack C, Mayer E, Meneveau N, Perrier A, Pruszczyk P, Rasmussen LH, Schindler TH, Svitil P, Vonk Noordegraaf A, Zamorano JL, Zompatori M; Task Force for the Diagnosis and Management of Acute Pulmonary Embolism of the European Society of Cardiology (ESC). 2014 ESC guidelines on the diagnosis and management of acute pulmonary embolism. *Eur Heart J* 2014;**35**:3033–3069, 3069a–3069k.
406. Nijkeuter M, Ginsberg JS, Huisman MV. Diagnosis of deep vein thrombosis and pulmonary embolism in pregnancy: A systematic review. *J Thromb Haemost* 2006;**4**:496–500.
407. Kline JA, Williams GW, Hernandez-Nino J. D-dimer concentrations in normal pregnancy: New diagnostic thresholds are needed. *Clin Chem* 2005;**51**:825–829.
408. To MS, Hunt BJ, Nelson-Piercy C. A negative D-dimer does not exclude venous thromboembolism (VTE) in pregnancy. *J Obstet Gynaecol* 2008;**28**:222–223.
409. Van der Pol LM, Mairuhu AT, Tromeur C, Couturaud F, Huisman MV, Klok FA. Use of clinical prediction rules and D-dimer tests in the diagnostic management of pregnant patients with suspected acute pulmonary embolism. *Blood Rev* 2017;**31**:31–36.
410. Konstantinides SV, Barco S, Lankeit M, Meyer G. Management of pulmonary embolism: An update. *J Am Coll Cardiol* 2016;**67**:976–990.
411. O'Connor C, Moriarty J, Walsh J, Murray J, Coulter-Smith S, Boyd W. The application of a clinical risk stratification score may reduce unnecessary investigations for pulmonary embolism in pregnancy. *J Matern Fetal Neonatal Med* 2011;**24**:1461–1464.
412. Parilla BV, Fournogerakis R, Archer A, Sulo S, Laurent L, Lee P, Chhotani B, Hesse K, Kulstad E. Diagnosing pulmonary embolism in pregnancy: Are biomarkers and clinical predictive models useful? *AJP Rep* 2016;**6**:e160–e164.
413. Bates SM, Greer IA, Pabinger I, Sofaer S, Hirsh J. Venous thromboembolism, thrombophilia, antithrombotic therapy, and pregnancy: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th edition). *Chest* 2008;**133**:844S–886S.
414. Ahearn GS, Hadjiliadis D, Govert JA, Tapson VF. Massive pulmonary embolism during pregnancy successfully treated with recombinant tissue plasminogen activator: A case report and review of treatment options. *Arch Intern Med* 2002;**162**:1221–1227.
415. Chan WS, Lee A, Spencer FA, Crowther M, Rodger M, Ramsay T, Ginsberg JS. Predicting deep venous thrombosis in pregnancy: Out in "left" field? *Ann Intern Med* 2009;**151**:85–92.
416. Le Gal G, Kercret G, Ben Yahmed K, Bressollette L, Robert-Ebadi H, Riberdy L, Louis P, Delluc A, Labalette ML, Baba-Ahmed M, Bounameaux H, Mottier D, Righini M. Diagnostic value of single complete compression ultrasonography in pregnant and postpartum women with suspected deep vein thrombosis: Prospective study. *BMJ* 2012;**344**:e2635.
417. Dargaud Y, Rugeri L, Vergnes MC, Arnuti B, Miranda P, Negrier C, Bestion A, Desmurs-Clavel H, Ninet J, Gaucherand P, Rudigoz RC, Berland M, Champion F, Trzeciak MC. A risk score for the management of pregnant women with increased risk of venous thromboembolism: A multicentre prospective study. *Br J Haematol* 2009;**145**:825–835.

Downloaded from https://academic.oup.com/eurheartj/article-abstract/39/34/3165/5078465 by guest on 13 September 2018

418. Sennstrom M, Rova K, Hellgren M, Hjertberg R, Nord E, Thurn L, Lindqvist PG. Thromboembolism and in vitro fertilization - a systematic review. *Acta Obstet Gynecol Scand* 2017;**96**:1045–1052.
419. McLintock C, Brighton T, Chunilal S, Dekker G, McDonnell N, McRae S, Muller P, Tran H, Walters BN, Young L. Recommendations for the diagnosis and treatment of deep venous thrombosis and pulmonary embolism in pregnancy and the postpartum period. *Aust N Z J Obstet Gynaecol* 2012;**52**:14–22.
420. Burnett AE, Mahan CE, Vazquez SR, Oertel LB, Garcia DA, Ansell J. Guidance for the practical management of the direct oral anticoagulants (DOACS) in VTE treatment. *J Thromb Thrombolysis* 2016;**41**:206–232.
421. Friedrich E, Hameed AB. Fluctuations in anti-factor Xa levels with therapeutic enoxaparin anticoagulation in pregnancy. *J Perinatol* 2010;**30**:253–257.
422. Turrentine MA, Braems G, Ramirez MM. Use of thrombolytics for the treatment of thromboembolic disease during pregnancy. *Obstet Gynecol Surv* 1995;**50**:534–541.
423. 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.
424. Dempfle CE. Minor transplacental passage of fondaparinux in vivo. *N Engl J Med* 2004;**350**:1914–1915.
425. Beyer-Westendorf J, Michalski F, Tittl L, Middeldorp S, Cohen H, Abdul Kadir R, Arachchillage DJ, Arya R, Ay C, Marten S. Pregnancy outcome in patients exposed to direct oral anticoagulants - and the challenge of event reporting. *Thromb Haemost* 2016;**116**:651–658.
426. Garg J, Palaniswamy C, Lanier GM. Peripartum cardiomyopathy: Definition, incidence, etiopathogenesis, diagnosis, and management. *Cardiol Rev* 2015;**23**:69–78.
427. Tanaka K, Tanaka H, Kamiya C, Katsuragi S, Sawada M, Tsuritani M, Yoshida M, Iwanaga N, Yoshimatsu J, Ikeda T. Beta-blockers and fetal growth restriction in pregnant women with cardiovascular disease. *Circ J* 2016;**80**:2221–2226.
428. Lip GY, Beevers M, Churchill D, Shaffer LM, Beevers DG. Effect of atenolol on birth weight. *Am J Cardiol* 1997;**79**:1436–1438.
429. Davis RL, Eastman D, McPhillips H, Raebel MA, Andrade SE, Smith D, Yood MU, Dublin S, Platt R. Risks of congenital malformations and perinatal events among infants exposed to calcium channel and beta-blockers during pregnancy. *Pharmacoepidemiol Drug Saf* 2011;**20**:138–145.
430. Godfrey LM, Erramouspe J, Cleveland KW. Teratogenic risk of statins in pregnancy. *Ann Pharmacother* 2012;**46**:1419–1424.
431. Winterfeld U, Allignol A, Panchaud A, Rothuizen LE, Merlob P, Cuppers-Maarschalkerweerd B, Vial T, Stephens S, Clementi M, De Santis M, Pistelli A, Berlin M, Eleftheriou G, Manakova E, Buclin T. Pregnancy outcome following maternal exposure to statins: A multicentre prospective study. *BJOG* 2013;**120**:463–471.
432. U.S. Food & Drug Administration. Pregnancy and lactation labeling (drugs) final rule. https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/Labeling/ucm093307.htm.
433. Magee LA, Schick B, Donnenfeld AE, Sage SR, Conover B, Cook L, McElhatton PR, Schmidt MA, Koren G. The safety of calcium channel blockers in human pregnancy: A prospective, multicenter cohort study. *Am J Obstet Gynecol* 1996;**174**:823–828.
434. Weber-Schoendorfer C, Hannemann D, Meister R, Elefant E, Cuppers-Maarschalkerweerd B, Arnon J, Vial T, Rodriguez-Pinilla E, Clementi M, Robert-Gnansia E, De Santis M, Malm H, Dolivo A, Schaefer C. The safety of calcium channel blockers during pregnancy: A prospective, multicenter, observational study. *Reprod Toxicol* 2008;**26**:24–30.
435. Schaefer C. Angiotensin II-receptor-antagonists: Further evidence of fetotoxicity but not teratogenicity. *Birth Defects Res A Clin Mol Teratol* 2003;**67**:591–594.
436. Cooper WO, Hernandez-Diaz S, Arbogast PG, Dudley JA, Dyer S, Gideon PS, Hall K, Ray WA. Major congenital malformations after first-trimester exposure to ACE inhibitors. *N Engl J Med* 2006;**354**:2443–2451.
437. American Academy of Pediatrics Committee on Drugs. American Academy of Pediatrics Committee on Drugs: The transfer of drugs and other chemicals into human milk. *Pediatrics* 1994;**93**:137–150.
438. Andrade SE, Gurwitz JH, Field TS, Kelleher M, Majumdar SR, Reed G, Black R. Hypertension management: The care gap between clinical guidelines and clinical practice. *Am J Manag Care* 2004;**10**:481–486.
439. Podymow T, August P. Antihypertensive drugs in pregnancy. *Semin Nephrol* 2011;**31**:70–85.

Downloaded from https://academic.oup.com/eurheartj/article-abstract/39/34/3165/5078465 by guest on 13 September 2018