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ESC Guidelines on the management of cardiovascular diseases during pregnancy

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

Endorsed by the European Society of Gynecology (ESG), the Association for European Paediatric Cardiology (AEPC), and the German Society for Gender Medicine (DGesGM)

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Abbreviations and acronyms

ABPM	ambulatory blood pressure monitoring
ACC	American College of Cardiology
ACE	angiotensin-converting enzyme
ACS	acute coronary syndrome
AF	atrial fibrillation
AHA	American Heart Association
aPTT	activated partial thromboplastin time
ARB	angiotensin receptor blocker
AS	aortic stenosis
ASD	atrial septal defect
AV	atrioventricular
AVSD	atrioventricular septal defect
BMI	body mass index
BNP	B-type natriuretic peptide
BP	blood pressure
CDC	Centers for Disease Control
CHADS	congestive heart failure, hypertension, age (>75 years), diabetes, stroke
CI	confidence interval
CO	cardiac output
CoA	coarction of the aorta
CT	computed tomography
CVD	cardiovascular disease
DBP	diastolic blood pressure
DCM	dilated cardiomyopathy
DVT	deep venous thrombosis
ECG	electrocardiogram
EF	ejection fraction
ESC	European Society of Cardiology
ESH	European Society of Hypertension
ESICM	European Society of Intensive Care Medicine
FDA	Food and Drug Administration
HCM	hypertrophic cardiomyopathy
ICD	implantable cardioverter-defibrillator
INR	international normalized ratio
i.v.	intravenous
LMWH	low molecular weight heparin
LV	left ventricular
LVEF	left ventricular ejection fraction
LVOTO	left ventricular outflow tract obstruction
MRI	magnetic resonance imaging
MS	mitral stenosis
NT-proBNP	N-terminal pro B-type natriuretic peptide
NYHA	New York Heart Association
OAC	oral anticoagulant
PAH	pulmonary arterial hypertension
PAP	pulmonary artery pressure
PCI	percutaneous coronary intervention
PPCM	peripartum cardiomyopathy
PS	pulmonary valve stenosis
RV	right ventricular
SBP	systolic blood pressure
SVT	supraventricular tachycardia
TGA	complete transposition of the great arteries
TR	tricuspid regurgitation
UFH	unfractionated heparin
VSD	ventricular septal defect

VT ventricular tachycardia
VTE venous thrombo-embolism
WHO World Health Organization

1. Preamble

Guidelines summarize and evaluate all available evidence, at the time of the writing process, on a particular issue with the aim of assisting physicians in selecting the best management strategies for an individual patient, with a given condition, taking into account the impact on outcome, as well as the risk–benefit ratio of particular diagnostic or therapeutic means. Guidelines are no substitutes but are complements for textbooks and cover the European Society of Cardiology (ESC) Core Curriculum topics. Guidelines and recommendations should help the physicians to make decisions in their daily practice. However, the final decisions concerning an individual patient must be made by the responsible physician(s).

A great number of Guidelines have been issued in recent years by the ESC as well as by other societies and organizations. 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-surveys/esc-guidelines/about/Pages/rules-writing.aspx). 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 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 diagnosis, management, and/or prevention 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. Estimates of expected health outcomes for larger populations were included, where data exist. The level of evidence and the strength of recommendation of particular treatment options were weighed and graded according to pre-defined scales, as outlined in *Tables 1* and *2*.

The experts of the writing and reviewing panels filled in declarations of interest forms which 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 Web Site (http://www.escardio.org/guidelines). Any changes in declarations of interest that arise during the writing period must be notified to the ESC and updated. The Task Force received its entire financial support from the ESC without any involvement from healthcare industry.

The ESC CPG supervises and coordinates the preparation of new Guidelines produced by Task Forces, expert groups, or consensus panels. 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 it is 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 task of developing Guidelines covers not only the integration of the most recent research, but also the creation of educational tools and implementation programmes for the recommendations. To implement the guidelines, condensed pocket guidelines versions, summary slides, booklets with essential messages, and an electronic version for digital applications (smartphones, etc.) are produced. These versions are abridged and, thus, if needed, one should always refer to the full text version which is freely available on the ESC website.

The National Societies of the ESC are encouraged to endorse, translate, and implement the ESC Guidelines. Implementation

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**

Table 2 Levels 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.

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, and implementing them into clinical practice.

The guidelines do not, however, override the individual responsibility of health professionals to make appropriate decisions in the circumstances of the individual patients, in consultation with that patient, and, where appropriate and necessary, the patient's guardian or carer. 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. General considerations

2.1 Introduction

At present, 0.2–4% of all pregnancies in western industrialized countries are complicated by cardiovascular diseases (CVD),[1] and the number of the patients who develop cardiac problems during pregnancy is increasing. Nevertheless, the number of such patients presenting to the individual physician is small. However, knowledge of the risks associated with CVD during pregnancy and their management are of pivotal importance for advising patients before pregnancy. Therefore, guidelines on disease management in pregnancy are of great relevance. Such guidelines have to give special consideration to the fact that all measures concern not only the mother, but the fetus as well. Therefore, the optimum treatment of both must be targeted. A therapy favourable for the mother can be associated with an impairment of the child, and in extreme cases treatment measures which protect the survival of the mother can cause the death of the fetus. On the other hand, therapies to protect the child may lead to a suboptimal outcome for the mother. Because prospective or randomized studies are lacking, with a few exceptions, recommendations in this guideline mostly correspond to the evidence level C.

Some general conclusions have arisen from these guidelines: counselling and management of women of childbearing age with suspected cardiac disease should start before pregnancy occurs; they should be managed by interdisciplinary teams; high risk patients should be treated in specialized centres; and diagnostic procedures and interventions should be performed by specialists with great expertise in the individual techniques and experience in treating pregnant patients. Registries and prospective studies are urgently needed to improve the state of knowledge.

2.2 Methods

The Guidelines are based on a systematic search of the literature of the last 20 years in the National Institutes of Health database (PubMed). The publications and recommendations of the European and American cardiological societies are also considered: American Heart Association/American College of Cardiology (AHA/ACC),[2] the ESC in 2003,[3] the Working Group Valvular Heart Disease of the ESC,[4] the guidelines of the German Society of Cardiology (German Society of Cardiology),[5,6] and the ESC Task Force on the Management of Valvular Heart Disease 2007.[7]

2.3 Epidemiology

The spectrum of CVD in pregnancy is changing and differs between countries. In the western world, the risk of CVD in pregnancy has increased due to increasing age at first pregnancy and increasing prevalence of cardiovascular risk factors—diabetes, hypertension, and obesity. Also the treatment of congenital heart disease has improved, resulting in an increased number of women with heart disease reaching childbearing age.[8] In western countries maternal heart disease is now the major cause of maternal death during pregnancy.[9]

Hypertensive disorders are the most frequent cardiovascular events during pregnancy, occurring in 6–8% of all pregnancies.[10] In the western world, congenital heart disease is the most frequent cardiovascular disease present during pregnancy (75–82%), with shunt lesions predominating (20–65%).[11,12] Congenital heart disease represents just 9–19% outside Europe and North America. Rheumatic valvular disease dominates in non-western countries, comprising 56–89% of all cardiovascular diseases in pregnancy.[11,12]

Cardiomyopathies are rare, but represent severe causes of cardiovascular complications in pregnancy. Peripartum cardiomyopathy (PPCM) is the most common cause of severe complications.[13]

2.4 Haemodynamic, haemostatic, and metabolic alterations during pregnancy

Pregnancy induces changes in the cardiovascular system to meet the increased metabolic demands of the mother and fetus. They include increases in blood volume and cardiac output (CO), and reductions in systemic vascular resistance and blood pressure (BP).

Plasma volume reaches a maximum of 40% above baseline at 24 weeks gestation. A 30–50% increase in CO occurs in normal pregnancy. In early pregnancy increased CO is primarily related to the rise in stroke volume; however, in late pregnancy, heart rate is the major factor. Heart rate starts to rise at 20 weeks and increases until 32 weeks. It remains high 2–5 days after delivery. Systemic BP (SBP) typically falls early in gestation and diastolic BP (DBP) is usually 10 mmHg below baseline in the second trimester. This decrease in BP is caused by active vasodilatation, achieved

through the action of local mediators such as prostacyclin and nitric oxide. In the third trimester, the DBP gradually increases and may normalize to non-pregnant values by term.

The heart can increase its size by up to 30%, which is partially due to dilatation. Data regarding systolic and diastolic function in pregnancy are scarce. Systolic function increases first but may decrease in the last trimester. Reports on diastolic function are conflicting.

Pregnancy induces a series of haemostatic changes, with an increase in concentration of coagulation factors, fibrinogen, and platelet adhesiveness, as well as diminished fibrinolysis, which lead to hypercoagulability and an increased risk of thrombo-embolic events. In addition, obstruction to venous return by the enlarging uterus causes stasis and a further rise in risk of thrombo-embolism.

Maternal glucose homeostasis may change and cholesterol levels increase in adaptation to fetal–maternal needs.

Physiological changes that occur during pregnancy can affect absorption, excretion, and bioavailability of all drugs.[14] The increased intravascular blood volume partly explains the higher dosages of drugs required to achieve therapeutic plasma concentrations, and the dose adaptations needed during treatment. Moreover, the raised renal perfusion and the higher hepatic metabolism increase drug clearance. The altered pharmacokinetics of drugs vary in magnitude during different stages of pregnancy, making careful monitoring of the patient and dose adjustments necessary.

Uterine contractions, positioning (left lateral vs. supine), pain, anxiety, exertion, bleeding, and uterine involution cause significant haemodynamic changes during labour and post-partum. Anaesthesia, analgesia, haemorrhage, and infection may induce additional cardiovascular stress. SBP and DBP increase 15–25% and 10–15%, respectively, during uterine contractions. Such increases are associated with a rise in pressure in the amniotic fluid, and in the intrathoracic venous, cerebrospinal, and extradural fluids. CO increases by 15% in early labour, by 25% during stage 1, and by 50% during expulsive efforts.[15] It reaches an increase of 80% early post-partum due to autotransfusion associated with uterine involution and resorption of leg oedema.

In conclusion, the physiological adaptations to pregnancy influence the evaluation and interpretation of cardiac function and clinical status.

2.5 Genetic testing and counselling

An important aspect concerning the care of young women with CVD is the consultation about the risk of inheritance of cardiac defects for their descendants. The risk is raised significantly in comparison with parents without CVD where the risk is ~1%. In addition, there are large differences between each of the hereditary heart disease conditions, and the risk for descendants is dependent on whether only the mother, only the father, or both parents suffer from hereditary cardiac defects.[16] In general, the risk is higher when the mother is affected rather than the father.[16] The recurrence risk varies between 3% and 50% depending on the type of maternal heart disease.

Children of parents with a cardiovascular condition inherited in an autosomal dominant manner (e.g. Marfan syndrome, hypertrophic cardiomyopathy, or long QT syndrome) have an inheritance risk of 50%, regardless of gender of the affected parent. The final phenotype will also be determined by incomplete penetrance and pleiotropic effects, and may vary significantly. For defects that are inherited in a polygenic manner, recurrence risk is less clearly defined. Autosomal recessive and X-chromosomal recessive inheritance are rare.

Genetic testing may be useful:

- in cardiomyopathies and channelopathies, such as long QT syndromes[17]
- when other family members are affected
- 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, 22q11 deletion, Williams–Beuren, Alagille, Noonan, and Holt–Oram syndrome.

For a steadily increasing number of genetic defects, genetic screening by chorionic villous biopsy can be offered in the 12th week of pregnancy. All women with congenital heart disease should be offered fetal echocardiography in the 19th to 22nd week of pregnancy. Measurement of nuchal fold thickness in the 12th to 13th week of pregnancy is an early screening test for women over 35 years of age. The sensitivity for the presence of a significant heart defect is 40%, while the specificity of the method is 99%. The incidence of congenital heart disease with normal nuchal fold thickness is ~1/1000.[18]

The inheritance pattern differs among the diseases, and therefore genetic counselling by a geneticist is highly recommended for patients and their family members.[17] Genetic testing after careful counselling has the rationale of identifying at-risk asymptomatic or disease-free relatives and to guide clinical surveillance for disease onset, thereby enhancing preventive and treatment interventions. It is advocated in patients with known genetic disorders and is more advisable if treatment options are available.[17]

2.6 Cardiovascular diagnosis in pregnancy

The following procedures are of relevance for the diagnosis and management of CVD in pregnancy.

History and clinical investigation

Many disorders can be identified by taking a careful personal and family history, particularly cardiomyopathies, the Marfan syndrome, congenital heart disease, juvenile sudden death, long QT syndrome, and catecholaminergic ventricular tachycardia (VT) or Brugada syndrome. It is important to ask specifically about possible sudden deaths in the family. The assessment of dyspnoea is important for diagnosis and prognosis of valve lesions and for heart failure. A thorough physical examination considering the physiological changes that occur during pregnancy (Section 2.4) is mandatory, including auscultation for new murmurs, changes in murmurs, and looking for signs of heart failure. When dyspnoea occurs during pregnancy or when a new pathological murmer is heard, echocardiography is indicated. It is crucial to measure the BP, in left lateral recumbency (see Section 9) using a standardized method, and to look for proteinuria, especially with a history or family history

of hypertension or pre-eclampsia. Oximetry should be performed in patients with congenital heart disease.

Electrocardiography

The great majority of pregnant patients have a normal electrocardiogram (ECG). The heart is rotated towards the left and on the surface ECG there is a 15–20 left axis deviation. Common findings include transient ST segment and T wave changes, the presence of a Q wave and inverted T waves in lead III, an attenuated Q wave in lead AVF, and inverted T waves in leads V1, V2, and, occasionally, V3. ECG changes can be related to a gradual change in the position of the heart and may mimic left ventricular (LV) hypertrophy and other structural heart diseases.

Holter monitoring should be performed in patients with known previous paroxysmal or persistent documented arrhythmia [VT, atrial fibrillation (AF), or atrial flutter] or those reporting symptoms of palpitations.

Echocardiography

Because echocardiography does not involve exposure to radiation, is easy to perform, and can be repeated as often as needed, it has become an important tool during pregnancy and is the preferred screening method to assess cardiac function.

Transoesophageal echocardiography

Multiplane transducers have made transoesophageal echocardiography a very useful echocardiographic method in the assessment of adults with, for example, complex congenital heart disease. Transoesophageal echocardiography, although rarely required, is relatively safe during pregnancy. The presence of stomach contents, risk of vomiting and aspiration, and sudden increases in intra-abdominal pressure should be taken into account, and fetal monitoring performed if sedation is used.

Exercise testing

Exercise testing is useful to assess objectively the functional capacity, chronotropic and BP response, as well as exercise-induced arrhythmias. It has become an integral part of the follow-up of grown up congenital heart disease patients as well as patients with asymptomatic valvular heart disease.[19,20] It should be performed in patients with known heart disease, preferably prior to pregnancy to assist in risk assessment.

This Committee recommends performing submaximal exercise tests to reach 80% of predicted maximal heart rate in asymptomatic pregnant patients with suspected CVD. There is no evidence that it increases the risk of spontaneous abortion.[21] Semi-recumbent cycle ergometry appears to be the most comfortable modality, but treadmill walking or upright cycle ergometry may also be used. Dobutamine stress should be avoided. If respiratory gas analysis is used, the limit is a respiratory exchange ratio of 1.0. Stress echocardiography using bicycle ergometry may add to the diagnostic specificity in detecting the presence and extent of ischaemia in high risk patients with possible coronary artery disease. This can also be useful prior to conception to assess myocardial reserve in patients with prior PPCM and recovered LV function [left ventricular ejection fraction (LVEF)], and also in patients with other cardiomyopathies, with valvular or congenital heart disease with borderline or mildly reduced LVEF. Nuclear scintigraphy should be avoided during pregnancy because of radiation exposure.

Radiation exposure

The effects of radiation on the fetus depend on the radiation dose and the gestational age at which exposure occurs. If possible, procedures should be delayed until at least the completion of the period of major organogenesis (>12 weeks after menses). There is no evidence of an increased fetal risk of congenital malformations, intellectual disability, growth restriction, or pregnancy loss at doses of radiation to the pregnant woman of <50 mGy[22,23] (www.bt.cdc.gov/radiation/prenatalphysician.asp; accessed 31 October 2007). There may be a small increase in risk (1:2000 vs. 1:3000) of childhood cancer. The threshold at which an increased risk of congenital malformations occurs has not been definitely determined. Some evidence suggests that risk of malformations is increased at doses >100 mGy, whereas the risk between 50 and 100 mGy is less clear. During the first 14 days after fertilization, intact survival without fetal abnormality or death are the most likely outcomes of radiation exposure >50 mGy. After the first 14 days, radiation exposure >50 mGy may be associated with an increased risk of congenital malformations, growth restriction, and intellectual disability.

Most medical procedures do not expose the fetus to such high levels of radiation (*Table 3*). For the majority of diagnostic medical procedures, involving doses to the fetus of up to ~1 mGy, the associated risks of childhood cancer are very low. (Documents of the Health Protection Agency. Radiation, Chemical and Environmental Hazards March 2009. RSE-9 Protection of pregnant patients during diagnostic medical exposures to ionising radiation. Advice from the Health Protection Agency, The Royal College of Radiologists, and the College of Radiographers.)

Table 3 Estimated fetal and maternal effective doses for various diagnostic and interventional radiology procedures

Procedure	Fetal exposure		Maternal exposure	
Chest radiograph (PA and lateral)	<0.01 mGy	<0.01 mSv	0.1 mGy	0.1 mSv
CT chest	0.3 mGy	0.3 mSv	7 mGy	7 mSv
Coronary angiography[a]	1.5 mGy	1.5 mSv	7 mGy	7 mSv
PCI or radiofrequency catheter ablation[a]	3 mGy	3 mSv	15 mGy	15 mSv

[a]Exposure depends on the number of projections or views.
CT = computed tomography; PA = postero-anterior; PCI = percutaneous coronary intervention.

As a general rule, according to the principle 'as low as reasonably achievable' (ALARA), all radiation doses due to medical exposures must be kept as low as reasonably achievable.[24]

Chest radiograph

The fetal dose from a chest radiograph is <0.01 mGy.[25] Nevertheless, a chest radiograph should only be obtained if other methods fail to clarify the cause of dyspnoea, cough, or other symptoms.[23]

If the required diagnostic information can be obtained with an imaging modality that does not use ionizing radiation, it should be used as a first-line test. If a study that uses ionizing radiation has to be performed, the radiation dose to the fetus should be kept as low as possible (preferably <50 mGy). The risks and benefits of performing or not performing the examination should be communicated. Documentation of the radiation dose to the mother in the medical records, particularly if the fetus is in the field of view, is highly recommended.[26,27]

Magnetic resonance imaging and computed tomography

Magnetic resonance imaging (MRI) may be useful in diagnosing complex heart disease or pathology of the aorta.[28] It should only be performed if other diagnostic measures, including transthoracic and transoesophageal echocardiography, are not sufficient for complete diagnosis. Limited data during organogenesis are available, but MRI is probably safe, especially after the first trimester.[29]

Gadolinium can be assumed to cross the fetal blood–placental barrier, but data are limited. The long-term risks of exposure of the developing fetus to free gadolinium ions[30] are not known, and therefore gadolinium should be avoided.

Computed tomography (CT)[31] is usually not necessary to diagnose CVD during pregnancy and, because of the radiation dose involved, is therefore not recommended. One exception is that it may be required for the accurate diagnosis or definite exclusion of pulmonary embolism. For this indication it is recommended if other diagnostic tools are not sufficient (see Section 10). Low radiation CT 1–3 mSv can be used in these situations.

Cardiac catheterization

During coronary angiography the mean radiation exposure to the unshielded abdomen is 1.5 mGy, and <20% of this reaches the fetus because of tissue attenuation. Shielding the gravid uterus from direct radiation and especially shortening fluoroscopic time will minimize radiation exposure. The radial approach is preferable and should be undertaken by an experienced operator. Most electrophysiological studies aiming for ablation should only be performed if arrhythmias are intractable to medical treatment and cause haemodynamic compromise. If undertaken, electroanatomical mapping systems should be used to reduce the radiation dose.[32]

General recommendations for diagnostic and therapeutic management during pregnancy are listed in *Table 9*.

2.7 Fetal assessment

First trimester ultrasound allows accurate measurement of gestational age and early detection of multiple pregnancy and of malformations. Diagnosis of congenital cardiac malformations can be made as early as 13 weeks, and, in families with heart disease, this timing is appropriate to start screening for congential heart disease. A review of the accuracy of first-trimester ultrasounds for detecting major congenital heart disease showed a sensitivity and specificity of 85% [95% confidence interval (CI) 78–90%] and 99% (95% CI 98–100%), respectively. Early examination in pregnancy allows parents to consider all options, including termination of pregnancy, if there are major malformations.[33]

The optimum time for screening of normal pregnancies for congenital heart diseases[34] is 18–22 weeks of gestation when visualization of the heart and outflow tracts is optimal. It becomes more difficult after 30 weeks since the fetus is more crowded within the amniotic cavity. Second-trimester screening (18–22 weeks) for detection of fetal anomalies should be performed by experienced specialists, particularly in pregnancies with risk factors for congenital heart anomalies.[35]

Cardiac anatomy and function, arterial and venous flow, and rhythm should be evaluated. When a fetal cardiac anomaly is suspected, it is mandatory to obtain the following.

(1) A full fetal echocardiography to evaluate cardiac structure and function, arterial and venous flow, and rhythm.
(2) Detailed scanning of the fetal anatomy to look for associated anomalies (particularly the digits and bones).
(3) Family history to search for familial syndromes.
(4) Maternal medical history to identify chronic medical disorders, viral illnesses, or teratogenic medications.
(5) Fetal karyotype (with screening for deletion in 22q11.2 when conotruncal anomalies are present).
(6) Referral to a maternal–fetal medicine specialist, paediatric cardiologist, geneticist, and/or neonatologist to discuss prognosis, obstetric, and neonatal management, and options.
(7) Delivery at an institution that can provide neonatal cardiac care, if needed.

Doppler velocimetry (uterine, umbilical, fetal renal, and cerebral arteries, and descending aorta) provides a non-invasive measure of the fetoplacental haemodynamic state. Abnormality of the Doppler index in the umbilical artery correlates to fetoplacental vascular maldevelopment, fetal hypoxia, acidosis, and adverse perinatal outcome. The most ominous pre-terminal findings of the umbilical artery Doppler waveform are absent end-diastolic velocity and reversed end-diastolic velocity. Reversed end-diastolic velocity beyond 28 weeks should prompt immediate delivery by caesarean delivery. Absent end-diastolic velocity should prompt immediate consideration of delivery beyond 32 completed weeks.[36]

Fetal biophysical profile testing is indicated in pregnancies at risk of fetal compromise. Testing should be performed one or more times per week, depending upon the clinical situation. Four echographic biophysical variables (fetal movement, tone, breathing, and amniotic fluid volume) and results of non-stress testing are used for scoring. Their presence implies absence of significant central nervous system hypoxaemia/acidaemia. A compromised fetus exhibits loss of accelerations of the fetal heart rate, decreased body movement and breathing, hypotonia, and, less acutely, decreased amniotic fluid volume. From 70% to 90% of late fetal deaths display evidence of chronic and/or acute compromise. Sonographic detection of signs of fetal compromise can allow

appropriate intervention that ideally will prevent adverse fetal sequelae.[37,38]

2.8 Interventions in the mother during pregnancy

2.8.1 Percutaneous therapy

The same restrictions which apply for diagnostic coronary angiography (see Section 2.6) are relevant. If an intervention is absolutely necessary, the best time to intervene is considered to be after the fourth month in the second trimester. By this time organogenesis is complete, the fetal thyroid is still inactive, and the volume of the uterus is still small, so there is a greater distance between the fetus and the chest than in later months. Fluoroscopy and cineangiography times should be as brief as possible and the gravid uterus should be shielded from direct radiation. Heparin has to be given at 40–70 U/kg, targeting an activated clotting time of at least 200 s, but not exceeding 300 s.

2.8.2 Cardiac surgery with cardiopulmonary bypass

Maternal mortality during cardiopulmonary bypass is now similar to that in non-pregnant women who undergo comparable cardiac procedures.[1] However, there is significant morbidity including late neurological impairment in 3–6% of children, and fetal mortality remains high.[39] For this reason cardiac surgery is recommended only when medical therapy or interventional procedures fail and the mother's life is threatened. The best period for surgery is between the 13th and 28th week.[40,41] Surgery during the first trimester carries a higher risk of fetal malformations, and during the third trimester there is a higher incidence of pre-term delivery and maternal complications. We know from previous studies that gestational age has a large impact on neonatal outcome.[42] Recent improvement in neonatal care has further improved survival of premature infants. At 26 weeks, survival is generally ~80%, with 20% having serious neurological impairment. For this reason, caesarean delivery may be considered before cardiopulmonary bypass if gestational age is >26 weeks.[43] Whether or not delivery is advantageous for the baby at this gestational age depends on several factors: gender, estimated weight, prior administration of corticosteroids before delivery, and the outcome statistics of the neonatal unit concerned. When gestational age is 28 weeks or more, delivery before surgery should be considered. Before surgery a full course (at least 24 h) of corticosteroids should be administered to the mother, whenever possible. During cardiopulmonary bypass, fetal heart rate and uterine tone should be monitored in addition to standard patient monitoring. Pump flow >2.5 L/min/m^2 and perfusion pressure >70 mmHg are mandatory to maintain adequate utero-placental blood flow; pulsatile flow, although controversial, seems more effective for preserving uteroplacental blood flow. Maternal haematocrit >28% is recommended to optimize the oxygen delivery. Normothermic perfusion, when feasible, is advocated, and state of the art pH management is preferred to avoid hypocapnia responsible for uteroplacental vasoconstriction and fetal hypoxia. Cardiopulmonary bypass time should be minimized.[44]

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

High risk delivery

Induction, management of labour, delivery, and post-partum surveillance require specific expertise and collaborative management by skilled cardiologists, obstetricians, and anaesthesiologists, in experienced maternal–fetal medicine units.[45,46]

Timing of delivery

Spontaneous onset of labour is appropriate for women with normal cardiac function and is preferable to induced labour for the majority of women with heart disease. Timing is individualized, according to the gravida's cardiac status, Bishop score (a score based upon the station of the presenting part and four characteristics of the cervix: dilatation, effacement, consistency, and position), fetal well-being, and lung maturity. Due to a lack of prospective data and the influence of individual patient characteristics, standard guidelines do not exist, and management should therefore be individualized. In women with mild unrepaired congenital heart disease and in those who have undergone successful cardiac surgical repair with minimal residua, the management of labour and delivery is the same as for normal pregnant women.

Labour induction

Oxytocin and artificial rupture of the membranes are indicated when the Bishop score is favourable. A long induction time should be avoided if the cervix is unfavourable. While there is no absolute contraindication to misoprostol or dinoprostone, there is a theoretical risk of coronary vasospasm and a low risk of arrhythmias. Dinoprostone also has more profound effects on BP than prostaglandin E_1 and is therefore contraindicated in active CVD. Mechanical methods such as a Foley catheter would be preferable to pharmacological agents, particularly in the patient with cyanosis where a drop in systemic vascular resistance and/or BP would be detrimental.[47]

Vaginal or caesarean delivery

The preferred mode of delivery is vaginal, with an individualized delivery plan which informs the team of timing of delivery (spontaneous/induced), method of induction, analgesia/regional anaesthesia, and level of monitoring required. In high risk lesions, delivery should take place in a tertiary centre with specialist multidisciplinary team care. Vaginal delivery is associated with less blood loss and infection risk compared with caesarean delivery, which also increases the risk of venous thrombosis and thrombo-embolism.[48] In general, caesarean delivery is reserved for obstetric indications. There is no consensus regarding absolute contraindications to vaginal delivery as this is very much dependent on maternal status at the time of delivery and the anticipated cardiopulmonary tolerance of the patient. Caesarean delivery should be considered for the patient on oral anticoagulants (OACs) in pre-term labour, patients with Marfan syndrome and an aortic diameter >45 mm, patients with acute or chronic aortic dissection, and those in acute intractable heart failure. Cesarean delivery may be considered in Marfan patients with an aortic diameter 40–45 mm.[7,49,50] (see also Section 4.3).

In some centres, caesarean delivery is advocated for women with severe aortic stenosis (AS) and in patients with severe forms of pulmonary hypertension (including Eisenmenger syndrome), or acute heart failure.[7,46] (see specific sections). Caesarean delivery may be considered in patients with mechanical heart valve prostheses to prevent problems with planned vaginal delivery. In such patients, a prolonged switch to heparin/low molecular weight heparin (LMWH) may indeed be required for a long time before vaginal birth, particularly, when the obstetrical situation is unfavourable. This would increase the maternal risk (see also Sections 5.5 and 5.6).

Haemodynamic monitoring

Systemic arterial pressure and maternal heart rate are monitored, because lumbar epidural anaesthesia may cause hypotension. Pulse oximetry and continuous ECG monitoring are utilized as required. A Swan–Ganz catheter for haemodynamic monitoring is rarely if ever indicated due to the risk of arrhythmia provocation, bleeding, and thrombo-embolic complications on removal.[51]

Anaesthesia/analgesia

Lumbar epidural analgesia is often recommendable because it reduces pain-related elevations of sympathetic activity, reduces the urge to push, and provides anaesthesia for surgery. Continuous lumbar epidural analgesia with local anaesthetics or opiates, or continuous opioid spinal anaesthesia can be safely administered. Regional anaesthesia can, however, cause systemic hypotension and must be used with caution in patients with obstructive valve lesions. Intravenous (i.v.) perfusion must be monitored carefully.[52]

Labour

Once in labour, the woman should be placed in a lateral decubitus position to attenuate the haemodynamic impact of uterine contractions.[53] The uterine contractions should descend the fetal head to the perineum, without maternal pushing, to avoid the unwanted effects of the Valsalva manoeuvre.[54,55]

Delivery may be assisted by low forceps or vacuum extraction. Routine antibiotic prophylaxis is not recommended. Continuous electronic fetal heart rate monitoring is recommended.

Delivery in anticoagulated women with prosthetic valves

OACs should be switched to LMWH or unfractionated heparin (UFH) from the 36th week. Women treated with LMWH should be switched to i.v. UFH, at least 36 h before the induction of labour or caesarean delivery. UFH should be discontinued 4–6 h before planned delivery, and restarted 4–6 h after delivery if there are no bleeding complications (see also Section 5.5). Urgent delivery in a patient with a mechanical valve taking therapeutic anticoagulation may be necessary, and there is a high risk of severe maternal haemorrhage. If emergent delivery is necessary while the patient is still on UFH or LMWH, protamine should be considered. Protamine will only partially reverse the anticoagulant effect of LMWH. In the event of urgent delivery in a patient on therapeutic OACs, caesarean delivery is preferred to reduce the risk of intracranial haemorrhage in the fully anticoagulated fetus. If emergent delivery is necessary, fresh frozen plasma should be given prior to caesarean delivery to achieve a target international normalized ratio (INR) of ≤ 2.[4] Oral vitamin K (0.5–1 mg) may also be given, but it takes 4–6 h to influence the INR. If the mother was on OACs at the time of delivery, the anticoagulated newborn may be given fresh frozen plasma and should receive vitamin K. The fetus may remain anticoagulated for 8–10 days after discontinuation of maternal OACs.

Ventricular arrhythmias during pregnancy and labour

Arrhythmias are the most common cardiac complication during pregnancy in women with and without structural heart disease.[12,56,57] They may manifest for the first time during pregnancy, or pregnancy may exacerbate pre-existing arrhythmias.[58–60] The 2006 ACC/AHA/ESC guidelines for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death recommend that pregnant women with prolonged QT syndrome who have had symptoms benefit from continued β-blocker therapy throughout pregnancy, during delivery, and post-partum unless there are definite contraindications. Use of β-blockers during labour does not prevent uterine contractions and vaginal delivery.[61]

Post-partum care

A slow i.v. infusion of oxytocin (<2 U/min), which avoids systemic hypotension, is administered after placental delivery to prevent maternal haemorrhage. Prostaglandin F analogues are useful to treat post-partum haemorrhage, unless an increase in pulmonary artery pressure (PAP) is undesirable. Methylergonovine is contraindicated because of the risk ($>10\%$) of vasoconstriction and hypertension.[62,63] Meticulous leg care, elastic support stockings, and early ambulation are important to reduce the risk of thrombo-embolism. Delivery is associated with important haemodynamic changes and fluid shifts, particularly in the first 12–24 h, which may precipitate heart failure in women with structural heart disease. Haemodynamic monitoring should therefore be continued for at least 24 h after delivery.[64]

Breastfeeding

Lactation is associated with a low risk of bacteraemia secondary to mastitis. In highly symptomatic/unwell patients, bottle-feeding should be considered.

2.10 Infective endocarditis

Infective endocarditis during pregnancy is rare, with an estimated overall incidence of 0.006% (1 per 100 000 pregnancies)[65] and an incidence of 0.5% in patients with known valvular or congenital heart disease.[66] The incidence is higher in drug addicts. Patients with the highest risk for infective endocarditis are those with a prosthetic valve or prosthetic material used for cardiac valve repair, a history of previous infective endocarditis, and some special patients with congenital heart disease.

2.10.1 Prophylaxis

The same measures as in non-pregnant patients with recent modifications of guidelines apply.[67] Endocarditis prophylaxis is now only recommended for patients at highest risk of aquiring endocarditis during high risk procedures, e.g. dental procedures. During delivery the indication for prophylaxis has been controversial and, given the lack of convincing evidence that infective endocarditis is related to either vaginal or caesarean delivery, antibiotic prophylaxis is not recommended during vaginal or caesarean delivery.[67,68]

2.10.2 Diagnosis and risk assessment

The diagnosis of infective endocarditis during pregnancy involves the same criteria as in the non-pregnant patient.[67] In spite of progress in the diagnosis and treatment of infective endocarditis, maternal morbidity and mortality remain high, reportedly 33% in one study (mainly due to heart failure and thrombo-embolic complications).[69] Fetal mortality is also high at 29%. Heart failure due to acute valve regurgitation is the most common complication, requiring urgent surgery when medical treatment cannot stabilize the patient.[67] Cerebral and peripheral embolizations are also frequent complications.

2.10.3 Treatment

Infective endocarditis should be treated the same way as in the non-pregnant patient, bearing in mind the fetotoxic effects of antibiotics (see Section 11). If infective endocarditis is diagnosed, antibiotics should be given guided by culture and antibiotic sensitivity results and local treatment protocols. Antibiotics that can be given during all trimesters of pregnancy are penicillin, ampicillin, amoxicillin, erythromycin, mezlocillin, and cephalosporins.[70] All of them are included in group B of the Food and Drug Administration (FDA) classification. Vancomycin, imipenem, rifampicin, and teicoplanin are all group C, which means risk cannot be excluded and their risk–benefit ratio must be carefully considered. There is a definite risk to the fetus in all trimesters of pregnancy with group D drugs (aminoglycosides, quinolones, and tetracyclines) and they should therefore only be used for vital indications.[71] Valve surgery during pregnancy should be reserved for cases where medical therapy has failed as per guidelines in non-pregnant patients.[67] A viable fetus should be delivered prior to surgery where possible (see Section 2.8.2).

2.11 Risk estimation: contraindications for pregnancy

2.11.1 Pre-pregnancy counselling

The risk of pregnancy depends on the specific heart disease and clinical status of the patient. Individual counselling by experts is recommended. Adolescents should be given advice on contraception, and pregnancy issues should be discussed as soon as they become sexually active. A risk assessment should be performed prior to pregnancy and drugs reviewed so that those which are contraindicated in pregnancy can be stopped or changed to alternatives where possible (see Section 11.2, *Table 21*). The follow-up plan should be discussed with the patient and, if possible, her partner. Women with significant heart disease should be managed jointly by an obstetrician and a cardiologist with experience in treating pregnant patients with heart disease from an early stage. High risk patients should be managed by an expert multidisciplinary team in a specialist centre. All women with heart disease should be assessed at least once before pregnancy and during pregnancy, and hospital delivery should be advised.

2.11.2 Risk assessment: estimation of maternal and offspring risk

To estimate the risk of maternal cardiovascular complications, several approaches are available. Disease-specific risk can be assessed, and is described in these guidelines in the respective sections dealing with specific diseases. In general, the risk of complications increases with increasing disease complexity.[56,72]

Disease-specific series are usually retrospective and too small to identify predictors of poor outcome. Therefore, risk estimation can be further refined by taking into account predictors that have been identified in studies that included larger populations with various diseases. Several risk scores have been developed based on these predictors, of which the CARPREG risk score is most widely known and used. This risk score has been validated in several studies and

Table 4 Predictors of maternal cardiovascular events and risk score from the CARPREG study[12]

Prior cardiac event (heart failure, transient ischaemic attack, stroke before pregnancy or arrhythmia).
Baseline NYHA functional class >II or cyanosis.
Left heart obstruction (mitral valve area <2 cm^2, aortic valve area <1.5 cm^2, peak LV outflow tract gradient >30 mmHg by echocardiography).
Reduced systemic ventricular systolic function (ejection fraction <40%).

CARPREG risk score: for each CARPREG predictor that is present a point is assigned. Risk estimation of cardiovascular maternal complications
0 point 5%
1 point 27%
>1 point 75%
LV = left ventricular; NYHA = New York Heart Association.

Table 5 Predictors of maternal cardiovascular events identified in congential heart diseases in the ZAHARA and Khairy study

ZAHARA predictors[57]
History of arrhythmia event.
Baseline NYHA functional class >II.
Left heart obstruction (aortic valve peak gradient >50 mm Hg).
Mechanical valve prosthesis.
Moderate/severe systemic atrioventricular valve regurgitation (possibly related to ventricular dysfunction).
Moderate/severe sub-pulmonary atrioventricular valve regurgitation (possibly related to ventricular dysfunction).
Use of cardiac medication pre-pregnancy.
Repaired or unrepaired cyanotic heart disease.
Predictors from Khairy[76]
Smoking history.
Reduced subpulmonary ventricular function and/or severe pulmonary regurgitation.

NYHA = New York Heart Association.

Table 6 Modified WHO classification of maternal cardiovascular risk: principles

Risk class	Risk of pregnancy by medical condition
I	No detectable increased risk of maternal mortality and no/mild increase in morbidity.
II	Small increased risk of maternal mortality or moderate increase in morbidity.
III	Significantly increased risk of maternal mortality or severe morbidity. Expert counselling required. If pregnancy is decided upon, intensive specialist cardiac and obstetric monitoring needed throughout pregnancy, childbirth, and the puerperium.
IV	Extremely high risk of maternal mortality or severe morbidity; pregnancy contraindicated. If pregnancy occurs termination should be discussed. If pregnancy continues, care as for class III.

Modified from Thorne *et al.*[72]
WHO = World Health Organization

Table 7 Modified WHO classification of maternal cardiovascular risk: application

Conditions in which pregnancy risk is WHO I
• 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
Conditions in which pregnancy risk is WHO II or III
WHO II *(if otherwise well and uncomplicated)*
• Unoperated atrial or ventricular septal defect
• Repaired tetralogy of Fallot
• Most arrhythmias
WHO II–III *(depending on individual)*
• Mild left ventricular impairment
• Hypertrophic cardiomyopathy
• Native or tissue valvular heart disease not considered WHO I or IV
• Marfan syndrome without aortic dilatation • Aorta <45 mm in aortic disease associated with bicuspid aortic valve
• Repaired coarctation
WHO III
• Mechanical valve
• Systemic right ventricle
• Fontan circulation
• Cyanotic heart disease (unrepaired)
• Other complex congenital heart disease
• Aortic dilatation 40–45 mm in Marfan syndrome • Aortic dilatation 45–50 mm in aortic disease associated with bicuspid aortic valve
Conditions in which pregnancy risk is WHO IV (pregnancy contraindicated)
• Pulmonary arterial hypertension of any cause
• Severe systemic ventricular dysfunction (LVEF <30%, NYHA III–IV)
• Previous peripartum cardiomyopathy with any residual impairment of left ventricular function
• Severe mitral stenosis, severe symptomatic aortic stenosis
• Marfan syndrome with aorta dilated >45 mm • Aortic dilatation >50 mm in aortic disease associated with bicuspid aortic valve
• Native severe coarctation

Adapted from Thorne *et al.*[73]
LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; WHO = World Health Organization.

appears valuable to predict maternal risk, although overestimation can occur.[57,73] The CARPREG risk score is described in *Table 4*. In women with congenital heart disease, the CARPREG score[12] may also be associated with a higher risk of late cardiovascular events post-pregnancy.[74] The predictors from the ZAHARA study[57] (*Table 5*) have not yet been validated in other studies. It should be noted that predictors and risk scores from the CARPREG and ZAHARA studies are highly population dependent. Important risk factors including pulmonary arterial hypertension (PAH) and dilated aorta were not identified because they were under-represented in these studies. The CARPREG study included acquired and congenital heart disease, while the ZAHARA study investigated a population with congenital heart disease only.

The Task Force recommends that maternal risk assessment is carried out according to the modified World Health Organization (WHO) risk classification.[72] This risk classification integrates all known maternal cardiovascular risk factors including the underlying heart disease and any other co-morbidity. It includes contraindications for pregnancy that are not incorporated in the CARPREG and ZAHARA risk scores/predictors. The general principles of this classification are depicted in *Table 6*. A practical application is given in *Table 7*. In women in WHO class I, risk is very low, and cardiology follow-up during pregnancy may be limited to one or two visits. Those in WHO II are at low or moderate risk, and follow-up every trimester is recommended. For women in WHO class III, there is a high risk of complications, and frequent (monthly or bimonthly) cardiology and obstetric review during pregnancy is recommended. Women in WHO class IV should be advised against pregnancy but, if they become pregnant and will not consider termination, monthly or bimonthly review is needed.

Neonatal complications occur in 20–28% of patients with heart disease[12,56,57,75,76] with a neonatal mortality between 1% and 4%.[12,56,57] Maternal and neonatal events are highly correlated.[57] Predictors of neonatal complications are listed in *Table 8*.

Table 8 Maternal predictors of neonatal events in women with heart disease

1. Baseline NYHA class >II or cyanosis[12]
2. Maternal left heart obstruction[12,76]
3. Smoking during pregnancy[12,57]
4. Multiple gestation[12,57]
5. Use of oral anticoagulants during pregnancy[12]
6. Mechanical valve prosthesis[57]

Modified from Siu *et al.*[12] (CARPREG investigators); Khairy *et al.*[76]; Drenthen/Pieper *et al.*[57] (ZAHARA investigators).
NYHA = New York Heart Association.

2.12 Methods of contraception and termination of pregnancy, and *in vitro* fertilization

2.12.1 Methods of contraception

Contraceptive methods include combined hormonal contraceptives (oestrogen/progestin), progestogen-only methods, intrauterine devices, and emergency contraception. Their use needs to be balanced against the risk of pregnancy.

In 2010, the Centers for Disease Control (CDC) modified the WHO suggestions for medical eligibility criteria for contraceptive use in women with CVD. [http://www.cdc.gov/Mmwr/preview/mmwrhtml/rr59e0528a13.htm]. Monthly injectables that contain medroxyprogesterone acetate are inappropriate for patients with heart failure because of the tendency for fluid retention. Low dose oral contraceptives containing 20 μg of ethinyl estradiol are safe in women with a low thrombogenic potential, but not in women with complex valvular disease.[77,78]

Apart from barrier methods (condom), the levonorgestrel-releasing intrauterine device is the safest and most effective contraceptive that can be used in women with cyanotic congenital heart disease and pulmonary vascular disease. It reduces menstrual blood loss by 40–50% and induces amenorrhoea in a significant proportion of users.[79] It should be borne in mind that ~5% of patients experience vasovagal reactions at the time of implant; therefore, for those with highly complex heart disease (e.g. Fontan, Eisenmenger) intrauterine implants are indicated only when progesterone-only pills or dermal implants have proved unacceptable and, if used, they should only be implanted in a hospital environment. A copper intrauterine device is acceptable in non-cyanotic or mildly cyanotic women. Antibiotic prophylaxis is not recommended at the time of insertion or removal since the risk of pelvic infection is not increased. If excessive bleeding occurs at the time of menses, the device should be removed. It is contraindicated in cyanotic women with haematocrit levels >55% because intrinsic haemostatic defects increase the risk of excessive menstrual bleeding.

2.12.2 Sterilization

Tubal ligation is usually accomplished safely, even in relatively high risk women. Because of the associated anaesthesia and abdominal inflation, it is, however, not without risk in patients with PAH, cyanosis, and Fontan circulation. The risk may be lower with the minimally invasive hysteroscopic techniques such as the Essure device. Hysteroscopic sterilization is performed by inserting a metal micro-insert or polymer matrix into the interstitial portion of each fallopian tube. Three months after placement, correct device placement and bilateral tubal occlusion are confirmed with pelvic imaging. Advantages of hysteroscopic sterilization include the ability to perform the procedure in an outpatient setting and without an incision. A disadvantage is the 3 month waiting period until tubal occlusion is confirmed.[80] Vasectomy for the male partner is another efficacious option, but the long-term prognosis of the female partner must be taken into account as the male partner may outlive her for many years. Given the lack of published data about contraception in heart disease, advice should be provided by physicians or gynaecologists with appropriate training.

2.12.3 Methods of termination of pregnancy

Pregnancy termination should be discussed with women in whom gestation represents a major maternal or fetal risk. The first trimester is the safest time for elective pregnancy termination, which should be performed in hospital, rather than in an outpatient facility, so that all emergency support services are available. The method, including the need for anaesthesia, should be considered on an individual basis. High risk patients should be managed in an experienced centre with on-site cardiac surgery. Endocarditis prophylaxis is not consistently recommended by cardiologists,[81] but treatment should be individualized. Gynaecologists routinely advise antibiotic prophylaxis to prevent post-abortal endometritis, which occurs in 5–20% of women not given antibiotics.[82,83]

Dilatation and evacuation is the safest procedure in both the first and second trimesters. If surgical evacuation is not feasible in the second trimester, prostaglandins E_1 or E_2, or misoprostol, a synthetic prostaglandin structurally related to prostaglandin E_1, can be administered to evacuate the uterus.[84] These drugs are absorbed into the systemic circulation and can lower systemic vascular resistance and BP, and increase heart rate, effects that are greater with E_2 than with E_1.[85]

Up to 7 weeks gestation, mifepristone is an alternative to surgery. When prostaglandin E compounds are given, systemic arterial oxygen saturation should be monitored with a transcutaneous pulse oximeter and norepinephrine infused at a rate that supports the DBP, which reflects systemic vascular resistance. Prostaglandin F compounds should be avoided because they can significantly increase PAP and may decrease coronary perfusion.[85]

Saline abortion should be avoided because saline absorption can cause expansion of the intravascular volume, heart failure, and clotting abnormalities.

2.12.4 *In vitro* fertilization

In vitro fertilization may be considered where the risk of the procedure itself, including hormonal stimulation and pregnancy, is low. Thrombo-embolism may complicate *in vitro* fertilization when high oestradiol levels may precipitate a prothrombotic state.[86]

2.13 General recommendations

Table 9 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.	I	C
Risk assessment should be performed in all women with cardiac diseases of childbearing age and after conception.	I	C
High risk patients should be treated in specialized centres by a multidisciplinary team.	I	C
Genetic counselling should be offered to women with congenital heart disease or congenital arrhythmia, cardiomyopathies, aortic disease or genetic malformations associated with CVD.	I	C
Echocardiography should be performed in any pregnant patient with unexplained or new cardiovascular signs or symptoms.	I	C
Before cardiac surgery a full course of corticosteroids should be administered to the mother whenever possible.	I	C
For the prevention of infective endocarditis in pregnancy the same measures as in non-pregnant patients should be used.	I	C
Vaginal delivery is recommended as first choice in most patients.	I	C
MRI (without gadolinium) should be considered if echocardiography is insufficient for diagnosis.	IIa	C
In patients with severe hypertension, vaginal delivery with epidural analgesia and elective instrumental delivery should be considered.	IIa	C
When gestational age is at least 28 weeks, delivery before necessary surgery should be considered.	IIa	C
Caesarean delivery should be considered for obstetric indications or for patients with dilatation of the ascending aorta >45 mm, severe aortic stenosis, pre-term labour while on oral anticoagulants, Eisenmenger syndrome, or severe heart failure.	IIa	C
Caesarean delivery may be considered in Marfan patients with an aortic diameter 40–45mm.	IIb	C
A chest radiograph, with shielding of the fetus, 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, timing, and shielding of the fetus.	IIb	C
CT and electrophysiological studies, with shielding of the fetus, may be considered in selected patients for vital indications.	IIb	C
Coronary bypass surgery or valvular surgery may be considered when conservative and medical therapy has failed, in situations that threaten the mother's life and that are not amenable to percutaneous treatment.	IIb	C
Prophylactic antibiotic therapy during delivery is not recommended.	III	C

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

3. Congenital heart disease and pulmonary hypertension

In many women with congenital heart disease, pregnancy is well tolerated. The risk of pregnancy depends on the underlying heart disease as well as on additional factors such as ventricular and valvular function, functional class, and cyanosis. The miscarriage rate is higher in more complex disease (*Figure 1*).[56] Maternal cardiac complications are present in 12% of completed pregnancies and are again more frequent as the disease becomes more complex. Patients who experience complications during pregnancy may also be at higher risk of late cardiac events after pregnancy.[74] Offspring complications, including offspring mortality (4%), are more frequent than in the general population.

Diagnosis

Usually, congenital heart diseases will be known and diagnosed before pregnancy. Pre-pregnancy assessment including medical history, echocardiography, and exercise testing is indicated in all patients, with other diagnostic tests indicated on an individual patient basis. Functional status before pregnancy and history of previous cardiac events are of particular prognostic value (see *Tables 4* and *5*). Also B-type natriuretic peptide (BNP)/N-terminal pro B-type natriuretic peptide (NT-pro-BNP) assessment may be helpful in risk stratification. An exercise test before pregnancy achieving <70% of expected workload, showing a drop in arterial pressure or a drop in oxygen saturation may identify women at risk of developing symptoms or complications during pregnancy. Diagnostic procedures that can be used during pregnancy are outlined in Section 2.6.[21] For further risk assessment see Section 2.11.

3.1 Maternal high risk conditions [World Health Organization (III)–IV; see also Section 2.11]

Patients in NYHA class III/IV or with severely reduced function of the systemic ventricle are at high risk during pregnancy, along with other specific conditions discussed below. In addition, some specific conditions are at particular high risk during pregnancy.

3.1.1 Pulmonary hypertension

Maternal risk

Pulmonary hypertension encompasses a group of diseases with different pathophysiologies which include PAH, pulmonary hypertension related to left heart disease, pulmonary hypertension related to lung disease and/or hypoxia, chronic thrombo-embolic pulmonary hypertension, and pulmonary hypertension with unclear and or multifactorial mechanisms. PAH includes the idiopathic and heritable forms of the disease as well as pulmonary hypertension associated with congenital heart disease, with or without previous corrective surgery. A mean PAP ≥25 mmHg at rest is indicative of pulmonary hypertension.[87] A high maternal mortality risk is reported (30–50% in older series and 17–33%

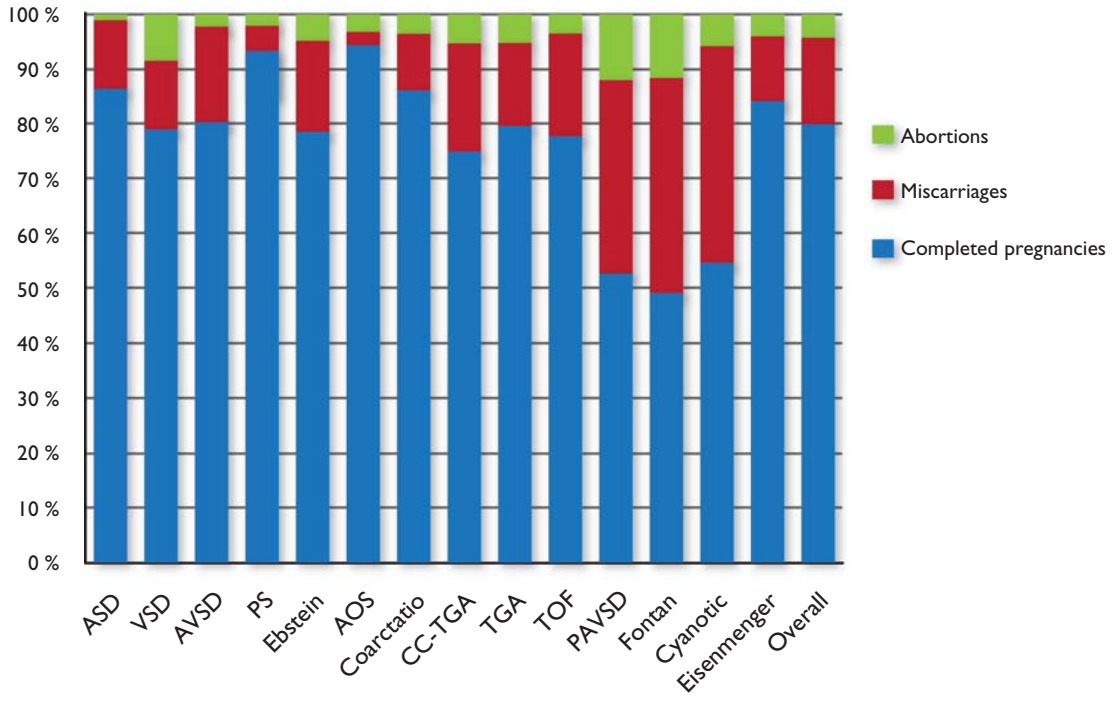

Figure 1 Distribution of miscarriages, completed pregnancies (>20 weeks pregnancy duration), and elective abortions for each congenital heart disease separately and the overall rates. ASD = atrial septal defect; AVSD = atrioventricular septal defect; AOS = aortic stenosis; CC-TGA = congenital corrected transposition of the great arteries; CHD = congenital heart disease; Coarctation = aortic coarctation; Ebstein = Ebstein's anomaly; Eisenmenger = Eisenmenger syndrome; Fontan = patients after Fontan repair; PAVSD = pulmonary atresia with ventricular septal defects; PS = pulmonary valve stenosis; TGA = complete transposition of the great arteries; TOF = tetralogy of Fallot; VSD = ventricular septal defect.

in more recent papers) in patients with severe PAH and Eisenmenger syndrome.[87,88] Maternal death occurs in the last trimester of pregnancy and in the first months after delivery because of pulmonary hypertensive crises, pulmonary thrombosis, or refractory right heart failure. This occurs even in patients with little or no disability before or during pregnancy. Risk factors for maternal death are: late hospitalization, severity of pulmonary hypertension, and general anaesthesia.[87] The risk probably increases with more elevated pulmonary pressures. However, even moderate forms of pulmonary vascular disease can worsen during pregnancy as a result of the decrease in systemic vascular resistance and overload of the right ventricle, and no safe cut-off value is known. Whether the risk is also high for congenital patients after successful shunt closure with mildly elevated pulmonary pressures [e.g. after atrial septal defect (ASD) closure with a mean pressure of 30 mmHg] is not well known, but these risks are probably lower and pregnancy can be considered after a careful risk assessment on the basis of all available diagnostic modalities in a specialized centre.[89]

Obstetric and offspring risk

Neonatal survival rates are reported to be 87–89%.[87]

Management

Follow-up. If pregnancy occurs, termination should be offered. In view of the risks of anaesthesia this should be performed in a tertiary centre experienced in the management of PAH patients. If patients choose to continue pregnancy despite the risk, they should be managed in a centre with expertise in PAH with all therapeutic options available.[68] Every effort should be made to maintain circulating volume, and to avoid systemic hypotension, hypoxia, and acidosis which may precipitate refractory heart failure. Supplemental oxygen therapy should be given if there is hypoxaemia. I.v. prostacyclin or aerosolized iloprost have been occasionally used antenatally and peripartum to improve haemodynamics during delivery.[90] In patients who are already taking drug therapy for PAH before becoming pregnant, continuation of this therapy should be considered, but patients should be informed about the teratogenic effects of some therapies, such as bosentan. Haemodynamic monitoring by Swan–Ganz catheter may be associated with serious complications such as pulmonary artery rupture, while its utility has not been demonstrated; therefore, it is rarely if ever indicated.

Medical therapy. In patients where the indication for anticoagulation outside pregnancy is established, anticoagulation should also be maintained during pregnancy.[89] In PAH associated with congenital cardiac shunts in the absence of significant haemoptysis, anticoagulant treatment should be considered in patients with pulmonary artery thrombosis or signs of heart failure. In PAH associated with connective tissue disorders, anticoagulant treatment should be considered on an individual basis. In PAH associated with portal hypertension, anticoagulation is not recommended in patients with increased risk of bleeding.

The type of anticoagulation during pregnancy (UFH vs. LMWH) needs to be decided on an individual basis. Randomized studies comparing the effectiveness of different heparins are not available; neither are studies available concerning the risks associated with replacement of OACs during the pregnancy by either UFH or LMWH. A risk assessment concerning the type of anticoagulation chosen should be performed. Because of the increased risk of bleeding in these patients, subcutaneous application of LMWH or UFH is favoured over oral anticoagulation during pregnancy. It should be recognized that potentially significant drug interactions with PAH-targeted therapies may occur, and careful monitoring of anticoagulation is necessary [INR monitoring with OACs; activated partial thromboplastin time (aPTT) monitoring in the case of UFH; anti-Xa levels in the case of LMWH].

Delivery. The mode of delivery should be individualized. Planned caesarean delivery and vaginal delivery are favoured over emergency caesarean delivery.

3.1.2 Patients with the 'Eisenmenger syndrome'

Maternal risk

Eisenmenger patients need special consideration because of the association of pulmonary hypertension with cyanosis due to the right-to-left shunt. Systemic vasodilatation increases the right-to-left shunt and decreases pulmonary flow, leading to increased cyanosis and eventually to a low output state. The literature reports a high maternal mortality of 20–50%, occurring most often in the peri- or post-partum period.[91]

Obstetric and offspring risk

Cyanosis poses a significant risk to the fetus, with a live birth unlikely (<12%) if oxygen saturation is <85%.

Management

Follow-up. When pregnancy occurs, the risks should be discussed and a termination of pregnancy offered; however, termination also carries a risk.[68] If the patient wishes to continue with pregnancy, care should be based in a specialist unit. Bed rest may be beneficial. Thrombo-embolism is a major risk for cyanotic patients, therefore patients should be considered for prophylaxis after haematology review and investigations for blood haemostasis. Anticoagulation must be used with caution, as patients with Eisenmenger syndrome are also prone to haemoptysis and thrombocytopenia. The risks and benefits of anticoagulation must therefore be carefully considered on an individual patient basis. In patients with heart failure, diuretics must be used judiciously and at the lowest effective dose to avoid haemoconcentration and intravascular volume depletion. Microcytosis and iron deficiency are frequent and should be treated with supplemental oral or i.v. iron, avoiding a rebound effect. Frequent clinical review with oxygen saturation measurement and full blood count are indicated.

Delivery. If the maternal or fetal condition deteriorates, an early caesarean delivery should be planned. In view of the risks of anaesthesia this should be performed in a tertiary centre experienced in the management of these patients. In others, timely hospital admission, planned elective delivery, and incremental regional anaesthesia may improve maternal outcome.[68]

3.1.3 Cyanotic heart disease without pulmonary hypertension

Maternal risk

Cyanotic congenital heart disease is usually corrected before pregnancy, but some inoperable or palliated cases do reach childbearing age. Maternal complications (heart failure, pulmonary or systemic thrombosis, supraventricular arrhythmias, infective endocarditis) occur in 30% of cyanotic pregnant patients. If resting oxygen saturation is <85%, a substantial maternal and fetal mortality risk is expected and pregnancy is contraindicated. If resting oxygen saturation is 85–90% it is advisable to measure it during exercise. If the saturation decreases significantly and early, patients should be advised that pregnancy has a poor prognosis.

Obstetric and offspring risk

The degree of maternal hypoxaemia is the most important predictor of fetal outcome. With resting maternal blood saturation >90%, fetal outcome is good (<10% fetal loss). If, however, maternal oxygen saturation is <85%, the chance of a live birth is ~12% and pregnancy should therefore be discouraged.[91]

Management

Follow-up. During pregnancy, restriction of physical activity and supplemental oxygen (monitoring oxygen saturation) are recommended. Because of the increased risk of paradoxical embolism, prevention of venous stasis (use of compression stockings and avoiding the supine position) is important. For prolonged bed rest, prophylactic heparin administration should be considered. Haematocrit and haemoglobin levels are not reliable indicators of hypoxaemia. Thrombo-embolism is a major risk for cyanotic patients, therefore patients should be considered for prophylaxis after haematology review and investigations for blood haemostasis.

Medical therapy. LMWH thromboprophylaxis should be considered if blood haemostasis is normal. Diuretics and iron therapy are indicated and managed in the same way as in patients with Eisenmenger syndrome.

Delivery. Vaginal delivery is advised in most cases. If the maternal or fetal condition deteriorates, an early caesarean delivery should be planned. In view of the risks of anaesthesia this should be performed in a tertiary centre experienced in the management of these patients. In others, timely hospital admission, planned elective delivery, and incremental regional anaesthesia may improve maternal outcome.[68]

3.1.4 Severe left ventricular outflow tract obstruction

Severe symptomatic left ventricular outflow tract obstruction (LVOTO) is a contraindication for pregnancy and should be treated before pregnancy, or women should be counselled against pregnancy. It may be valvular, supravalvular, or caused by discrete membranous or tunnel-type subvalvular AS. The management of supravalvular and subvalvular stenosis is only described in case reports during pregnancy and is probably similar to the management of patients with valvular stenosis, although balloon valvulotomy is not a therapeutic option.[92] The management of pregnancy in (severe) AS is described in the section on valvular heart disease (Section 5).

3.2 Maternal low and moderate risk conditions (World Health Organization I, II, and III; see also *Tables* 6 and 7)

In patients who have undergone previous successful surgical repair without mechanical heart valve implantation, pregnancy is often well tolerated if exercise tolerance is good, ventricular function is normal, and functional status is good. Although patients need to be informed about the (often small) additional risk, pregnancy should not be discouraged. Patients should be seen by the end of the first trimester and a follow-up plan with time intervals for review and investigations such as echocardiograms defined. The follow-up plan should be individualized taking into account the complexity of the heart disease and clinical status of the patient. Some congenital conditions may deteriorate during pregnancy, therefore follow-up timelines need to be flexible. Vaginal delivery can be planned in most cases.[3,93,94]

3.3 Specific congenital heart defects

3.3.1 Atrial septal defect

Maternal risk

Pregnancy is well tolerated by most women with an ASD. The only contraindication is the presence of PAH or Eisenmenger syndrome (see Sections 3.2.1 and 3.2.2).[95] Closure of a haemodynamically significant ASD should be performed before pregnancy. Thrombo-embolic complications have been described in up to 5%.[56] Arrhythmias occur more often than in healthy women, especially when the ASD is unrepaired or closed at older age and the pregnant woman is >30 years old.[95,96]

Obstetric and offspring risk

In women with unrepaired ASD, pre-eclampsia and small for gestational age births may occur more frequently. In repaired ASD, no extra risk is encountered.

Management

Usually follow-up twice during pregnancy is sufficient. For a secundum defect, catheter device closure can be performed during pregnancy, but is only indicated when the condition of the mother is deteriorating (with transoesophageal or intracardiac echocardiographic guidance). Closure of a small ASD or persistent foramen ovale for the prevention of paradoxical emboli is not indicated. Because of the increased risk of paradoxical embolism, in women with a residual shunt, prevention of venous stasis (use of compression stockings and avoiding the supine position) is important, as is early ambulation after delivery. For prolonged bed rest, prophylactic heparin administration should be considered.[97] Diligent care is important to eliminate air in i.v. lines which could lead to systemic embolization due to right-to-left shunting during labour.

Spontaneous vaginal delivery is in most cases appropriate.

3.3.2 Ventricular septal defect

Maternal risk

For large ventricular septal defects (VSDs) with pulmonary hypertension, see maternal high risk conditions (Section 3.1). Small perimembranous VSDs (without left heart dilatation) have a low risk of complications during pregnancy.[98] Corrected VSDs have a good prognosis during pregnancy, when LV function is preserved. Pre-pregnancy evaluation of the presence of a (residual) defect, cardiac dimensions, and an estimation of pulmonary pressures is recommended.

Obstetric and offspring risk

Pre-eclampsia may occur more often than in the normal population.[98]

Management

Usually follow-up twice during pregnancy is sufficient and spontaneous vaginal delivery is appropriate.

3.3.3 Atrioventricular septal defect

Maternal risk

After correction, pregnancy is usually well tolerated when residual valve regurgitation is not severe and ventricular function is normal (WHO risk class II). Patients with severe (residual) left atrioventricular (AV) valve regurgitation with symptoms and/or impaired ventricular function should be treated surgically pre-pregnancy, favouring valve repair.[7] For atrioventricular septal defect (AVSD) with pulmonary hypertension, see maternal high risk conditions (Section 3.1.1). Correction of a haemodynamically significant AVSD before pregnancy should be considered.[19] Arrhythmias and worsening of NYHA class as well as worsening of AV valve regurgitation have been described during pregnancy.[99] The risk of heart failure is low and only exists in women with severe regurgitation or impaired ventricular function.

Obstetric and offspring risk

Obstetric complications are mainly related to the risk of acute heart failure during or just after delivery and they depend on symptoms and PAP during pregnancy. Offspring mortality has been reported in 6%, primarily due to the occurrence of complex congenital heart disease.[99]

Management

Follow-up. Follow-up during pregnancy is advisable at least once each trimester. Clinical and echocardiographic follow-up is indicated monthly or bimonthly in patients with moderate or severe valve regurgitation or impaired ventricular function. In uncorrected AVSD, the risk of paradoxical embolization exists. For recommended preventive measures for thrombo-embolism, see Section 3.3.1.

Delivery. Spontaneous vaginal delivery is appropriate in most cases.

3.3.4 Coarctation of the aorta

Maternal risk

Pregnancy is often well tolerated in women after repair of coarctation of the aorta (CoA) (WHO risk class II). Significant (re)

coarctation should be corrected before pregnancy. Women with unrepaired native CoA and those repaired who have residual hypertension, residual CoA, or aortic aneurysms have an increased risk of aortic rupture and rupture of a cerebral aneurysm during pregnancy and delivery. Other risk factors for this complication include aortic dilatation and bicuspid aortic valve, and they should be looked for pre-pregnancy.

Obstetric and offspring risk

An excess of hypertensive disorders and miscarriages has been reported.[100,101]

Management

Close surveillance of BP is warranted, and regular follow-up at least every trimester is indicated. Hypertension should be treated, although aggressive treatment in women with residual coarctation must be avoided to prevent placental hypoperfusion. Percutaneous intervention for re-CoA is possible during pregnancy, but it is associated with a higher risk of aortic dissection than outside pregnancy and should only be performed if severe hypertension persists despite maximal medical therapy and there is maternal or fetal compromise. The use of covered stents may lower the risk of dissection.

Delivery. Spontaneous vaginal delivery is preferred with use of epidural anaesthesia particularly in hypertensive patients.

3.3.5 Pulmonary valve stenosis and regurgitation

Maternal risk

Pulmonary valve stenosis (PS) is generally well tolerated during pregnancy.[102–104] However, severe stenosis may result in complications including right ventricular (RV) failure and arrhythmias. Pre-pregnancy relief of stenosis (usually by balloon valvuloplasty) should be performed in severe stenosis (peak Doppler gradient $>$64 mmHg).[19,68,105]

Severe pulmonary regurgitation has been identified as an independent predictor of maternal complications, especially in patients with impaired ventricular function.[76,106] In symptomatic women or when RV function is abnormal due to severe pulmonary regurgitation, pre-pregnancy pulmonary valve replacement (preferably bioprosthesis) should be considered.

Obstetric and offspring risk

The incidence of maternal obstetric complications, particularly hypertension-related disorders including (pre-)eclampsia, may be increased in women with PS.[103] The incidence of offspring complications also appears to be higher than in the general population.[103] Pulmonary regurgitation generally carries no additional offspring risk.

Management

Follow-up. Mild and moderate PS are regarded low-risk lesions (WHO risk classes I and II) (*Tables 6* and *7*), and follow-up once every trimester is sufficient. In patients with severe PS, monthly or bimonthly cardiac evaluations including echocardiography are advised to determine clinical status and for surveillance of RV function. During pregnancy in severely symptomatic PS not responding to medical therapy and bed rest, percutaneous valvuloplasty can be undertaken.

Delivery. Vaginal delivery is favoured in patients with non-severe PS, or severe PS in NYHA class I/II. Caesarean section is considered in patients with severe PS and in NYHA class III/IV despite medical therapy and bed rest, in whom percutaneous pulmonary valvotomy cannot be performed or has failed.

3.3.6 Aortic stenosis

Congenital AS is most often caused by a bicuspid aortic valve. The rate of progression of stenosis in these young patients is lower than in older patients.[107] Because bicuspid aortic valve is associated with aortic dilatation and aortic dissection, aortic dimensions should be measured pre-pregnancy and during pregnancy. The risk of dissection is increased during pregnancy (see also Section 4.3).[108,109] All women with a bicuspid aortic valve should undergo imaging of the ascending aorta before pregnancy, and surgery should be considered when the aortic diameter is $>$50 mm. For recommendations on the management of pregnant women with AS, see Section 5 on valvular heart disease.

3.3.7 Tetralogy of Fallot

Maternal risk

In unrepaired patients, surgical repair is indicated before pregnancy. Women with repaired tetralogy of Fallot usually tolerate pregnancy well (WHO risk class II). Cardiac complications during pregnancy have been reported in up to 12% of patients. Arrhythmias and heart failure in particular may occur.[110] Other complications include thrombo-embolism, progressive aortic root dilatation, and endocarditis. Dysfunction of the right ventricle and/or moderate to severe pulmonary regurgitation are risk factors for cardiovascular complications, and pregnancy may be associated with a persisting increase in RV size. In symptomatic women with marked dilatation of the right ventricle due to severe pulmonary regurgitation, pre-pregnancy pulmonary valve replacement (homograft) should be considered.[19]

Obstetric and offspring risk

The risk of offspring complications is increased.

Management

Follow-up. Follow-up every trimester is sufficient in the majority of women. In women with severe pulmonary regurgitation, monthly or bimonthly cardiac evaluation with echocardiography is indicated. If RV failure occurs during pregnancy, treatment with diuretics should be started and bed rest advised. Transcatheter valve implantation or early delivery should be considered in those who do not respond to conservative treatment.

Delivery. The preferred mode of delivery is vaginal in almost all cases.

3.3.8 Ebstein's anomaly

Maternal risk

In women with Ebstein's anomaly without cyanosis and heart failure, pregnancy is often tolerated well (WHO risk classII). Symptomatic patients with cyanosis and/or heart failure should be treated before pregnancy or counselled against pregnancy. In severe symptomatic tricuspid regurgitation (TR), repair should be considered pre-pregnancy. The haemodynamic problems seen during pregnancy depend largely on the severity of the TR and

the functional capacity of the right ventricle.[111,112] An ASD and also the Wolff–Parkinson–White syndrome are common associated findings. The incidence of arrhythmias may rise during pregnancy and is associated with a worse prognosis.[111]

Obstetric and offspring risk
The risk of premature delivery and fetal mortality is elevated.[112]

Management
Follow-up. Even severe TR with heart failure can usually be managed medically during pregnancy. Women with Ebstein's anomaly and interatrial shunting can develop shunt reversal and cyanosis in pregnancy. There is also a risk of paradoxical emboli (see Section 3.4.2).

Delivery. The preferred mode of delivery is vaginal in almost all cases.

3.3.9 Transposition of the great arteries

Maternal risk
Though many women tolerate pregnancy relatively well, after an atrial switch operation (Senning or Mustard repair) patients have an increased risk of developing complications such as arrhythmias (sometimes life-threatening), and heart failure (WHO risk class III).[93] Some of these women will have underlying bradycardia or junctional rhythm. In these scenarios, β-blockers need to be used cautiously, if at all. An irreversible decline in RV function has been described in 10% of cases. Patients with more than moderate impairment of RV function or severe TR should be advised against pregnancy.

Obstetric and offspring risk
Pre-eclampsia and pregnancy-induced hypertension as well as offspring complications are more often encountered than in normal pregnancy.

Management
Follow-up. It is recommended that patients with a Mustard or Senning repair have monthly or bimonthly cardiac and echocardiographic surveillance of symptoms, systemic RV function, and heart rhythm.

Delivery. In asymptomatic patients with moderate or good ventricular function, vaginal delivery is advised. If ventricular function deteriorates, an early caesarean delivery should be planned to avoid the development or worsening of heart failure.[113]

Arterial switch operation
Only small series of patients with an arterial switch operation and pregnancy have been described so far.[114] The risk of pregnancy seems low in these patients when there is a good clinical condition pre-pregnancy. Vaginal delivery is advised.

3.3.10 Congenitally corrected transposition of the great arteries

Maternal risk
In patients with congenitally corrected transposition of the great arteries (also called atrioventricular and ventriculo-arterial discordance), risk depends on functional status, ventricular function, presence of arrhythmias, and associated lesions. Patients have an increased risk of developing complications such as arrhythmias (sometimes life-threatening), and heart failure (WHO risk class III). These patients are pre-disposed to developing AV block; therefore, β-blockers must be used with extreme caution. An irreversible decline in RV function has been described in 10% of cases.[115,116] Patients with NYHA functional class III or IV, important ventricular dysfunction [ejection fraction (EF) <40%], or severe TR should be counselled against pregnancy.

Obstetric and offspring risk
The rate of fetal loss is increased.

Management
Follow-up. It is recommended that patients have frequent echo surveillance of systemic RV function (every 4–8 weeks) and assessment of symptoms and heart rhythm.

Delivery. In asymptomatic patients with moderate or good ventricular function, vaginal delivery is advised. If ventricular function deteriorates, an early caesarean delivery should be planned to avoid the development or worsening of heart failure.

3.3.11 Fontan circulation

Maternal risk
Although successful pregnancy is possible in selected patients with intensive monitoring, these are moderate to high risk pregnancies and patients should be counselled carefully (WHO risk class III or IV). There is probably a higher maternal risk if the Fontan circuit is not optimal, and careful assessment pre-pregnancy is indicated. Atrial arrhythmias and NYHA class deterioration have been described.[117,118] Patients with oxygen saturation <85% at rest, depressed ventricular function, and/or moderate to severe AV regurgitation or with protein-losing enteropathy should be counselled against pregnancy.

Obstetric and offspring risk
The offspring risk includes premature birth, small for gestational age, and fetal death in up to 50%.

Management
Follow-up. It is recommended that Fontan patients have frequent surveillance during pregnancy and the first weeks after delivery (every 4 weeks), and care in a specialist unit is recommended. Angiotensin-converting enzyme (ACE) inhibitors must be withdrawn, and anticoagulant management is an issue. Even though thrombo-embolic complications were not described in a literature review on pregnancy in Fontan patients, the risk must be considered high and therapeutic anticoagulation should be considered.[119] The thrombo-embolic risk may be lower in patients treated with a total cavopulmonary Fontan correction.

Delivery. In principal, vaginal delivery is first choice. If ventricular function deteriorates, an early caesarean delivery should be planned in an experienced centre to avoid the development or worsening of heart failure.

3.4 Recommendations for the management of congenital heart disease

Table 10 Recommendations for the management of congenital heart disease

Recommendations	Class[a]	Level[b]
Pre-pregnancy relief of stenosis (usually by balloon valvulotomy) should be performed in severe pulmonary valve stenosis (peak Doppler gradient >64 mmHg).	I	B[68,105]
Individual follow-up schedules should be arranged; ranging from twice during pregnancy to monthly.	I	C
Symptomatic patients with Ebstein's anomaly with cyanosis and/or heart failure should be treated before pregnancy or advised against pregnancy.	I	C
In symptomatic women with marked dilatation of the right ventricle due to severe pulmonary regurgitation, pre-pregnancy pulmonary valve replacement (bioprosthesis) should be performed.	I	C
In asymptomatic women with a severely dilated right ventricle due to severe pulmonary regurgitation, pre-pregnancy pulmonary valve replacement (bioprosthesis) should be considered.	IIa	C
All women with a bicuspid aortic valve should undergo imaging of the ascending aorta before pregnancy, and surgery should be considered when the aortic diameter is >50 mm.	IIa	C
Anticoagulation treatment should be considered during pregnancy in Fontan patients.	IIa	C
In PAH, associated anticoagulant treatment should be considered in patients with suspicion of pulmonary embolism as the cause (or partly the cause) of the pulmonary hypertension.	IIa	C
In patients who are already taking drug therapy for PAH before becoming pregnant, continuation should be considered after information about the teratogenic effects.	IIa	C
Women with pulmonary hypertension should be advised against pregnancy.[c]	III	C
Women with an oxygen saturation below 85% at rest should be advised against pregnancy.	III	C
Patients with TGA and a systemic right ventricle with more than moderate impairment of RV function and/or severe TR should be advised against pregnancy.	III	C
Fontan patients with depressed ventricular function and/or moderate to severe atrioventricular valvular regurgitation or with cyanosis or with protein-losing enteropathy should be advised against pregnancy.	III	C

[a]Class of recommendation.
[b]Level of evidence.
[c]See the text for detailed description and exceptions.
PAH = pulmonary arterial hypertension; RV = right ventricular; TGA = complete transposition of the great arteries; TR = tricuspid regurgitation.

4. Aortic diseases

Several heritable disorders affect the thoracic aorta, pre-disposing patients to both aneurysm formation and aortic dissection. These include the Marfan syndrome, bicuspid aortic valve, Ehlers–Danlos syndrome, Turner syndrome, and familial forms of aortic dissection, aneurysm, or annuloaortic ectasia. Also other forms of congenital heart disease (e.g. tetralogy of Fallot, aortic coarctation) may be accompanied by aortic dilatation or aneurysm formation, and finally non-heritable aortic pathology may occur. Risk factors for aortic pathology in the general population are hypertension and advanced maternal age. Pregnancy is a high risk period for all patients with aortic pathology, and aortic pathology is reported as one of the leading causes of maternal mortality in the 2003–2005 report of the UK Confidential Enquiry into Maternal And Child Health.[9] Recently, guidelines for the diagnosis and management of patients with thoracic aortic disease have been published.[50]

Diagnosis. A number of imaging procedures and genetic tests are available, and are discussed in Sections 2.5 and 2.6.

4.1 Maternal and offspring risk

In addition to haemodynamic changes, hormonal changes occur during pregnancy which lead to histological changes in the aorta, increasing the susceptibility to dissection.[120] Dissection occurs most often in the last trimester of pregnancy (50%) or the early postpartum period (33%). In all women with known aortic disease and/or an enlarged aortic root diameter, the risks of pregnancy should be discussed before conception. Women with previous aortic dissection are at high risk of aortic complications during pregnancy. Unfortunately, not all patients with aortic pathology are aware that they are at risk. Therefore, all women with genetically proven Marfan syndrome or other 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 2.7). No irreversible effect of pregnancy on aortic dilatation has been proven.[121] The diagnosis of aortic dissection should be considered in all patients with chest pain during pregnancy as this diagnosis is often missed.

4.2 Specific syndromes

4.2.1 Marfan syndrome

Patients with Marfan syndrome[122,123] and a normal aortic root diameter have a 1% risk of aortic dissection or other serious

cardiac complication during pregnancy.[124] In pregnant women with Marfan syndrome, an aortic root diameter >4 cm and an increase in aortic root diameter during pregnancy are risk factors for dissection.[109,125] Although data about pregnancy in women with Marfan syndrome and aortic root diameters >45 mm are scarce, pregnancy should be discouraged in these patients. Dissection is rare with an aortic diameter <40 mm, although a completely safe diameter does not exist.[126] With an aortic diameter of 40–45 mm, risk factors for dissection (family history of dissection, rapid growth) should be taken into account.[121] Consideration of body surface area is important, especially in women of small stature. Following elective aortic root replacement, patients remain at risk for dissection in the residual aorta.[127]

In addition to life-threatening aortic dissection in these patients, an increase in mitral regurgitation may occur and may lead to complications such as supraventricular arrhythmias or heart failure, especially in those patients who already had moderate to severe regurgitation before pregnancy (see also Section 5 on valvular disease).

4.2.2 Bicuspid aortic valve

Approximately 50% of the patients with a bicuspid aortic valve and AS have dilatation of the ascending aorta.[128] Dilatation is often maximal in the distal part of the ascending aorta, which cannot be adequately visualized echocardiographically; therefore, MRI or CT should be performed pre-pregnancy. Dissection does occur, although less frequently than in Marfan patients.[109] The risk of pregnancy in women with bicuspid aortic valve and dilated aorta has not been systematically investigated. In patients with an aortic root >50 mm, pre-pregnancy surgery should be considered.[19]

4.2.3 Ehlers–Danlos syndrome

Aortic involvement occurs almost exclusively in Ehlers–Danlos syndrome type IV which is transmitted as an autosomal dominant trait. During pregnancy women may show increased bruising, hernias, and varicosities, and suffer rupture of large vessels or rupture of the uterus. Because of the risk of uterine rupture, Ehlers–Danlos syndrome type IV is a contraindication for pregnancy. Aortic dissection may occur without dilatation. The role of prophylactic surgery is less well established in this patient group because the risk–benefit ratio is influenced by the fact that surgical repair may be complicated by tissue fragility, tendency to haemorrhage extensively, and poor wound healing.[129,130]

4.2.4 Turner syndrome

The prevalence of cardiovascular malformations in Turner syndrome is 25–50% and hypertension is also often present. Although no quantitative evidence exists on the risk of dissection attributable to pregnancy in women with Turner syndrome, the risk probably is increased and is higher if the woman has additional risk factors such as bicuspid aortic valve, CoA, and/or hypertension.[131] Women at highest risk are those with aortic dilatation, but dissection may also occur in the absence of any dilatation. Thoracic aortic diameters must be evaluated in relation to body surface area as these patients often have short stature. An aortic diameter index >27 mm/m^2 is associated with a high risk of dissection, and prophylactic surgery should be considered. Aortic complications during pregnancy are associated with maternal mortality of up to 11%, mainly attributable to type A dissection. The risk of (pre)eclampsia is increased, and treatment of hypertension is important, especially during pregnancy.

4.3 Management

Follow-up and medical therapy. Depending on the aortic diameter, patients with aortic pathology should be monitored by echocardiography at 4–12 week intervals throughout the pregnancy and 6 months post-partum. Pregnancy should be supervised by a cardiologist and obstetrician who are alert to the possible complications. Treatment with β-blocking agents may reduce the rate of aortic dilatation and might improve survival. However, in a recent meta-analysis,[132] including mostly studies with non-pregnant patients, a beneficial effect was not confirmed. In spite of these uncertainties, the Task Force recommends the use of β-blockers in patients with Marfan syndrome during pregnancy to prevent dissection. In patients with Ehlers–Danlos syndrome type IV, celiprolol is recommended because of the very high risk of dissections and the benefit demonstrated in non-pregnant patients.[130] Fetal growth should be monitored when the mother is taking β-blockers.

Interventions. In patients with Marfan syndrome or other syndromes with high risk of dissection, such as Loeys–Dietz syndrome, Ehlers–Danlos, or Smad-3 gen mutation,[133] pre-pregnancy surgery is recommended when the ascending aorta is ≥45 mm, depending on individual characteristics. In other patients with dilatation of the aorta, pre-pregnancy surgery should be considered when the ascending aorta is ≥50 mm. Body surface area should probably be taken into account in small women. An aortic diameter index >27 mm/m^2 is associated with a high risk of dissection, and prophylactic surgery should be considered. When progressive dilatation occurs during pregnancy, before the fetus is viable, aortic repair with the fetus *in utero* should be considered. When the fetus is viable, caesarean delivery followed directly by aortic surgery is recommended (see Section 2.8.2). Caesarean section should be performed in a hospital in which cardiothoracic surgery and neonatal intensive care facilities are available. Ascending aortic dissection occurring during pregnancy is a surgical emergency; senior cardiothoracic, cardiology, obstetric, and anaesthetic physicians must act rapidly to deliver the fetus (if viable) by caesarean delivery in cardiac theatres and proceed directly to repair of the dissection.

Delivery (see also Section 2.9). 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 β-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 is advised to prevent BP peaks, which may induce dissection. Caesarean delivery may also be considered in these patients, based on the individual situation. Regional anaesthesia techniques can be difficult in Marfan patients, depending on the presence and severity of scoliosis and presence of dural ectasia.[134] Caesarean delivery should be considered when the aortic diameter exceeds 45 mm. It is advised to perform early caesarean delivery for women with Ehlers–Danlos syndrome type IV.

4.4 Recommendations for the management of aortic disease

Table 11 Recommendations for the management of aortic disease

Recommendations	Class[a]	Level[b]
Women with Marfan syndrome or other known aortic disease should be counselled about the risk of aortic dissection during pregnancy and the recurrence risk for the offspring.	I	C
Imaging of the entire aorta (CT/MRI) should be performed before pregnancy in patients with Marfan syndrome or other known aortic disease.	I	C
Women with Marfan syndrome and an ascending aorta >45 mm should be treated surgically pre-pregnancy.	I	C
In pregnant women with known aortic dilatation, (history of) type B dissection or genetic predisposition for dissection strict blood pressure control is recommended.	I	C
Repeated echocardiographic imaging every 4–8 weeks should be performed during pregnancy in patients with ascending aorta dilatation.	I	C
For imaging of pregnant women with dilatation of the distal ascending aorta, aortic arch or descending aorta, MRI (without gadolinium) is recommended.	I	C
In women with a bicuspid aortic valve imaging of the ascending aorta is recommended.	I	C
In patients with an ascending aorta <40 mm, vaginal delivery is favoured.	I	C
Women with aortic dilatation or (history of) aortic dissection should deliver in a centre where cardiothoracic surgery is available.	I	C
In patients with an ascending aorta >45 mm, caesarean delivery should be considered.	I	C
Surgical treatment pre-pregnancy should be considered in women with aortic disease associated with a bicuspid aortic valve when the aortic diameter is >50mm (or >27 mm/m^2 BSA).	IIa	C
Prophylactic surgery should be considered during pregnancy if the aortic diameter is ≥50 mm and increasing rapidly.	IIa	C
In Marfan, and other patients with an aorta 40–45 mm, vaginal delivery with epidural anaesthesia and expedited second stage should be considered.	IIa	C
In Marfan, and other patients with an aorta 40–45 mm, caesarean section may be considered.	IIb	C
Patients with (or history of) type B dissection should be advised against pregnancy.	III	C

[a]Class of recommendation.
[b]Level of evidence.
CT = computed tomography; MRI = magnetic resonance imaging.

5. Valvular heart disease

Both acquired and congenital valvular heart diseases are important causes of maternal and fetal morbidity and mortality. Rheumatic heart disease remains a major problem in developing countries and is still seen in western countries, especially in immigrants. Stenotic valve diseases carry a higher pregnancy risk than regurgitant lesions, and left-sided valve diseases have a higher complication rate than right-sided valve lesions.[12,56,57,135] Specific problems, mainly related to anticoagulant therapy, are present in women with mechanical valve prostheses.

5.1 Stenotic valve lesions

In stenotic valve diseases, increased CO causes an increase in transvalvular gradient and, thus, upstream pressures, and there is an increased risk of maternal and fetal complications.[12,102]

5.1.1 Mitral stenosis

Moderate or severe mitral stenosis (MS) is poorly tolerated during pregnancy. MS is responsible for most of the morbidity and mortality of rheumatic heart disease during pregnancy. The diagnosis is based on echocardiography.[7,136] Pressure half-time is less reliable than direct planimetry but can be used during pregnancy.[136] Gradient and PAP do not directly reflect the severity of MS during pregnancy but have an important prognostic value.[136] The assessment of mitral anatomy and the quantitation of associated regurgitation or other valvular diseases are particularly important when percutaneous mitral commissurotomy is considered.[7,136] Exercise testing is useful to reveal symptoms and assess exercise tolerance.

Maternal risk

The risk of decompensation depends on the severity of MS.[102,137] Heart failure occurs frequently in pregnant women with moderate or severe MS (valve area <1.5 cm^2), particularly during the second and third trimesters, even in previously asymptomatic women.[102,135,137] Heart failure is often progressive. Pulmonary oedema may occur, particularly when MS is unknown or if AF occurs. AF, although rare (<15%), carries the additional risk of thrombo-embolic events.[102,137] Mortality is between 0 and 3%.[102,135,137] Symptoms may be precipitated in women with mild MS, but they are generally not severe and are well tolerated.[102,135]

Obstetric and offspring risk

Obstetric complications are mainly related to the risk of acute heart failure during or just after delivery, and they depend on symptoms and PAP during pregnancy.[135] Prematurity rates are 20–30%, intrauterine growth retardation 5–20%, and stillbirth 1–3%.[102,137] Offspring risk is higher in women in NYHA class III/IV during pregnancy.[12,135]

Management

All patients with moderate or severe MS (even when asymptomatic) should be counselled against pregnancy and intervention should be performed pre-pregnancy, favouring percutaneous interventions.[7]

Follow-up. 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.

Medical therapy. When symptoms or pulmonary hypertension (echocardiographically estimated systolic PAP >50 mmHg) develop, activity should be restricted and β1-selective blockers commenced.[7,64] Diuretics may be used if symptoms persist, avoiding high doses.[64] Therapeutic anticoagulation is recommended in the case of paroxysmal or permanent AF, left atrial thrombosis, or prior embolism.[7,64] It should also be considered in women with moderate or severe MS and spontaneous echocardiographic contrast in the left atrium, large left atrium ($\geq$40 mL/m^2), low CO, or congestive heart failure, because these women are at very high thrombo-embolic risk.

Interventions during pregnancy. Percutaneous mitral commissurotomy is preferably performed after 20 weeks gestation. It should only be considered in women with NYHA class III/IV and/or estimated systolic PAP >50 mmHg at echocardiography despite optimal medical treatment, in the absence of contraindications and if patient characteristics are suitable.[7,64] It should be performed by an experienced operator, and in experienced hands has a low complication rate. Abdominal lead shielding is recommended.[7,64] The radiation dose should be minimized by keeping screening time as short as possible.[7,64] Given the risk of complications, percutaneous mitral commissurotomy should not be performed in asymptomatic patients. Closed commissurotomy remains an alternative in developing countries when percutaneous commissurotomy is not available. Open-heart surgery should be reserved for cases in which all other measures fail and the mother's life is threatened.

Delivery. Vaginal delivery should be considered in patients with mild MS, and in patients with moderate or severe MS in NYHA class I/II without pulmonary hypertension. Caesarean section is considered in patients with moderate or severe MS who are in NYHA class III/IV or have pulmonary hypertension despite medical therapy, in whom percutaneous mitral commissurotomy cannot be performed or has failed.

5.1.2 Valvular aortic stenosis

In women of childbearing age the main cause of AS is congenital bicuspid aortic valve. Patients can be asymptomatic, even with severe AS.[7] Symptoms may first occur during pregnancy. Echocardiography is mandatory for the diagnosis.[7,136] Exercise testing is recommended in asymptomatic patients before pregnancy to confirm asymptomatic status and evaluate exercise tolerance, BP response, arrhythmias, and/or the need for interventions. In women with bicuspid aortic valve, aortic diameters should be assessed before and during pregnancy.

Maternal risk

Cardiac morbidity during pregnancy is related to severity of AS and symptoms. With asymptomatic mild or moderate AS, pregnancy is well tolerated. Also patients with severe AS may sustain pregnancy well, as long as they remain asymptomatic during exercise testing and have a normal BP response during exercise.[19,139]

The increase in CO can lead to a marked increase in gradient.[135,139] Heart failure occurs in ~10% of patients with severe AS and arrhythmias in 3–25%.[140] Mortality is now rare if careful management is provided.[8,56,74,102,135,139,140] Women with bicuspid aortic valve have a risk of aortic dilatation and dissection (see Section 4.3.2).

Obstetric and offspring risk

Obstetric complications may be increased in patients with severe AS (hypertension-related disorders in 13%, premature labour).[140]

Pre-term birth, intrauterine growth retardation, and low birth weight occur in up to 25% of the offspring of mothers with moderate and severe AS.

Management

All symptomatic patients with severe AS or asymptomatic patients with impaired LV function or a pathological exercise test should be counselled against pregnancy, and valvuloplasty or surgery should be performed pre-pregnancy, according to guidelines.[7,19] Pregnancy needs not be discouraged in asymptomatic patients, even with severe AS, when LV size and function as well as the exercise test are normal and severe LV hypertrophy (posterior wall >15 mm) has been excluded. There should also be no evidence of recent progression of AS.[74,139,140,141] Regardless of symptoms, pre-pregnancy surgery should be considered in patients with an ascending aorta >50 mm (27.5 mm/m^2).

Follow-up. Regular follow-up during pregnancy is required by an experienced team. In severe AS, monthly or bimonthly cardiac evaluations including echocardiography are advised to determine symptom status, progression of AS, or other complications.

Medical therapy. Medical treatment and restricted activities are indicated for patients developing signs or symptoms of heart failure during pregnancy. Diuretics can be administered for congestive symptoms. A β-blocker or a non-dihydropyridine calcium channel antagonist should be considered for rate control in AF. If both are contraindicated, digoxin may be considered.[142]

Interventions during pregnancy. During pregnancy in severely symptomatic patients not responding to medical therapy, percutaneous valvuloplasty can be undertaken in non-calcified valves with minimal regurgitation.[143] 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 Section 2.7.2).

Delivery. In severe AS, particularly with symptoms during the second half of the pregnancy, caesarean delivery should be preferred with endotracheal intubation and general anaesthesia. In non-severe AS, vaginal delivery is favoured, avoiding a decrease in peripheral vascular resistance during regional anaesthesia and analgesia.

5.2 Regurgitant lesions

5.2.1 Mitral and aortic regurgitation

Mitral and aortic regurgitation at childbearing age can be of rheumatic, congenital, or degenerative origin. Previous valvulotomy and infective endocarditis can be associated factors. A rare cause of acute valvular regurgitation during pregnancy is antiphospholipid syndrome. Left-sided regurgitant valve lesions carry a lower pregnancy risk than stenotic valve lesions because the decreased systemic vascular resistance reduces regurgitant volume. Severe regurgitation with LV dysfunction is poorly tolerated, as is acute severe regurgitation. Evaluation is preferably performed preconception, and should include assessment of symptoms, echocardiographic evaluation of regurgitation severity (integrative approach according to ESC criteria), and LV dimensions and function.[7] In moderate/severe regurgitation, exercise testing is recommended pre-pregnancy. Ascending aortic diameters should be measured in

women with aortic regurgitation, especially in those with bicuspid valves.

Maternal risk

Maternal cardiovascular risk depends on regurgitation severity, symptoms, and LV function.[135] Women with severe regurgitation and symptoms or compromised LV function are at high risk of heart failure.[135] In asymptomatic women with preserved LV function the most frequent complications are arrhythmias. In women with congenital heart disease, significant left AV valve regurgitation has been reported to be associated with cardiac complications during pregnancy. This association may be partly attributable to ventricular dysfunction. A persistent worsening of regurgitation may occur.[57,99]

Obstetric and offspring risk

No increased risk of obstetric complications has been reported. In symptomatic regurgitation the risk of offspring complications is increased.[12]

Management

Patients with severe regurgitation and symptoms or compromised LV function or LV dilatation (according to criteria of guidelines for valvular heart disease)[7] should be referred for pre-pregnancy surgery favouring valve repair.

Follow-up. Follow-up is required every trimester in mild/moderate regurgitation, and more often in severe regurgitation. Follow-up plans need to be individualized according to clinical status and symptoms.

Medical therapy and intervention during pregnancy. Symptoms of fluid overload can usually be managed medically. In acute severe regurgitation with therapy-refractory heart failure, surgery is sometimes unavoidable during pregnancy. If the fetus is sufficiently mature, delivery should be undertaken prior to cardiac surgery (see Section 2.8.2).

Delivery. Vaginal delivery is preferable; in symptomatic patients epidural anaesthesia and shortened second stage is advisable.

5.2.2 Tricuspid regurgitation

TR is usually functional (annular dilatation due to RV pressure or volume overload); alternatively, endocarditis or Ebstein's anomaly can be the cause. The diagnostic work-up consists of clinical and echocardiographic assessment.[7] Maternal cardiovascular risk is usually determined by primary left-sided valve disease or pulmonary hypertension. However, maternal risk can be increased in severe symptomatic TR or in women with RV dysfunction.[76] In women with congenital heart disease, moderate/severe tricuspid AV valve regurgitation may be associated with maternal cardiac complications (possibly dependent on ventricular function), mainly arrhythmias.[57]

Even severe TR with heart failure can usually be managed conservatively during pregnancy (*Table 12*). When surgery is necessary for left-sided valve lesions before or during pregnancy, additional tricuspid repair is indicated in severe TR and should be considered in moderate TR and moderate secondary TR with annular dilatation (>40 mm).[7] In severe symptomatic TR, repair should be considered pre-pregnancy. The preferred mode of delivery is vaginal in almost all cases.

5.3 Valvular atrial fibrillation (native valves)

A high thrombo-embolic risk is associated with valvular AF. This is particularly pronounced in patients with severe MS. With the occurrence of AF, immediate anticoagulation with i.v. UFH is required, followed by LMWH in the first and last trimester and OACs or LMWH for the second trimester. LMWH should be given in weight-adjusted therapeutic doses (twice daily) until 36 h prior to delivery. If OACs are used, the INR can be kept between 2.0 and 2.5, thus minimizing the risk for the fetus.

5.4 Prosthetic valves

5.4.1 Choice of valve prosthesis

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

Mechanical valves offer excellent haemodynamic performance and long-term durability, but the need for anticoagulation increases fetal and maternal mortality and morbidity. Bioprosthetic valves also offer good haemodynamic performance and are much less thrombogenic. Their use in young women, however, is associated with a high risk of structural valve deterioration, occurring in ~50% of women <30 years of age at 10 years post-implantation, and is greater in the mitral position than in the aortic and tricuspid position. In the pulmonary position, transcatheter valve implantation is an option in an increasing number of patients, particularly after previous bioprosthesis implantation. There is conflicting evidence as to whether or not pregnancy accelerates bioprosthetic degeneration.[144] However, young patients with a biological valve will almost certainly need a reoperation, with a mortality risk of 0–5%, depending on valve position and degree of emergency.

In patients with aortic valve disease, the Ross operation (pulmonary autograft transferred to the aortic position and pulmonary valve replacement with a homograft) can be an alternative. There is no risk of valve thrombosis, and valve haemodynamics are excellent. Yet this is a two-valve operation requiring specific surgical expertise, and with a significant reoperation rate after 10 years. Moreover, only few data are available about pregnancy in women after a Ross procedure.[145] A desire for pregnancy is considered a class IIb indication for a biological valve.[7] The choice for a specific prosthesis should be made after extensive patient information and discussion with the patient.

5.4.2 Bioprosthesis

Pregnancy is generally well tolerated in women with a bioprosthetic valve. Maternal cardiovascular risk is mainly dependent on bioprosthesis function. The risk is low in women with no or minimal bioprosthesis dysfunction and uncompromised ventricular function.[144]

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.

5.5 Mechanical prosthesis and anticoagulation

Haemodynamically, women with well-functioning mechanical valves tolerate pregnancy well. Yet the need for anticoagulation

raises specific concerns because of an increased risk of valve thrombosis, of haemorrhagic complications, and of offspring complications. Pregnancy is associated with increased maternal risk. The character and magnitude of the risk depend on the anticoagulation regimen used during pregnancy and the quality of anticoagulation control. Pre-pregnancy evaluation should include assessment of symptoms and echocardiographic evaluation of ventricular function, and prosthetic and native valve function.

Maternal risk

Mechanical valves carry the risk of valve thrombosis which is increased during pregnancy. In a large review, this risk was 3.9% with OACs throughout pregnancy, 9.2% when UFH was used in the first trimester and OACs in the second and third trimester, and 33% with UFH throughout pregnancy.[146] Maternal death occurred in these groups in 2, 4, and 15%, respectively, and was usually related to valve thrombosis.[146] A review of the recent literature confirmed the low risk of valve thrombosis with OACs throughout pregnancy (2.4%, 7/287 pregnancies) compared with UFH in the first trimester (10.3%, 16/156 pregnancies).[147] The risk is probably lower with adequate dosing and is also dependent on the type and position of the mechanical valve, as well as on additional patient-related risk factors.[7] UFH throughout pregnancy is additionally associated with thrombocytopenia and osteoporosis. LMWHs are also associated with the risk of valve thrombosis.[148,149] The risk is lower, but still present, with dose adjusting according to anti-Xa levels.[147,148,150–152] In 111 pregnancies in which LMWH with dose adjustment according to anti-Xa levels was used throughout pregnancy, valve thrombosis occurred in 9%.[147,150–152] Too low target anti-Xa levels or poor compliance probably contributed to valve thrombosis in all but one pregnancy. A review reported lower frequency of valve thrombosis with LMWH in the first trimester only, but in a small patient group (3.6%, 2/56 pregnancies).[147]

The use of LMWH during pregnancy in women with mechanical prostheses is still controversial because evidence is scarce. Unresolved questions concern optimal anti-Xa levels, the importance of peak vs. pre-dose levels, and the best time intervals for anti-Xa monitoring. Studies are urgently needed.

There is a marked increase in dose requirement during pregnancy to keep the anti-Xa levels in the therapeutic range,[151,153] because of increased volume of distribution and increased renal clearance. Therefore, regular monitoring of anti-Xa levels is necessary. It has been demonstrated that pre-dose anti-Xa levels are often subtherapeutic when peak levels are between 0.8 and 1.2 U/mL.[153,154] Even when pre-dose anti-Xa level monitoring and more frequent dosing lead to higher pre-dose levels combined with lower peak levels, there are no data available to show that this approach achieves a stable, consistent therapeutic intensity of anticoagulation and will prevent valve thrombosis and bleeding.[152–154]

Current evidence indicates that OACs throughout pregnancy, under strict INR control, is the safest regimen for the mother.[146,147,155] However, adequate randomized studies that compare different regimens are not available. The superiority of either UFH or LMWH in the first trimester is unproven, though a recent review suggests higher efficacy of LMWH.[147] No LMWH is officially approved (labelled) for pregnant women with mechanical valves.

Obstetric and offspring risk. All anticoagulation regimens carry an increased risk of miscarriage and of haemorrhagic complications, including retroplacental bleeding leading to premature birth and fetal death.[144,146,148,150–152] Comparison between studies is hampered, however, by reporting differences. OACs cross the placenta and their use in the first trimester can result in embryopathy in 0.6–10% of cases.[146,156–158] UFH and LMWH do not cross the placenta and embryopathy does not occur. Substitution of OACs with UFH in weeks 6–12 greatly decreases the risk. The incidence of embryopathy was low (2.6%) in a small series when the warfarin dose was <5 mg and 8% when the warfarin dose was >5 mg daily.[159] The dose dependency was confirmed in a recent series.[155] Major central nervous system abnormalities occur in 1% of children when OACs are used in the first trimester.[158] A low risk of minor central nervous system abnormalities exists with OACs outside the first trimester only.[158] Vaginal delivery while the mother is on OACs is contraindicated because of the risk of fetal intracranial bleeding.

Management

Valve and ventricular dysfunction should be considered, and the type and position of valve(s) as well as the history of valve thrombosis should be taken into account. The advantages and disadvantages of different anticoagulation regimens should be discussed extensively. The mother and her partner must understand that according to current evidence use of OACs is the most effective regimen to prevent valve thrombosis, and therefore is the safest regimen for her, and risks for the mother also jeopardize the baby. On the other hand the risk of embryopathy and fetal haemorrhage needs to be discussed, considering OAC dose. Compliance with prior anticoagulant therapy should be considered. The management of the regimen that is chosen should be planned in detail.

Follow-up. The effectiveness of the anticoagulation regimen should be monitored weekly and clinical follow-up including echocardiography should be performed monthly.

Medical therapy. The main goal of anticoagulation therapy in these women is to prevent the occurrence of valve thrombosis and its lethal consequences for both mother and fetus. The following recommendations should be seen in this perspective. OACs should be continued until pregnancy is achieved. UFH or LMWH throughout pregnancy is not recommended because of the high risk of valve thrombosis with these regimens in combination with low fetal risk with OACs in the second and third trimester. Continuation of OACs throughout pregnancy should be considered when the warfarin dose is <5 mg daily (or phenprocoumon <3 mg or acenocoumarol <2 mg daily) because the risk of embryopathy is low, while OACs are in large series the most effective regimen to prevent valve thrombosis.[146,147] After the mother has been given full information that OACs throughout pregnancy is by far the safest regimen for her and the risk for embryopathy is $<3\%$, discontinuation of OACs and a switch to UFH or LMWH between weeks 6 and 12 under strict dose control and supervision (as indicated below) may be considered after discussion on an individual basis in patients with a low dose requirement. When a higher dose of OACs is required, discontinuation of OACs between weeks 6 and 12 and replacement by adjusted-dose UFH (aPTT

≥2 times the control, in high risk patients applied as an i.v. fusion) or LMWH twice daily with dose adjustment according to weight and according to anti-Xa levels (*Table 12*) should be considered. The anti-Xa level should be maintained between 0.8 and 1.2 U/mL, determined 4–6 h after application (*Table 12*).[4,7] The Task Force advises weekly control of peak anti-Xa levels because of the need for increasing dosages of LMWH during pregnancy.[2,4,7,147,151,153] As an alternative, continuation of OACs may be considered in these patients after fully informed consent.

The importance of also monitoring the pre-dose level of anti-Xa, and the need to maintain this level above 0.6 IU/mL, has not been studied sufficiently, particularly in relation to thrombo-embolic events and bleeding, to make firm recommendations. The starting dose for LMWH is 1 mg/kg body weight if enoxaparin is chosen and 100 IU/kg for dalteparin, given twice daily subcutaneously. The dose should be adjusted according to increasing weight during pregnancy[160] and anti-Xa levels. The Task Force does not recommend the addition of acetylsalicylic acid to this regimen because there are no data to prove its efficacy and safety in pregnant women. The use of LMWH in the first trimester is limited by the scarceness of data about its efficacy[147] and safety, uncertainties concerning optimal dosing to prevent both valve thrombosis and bleeding, and variable availability of anti-Xa level testing.

Irrespective of the regimen used, the effect of the anticoagulants should be monitored very carefully, and in the case of OACs the INR should be determined at weekly intervals. The intensity of the INR should be chosen according to the type and location of the prosthetic valve, according to present guidelines.[4,7] Intense education about anticoagulation and self-monitoring of anticoagulation in suitable patients is recommended. In case UFH is used it should, when a stable aPTT has been achieved, be monitored weekly by the aPTT, 4–6 h after starting the first dose, with a prolongation of ≥2 times the control.

Diagnosis and management of valve thrombosis. When a woman with a mechanical valve presents with dyspnoea and/or an embolic event, immediate transthoracic echocardiography is indicated to search for valve thrombosis, usually followed by transoesophageal echocardiography. If necessary, fluoroscopy can be performed with limited fetal risk. Management of valve thrombosis is comparable with management in non-pregnant patients. This includes optimizing anticoagulation with i.v. heparin and 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.[7] Most fibrinolytic agents do not cross the placenta, but the risk of embolization (10%) and of 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. Because fetal loss is high with surgery, fibrinolysis may be considered instead of surgery in non-critically ill patients when anticoagulation fails. Fibrinolysis is the therapy of choice in right-sided prosthetic valve thrombosis.[7] The mother should be informed about the risks.

Delivery (see also Section 2.9). Planned vaginal delivery is usually preferred, with prior switch to heparin. A planned caesarean section may be considered as an alternative, especially in patients with a high risk of valve thrombosis, in order to keep the time without OACs as short as possible. Caesarean delivery should be performed if labour onset occurs while the patient is still on OACs.

5.6 Recommendations for the management of valvular heart disease

Table 12 Recommendations for the management of valvular heart disease

Recommendations	Class[a]	Level[b]
Mitral stenosis		
In patients with symptoms or pulmonary hypertension, restricted activities and β1-selective blockers are recommended.	I	B [7,64]
Diuretics are recommended when congestive symptoms persist despite β-blockers.	I	B [64]
Patients with severe MS should undergo intervention before pregnancy.	I	C
Therapeutic anticoagulation is recommended in the case of atrial fibrillation, left atrial thrombosis, or prior embolism.	I	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		
Patients with severe AS should undergo intervention pre-pregnancy if:		
• they are symptomatic	I	B [7]
• or LV dysfunction (LVEF <50%) is present	I	C
Asymptomatic patients with severe AS should undergo intervention pre-pregnancy when they develop symptoms during exercise testing.	I	C
Asymptomatic patients with severe AS should be considered for intervention pre-pregnancy when a fall in blood pressure below baseline during exercise testing occurs.	IIa	C

Continued

Table 12 *Continued*

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

[a]Class of recommendation.
[b]Level of evidence.
aPTT = activated partial thromboplastin time; AS = aortic stenosis; LMWH = low molecular weight heparin; LVEF = left ventricular ejection fraction; MS = mitral stenosis; OACs = oral anticoagulants; UFH = unfractionated heparin.

6. Coronary artery disease and acute coronary syndromes

The diagnostic criteria of acute coronary syndrome (ACS) during pregnancy or in the puerperium are similar to those for non-pregnant patients and consist of chest pain, ECG changes, and cardiac biomarkers. However, negative T waves may appear at an increased rate in pregnancy in non-ischaemic conditions. An increase in the level of troponin I should lead the investigating physician to consider the diagnosis of underlying ischaemic heart disease, even if pre-eclampsia is present.[161] Timely diagnosis is often delayed, as presenting symptoms may be attributed to pregnancy. The main differential diagnoses of acute ischaemic chest pain are pre-eclampsia, acute pulmonary embolism, and aortic dissection. Echocardiography can be safely used to evaluate the presence of wall motion abnormalities. Exercise ECG or exercise echocardiography can be performed in stable patients, whereas radionuclide stress tests should be avoided because of radiation. Severe post-partum haemorrhage with haemorrhagic shock may also lead to elevated troponin levels with ischaemic ECG changes and LV wall motion abnormalities.

6.1 Maternal and offspring risk

With the rise in maternal age and the increasing number of high risk women who become pregnant, pregnancy-related ACS are expected to increase. Pregnancy may be considered in women with known coronary artery disease in the absence of residual ischaemia and clinical signs of LV dysfunction. Cardiac risk assessment before conception is highly recommended (see Section 2.11). During pregnancy an ACS is rare and estimated at 3–6 per 100 000 deliveries.[162–164] It is strongly related to the major coronary heart disease risk factors, such as smoking, hypertension,

hyperlipidaemia, older age, diabetes mellitus, and a positive family history. Other conditions that contribute to ACS risk are (pre)eclampsia, thrombophilia, post-partum infections, and severe post-partum haemorrhage.[161,163–165] Pregnancy-related ACS can occur during all stages of gestation. Spontaneous coronary artery dissections are more prevalent among pregnant than non-pregnant women, and are mostly reported around delivery or in the early post-partum period.[163] They may be related to high progesterone levels with subsequent structural changes in the collagen of the vessel wall. Ergometrine given for bleeding post-partum may lead to coronary vasospasm and ischaemia. Thrombi and dissections occur more frequently in the peripartum period than before delivery.[163]

Maternal mortality after ACS is estimated at 5–10% and is highest during the peripartum period. Survival has improved with primary percutaneous coronary intervention (PCI).[162–164] Long-term maternal prognosis mainly depends on infarct size and the cardiovascular risk profile. Before delivery, ACS may result in fetal mortality and prematurity, the risk of which is mainly related to the severity of maternal heart disease.

6.2 Management

The first step in ST-elevation ACS is to refer the patient immediately to a skilled intervention centre for a diagnostic angiogram and a primary PCI.

Interventions during pregnancy. Coronary angiography with the possibility of coronary intervention (PCI) is preferred to thrombolysis as it will also diagnose coronary artery dissection. The risk of potential damage to the fetus should be kept in mind, especially in the first trimester. All reported stenting during the acute phase of ST-elevation myocardial infarction during pregnancy utilized bare metal stents; the safety of drug-eluting stents in pregnant woman is therefore still unknown. As drug-eluting stents also require prolonged dual antiplatelet therapy they should be avoided. Although recombinant tissue plasminogen activator does not cross the placenta it may induce bleeding complications (subplacental bleeding); therefore, thrombolytic therapy should be reserved for life-threatening ACS when there is no access to PCI.[166] In women with non-ST elevation ACS with intermediate or high risk criteria, an invasive approach to assess coronary anatomy is indicated, while in stable conditions with exertional symptoms, watchful waiting and medical therapy is the treatment of choice.[167] In all patients, if there is a deterioration in clinical status, an invasive strategy is indicated. In the case of recurrent coronary dissections, pre-term delivery can be considered according to fetal viability. Data on emergency coronary artery bypass graft surgery during pregnancy are rare, with a potentially high mortality rate.[163,164]

Medical therapy. The use of ACE inhibitors, angiotensin receptor blockers (ARBs), and renin inhibitors is contraindicated during pregnancy (see Section 11). β-Blockers and low dose acetylsalicylic acid are considered to be relatively safe, while this is unknown for thienopyridines. Clopidogrel should therefore only be used during pregnancy when strictly needed (e.g. after stenting) and for the shortest duration possible. In the absence of safety data regarding glycoprotein IIb/IIIa inhibitors, bivalirudin, prasugrel, and ticagrelor, the use of these dugs is not recommended during pregnancy.

Delivery. In most cases, vaginal delivery will be appropriate. Delivery is discussed in Section 2.9.

6.3 Recommendations for the management of coronary artery disease

Table 13 Recommendations for the management of coronary artery disease

Recommendations	Class[a]	Level[b]
ECG and troponin levels should be performed in the case of chest pain in a pregnant woman.	I	C
Coronary angioplasty is the preferred reperfusion therapy for STEMI during pregnancy.	I	C
A conservative management should be considered for non ST-elevation ACS without risk criteria.	IIa	C
An invasive management should be considered for non ST-elevation ACS with risk criteria (including NSTEMI).	IIa	C

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

7. Cardiomyopathies and heart failure

The current incidence rate of cardiomyopathies associated with pregnancy in Europe is not known. The aetiology of cardiomyopathies occurring in association with pregnancy is diverse, with acquired and inherited [peripartum cardiomyopathy (PPCM), toxic cardiomyopathy, hypertrophic cardiomyopathy (HCM), dilated cardiomyopathy (DCM), storage disease, etc.] forms of cardiomyopathy. Cardiomyopathies are rare diseases but may cause severe complications in pregnancy.[168]

7.1 Peripartum cardiomyopathy

PPCM has recently been reviewed.[168] The most important aspects are briefly described here. The incidence varies from 1:300 to 1:4000 pregnancies, emphasizing the involvement of genetic and/or cultural factors.[168,169] Predisposing factors seem to be multiparity and multiple childbirths, family history, ethnicity, smoking, diabetes, hypertension, pre-eclampsia,

malnutrition, advanced age of mothers or teenage pregnancy, and prolonged use of β-agonists.[168,169] The aetiology of PPCM is uncertain; infections, inflammation, and autoimmune processes may play a role.[170] PPCM is suspected to be the consequence of an unbalanced oxidative stress leading to proteolytic cleavage of the lactating hormone prolactin into a potent angiostatic factor and into pro-apoptotic fragments.[171]

According to current definitions, PPCM is an idiopathic cardiomyopathy presenting with heart failure secondary to LV systolic dysfunction towards the end of pregnancy or in the months following delivery. It is a diagnosis of exclusion when no other cause of heart failure is found. The LV may not be dilated, but the EF is nearly always reduced below 45%.[168]

Symptoms and signs are often typical for heart failure but, due to the special physiological situation of pregnancy and post-partum, a broad spectrum of symptoms is reported in PPCM patients. PPCM should be suspected in all women with a delayed return to the pre-pregnancy state. Frequently the patients present with acute heart failure. Complex ventricular arrhythmias and sudden cardiac arrest are also described.

In some cases, not all diagnostic criteria may be strictly fulfilled. Echocardiography is the preferred method to assess LV function. Genetically transmitted DCM may manifest in the same time interval and is not distinguishable from PPCM.[172,173]

Management

Heart failure in PPCM can develop very rapidly, and the guidelines for the management of acute heart failure apply.[174]

Interventions

If a patient is dependent on inotropes despite optimal medical therapy, she should be transferred to a facility where intra-aortic balloon pump counterpulsation, ventricular assist devices, and transplant consult teams are available. Use of aortic counterpulsation and implantation of an assist device should be discussed with specialists. It is important to note that the prognosis of PPCM is different from that of DCM, with a significant proportion improving or normalizing their LV function over the first 6 months after diagnosis. The relatively high rate (~50%) of spontaneous recovery must be considered when decisions are made.[175]

Devices and cardiac transplantation

For women presenting with symptoms and severe LV dysfunction 6 months following first presentation, despite optimal medical therapy and QRS duration >120 ms, most clinicians would advise cardiac resynchronization therapy or implantable cardioverter-defibrillator (ICD) treatment. Cardiac transplantation should be reserved for patients where mechanical circulatory support is not possible or not desirable for individual reasons or for patients who do not recover after 6–12 months on mechanical circulatory support. Patients with PPCM have a similar prognosis after transplantation to patients with DCM.[176]

Medical therapy

For treatment of chronic heart failure, the pregnancy status of the patient is important. Most patients with PPCM present peri- or post-partum. Women who present with PPCM during pregnancy require joint cardiac and obstetric care. Possible adverse effects on the fetus must be considered when prescribing drugs. Urgent delivery, irrespective of gestation, may need to be considered in women presenting or remaining in advanced heart failure with haemodynamic instability. As soon as the baby is delivered, and the patient is haemodynamically stable, standard therapy for heart failure can be applied (Section 7.4).

Care should be taken with anticoagulation therapy in the immediate phase after delivery but, once the bleeding is stopped, it should be considered in patients with very low EF because peripheral embolism including cerebral embolism and ventricular thrombi are frequent in PPCM patients.[168] This is in part due to increased procoagulant activity in the peripartum phase.[177]

Heart failure should be treated according to guidelines on acute and chronic heart failure.[174] During pregnancy, ACE inhibitors, ARBs, and renin inhibitors are contraindicated because of fetotoxicity.[178,179] When ACE inhibitors are needed during breastfeeding, benazepril, captopril, or enalapril should be preferred. Hydralazine and nitrates can be used instead of ACE inhibitors/ARBs for afterload reduction. Dopamine and levosimendan can be used if inotropic drugs are needed. β-Blocker treatment is indicated for all patients with heart failure, if tolerated.[3] β1-Selective drugs (i.e. metoprolol) should be preferred. Atenolol should not be used.[180] Newborns should be supervised for 24–48 h after delivery to exclude hypoglycaemia, bradycardia, and respiratory depression. Diuretics should only be used if pulmonary congestion is present since they may decrease blood flow over the placenta.[169] Furosemide and hydrochlorothiazide are most frequently used. Aldosterone antagonists should be avoided.[181] Spironolactone can be associated with antiandrogenic effects in the first trimester. Data for eplerenone are lacking.

Coagulation activity is increased during pregnancy (see Section 2.4).[177] In the context of reduced EF in PPCM, treatment with LMWH or oral anticoagulation should be considered. Anticoagulation is recommended in patients with intracardiac thrombus detected by imaging or evidence of systemic embolism,[174] as well as in patients with heart failure and paroxysmal or persistent AF. LMWH or vitamin K antagonists are recommended according to the stage of pregnancy to prevent stroke.[142,174,182]. When LMWH is used, anti-Xa levels should be monitored.

Delivery

Vaginal delivery is always preferable if the patient is haemodynamically stable and there are no obstetric indications for caesarean delivery. Close haemodynamic monitoring is required. Epidural analgesia is preferred. Pre-term delivery has been reported in 17% of patients with no marked negative effects on the child.[183] Urgent delivery irrespective of gestation duration should be

considered in women with advanced heart failure and haemodynamic instability despite treatment. Caesarean section is recommended with combined spinal and epidural anaesthesia.[184] An experienced interdisciplinary team is required.

Breastfeeding

Some ACE inhibitors (benazepril, captopril, enalapril) have been sufficiently tested in breastfeeding women and use by the mother is safe for the babies.[185] Children's weight monitoring during the first 4 weeks is essential as an indicator of kidney dysfunction. A recent small prospective randomized pilot study supports the hypothesis that the addition of bromocriptine to standard heart failure therapy has beneficial effects on ventricular EF and clinical outcome in women with acute severe PPCM.[186] In addition, due to high metabolic demands of lactation and breastfeeding, preventing lactation may be considered.

Prognosis and counselling for repeated pregnancy

Worldwide data about mortality rates vary from 0% to 9% in the white population of the USA to up to 15% in African Americans as well as in populations in South Africa and Haiti. Systematic studies from European countries are not available so far. Deterioration in LV function is reported in up to 50% of cases despite optimal medical treatment.[187]

A subsequent pregnancy carries a recurrence risk for PPCM of 30–50%.[169,175] When the EF has not normalized, a subsequent pregnancy should be discouraged. Even if the EF is normalized, there is still a need for counselling because of the risk of recurrence with a new pregnancy.

7.2 Dilated cardiomyopathy

DCM is defined by the presence of typical symptoms of heart failure, LV dilation, and LV systolic dysfunction of unknown origin. Differentiation from PPCM is supported by the time of manifestation. If not known before conception, the condition is most often unmasked during the first or second trimester when the haemodynamic load is increasing. A family history of DCM speaks in favour of the DCM diagnosis and against PPCM. The few cases of classical DCM in pregnancy describe marked deterioration during pregnancy.[188]

Secondary cardiomyopathies, such as infiltrative or toxic cardiomyopathies, or storage diseases and other rare forms, can also manifest themselves in pregnancy. Hypertensive or ischaemic heart diseases can also cause similar clinical pictures.

Maternal and offspring risk

Women with DCM should be informed about the risk of deterioration of the condition during gestation and peripartum (see Section 2). They should be counselled based on individual risk stratification. If pregnancy occurs, LVEF $<40\%$ is a predictor of high risk, and close monitoring in a tertiary centre should be advised. If LVEF is $<20\%$, maternal mortality is very high and termination of the pregnancy should be considered.

Management

Anticoagulation with LMWH or Vitamin K antagonists according to stage of pregnancy should be considered for those with atrial arrhythmias.

DCM is treated in accordance with the current ESC/European Society of Intensive Care Medicine (ESICM) guidelines for heart failure,[174] with the adaptations during pregnancy described above for PPCM.

7.3 Hypertrophic cardiomyopathy

HCM is the most common genetic cardiac disease.[189] The disease is frequently diagnosed for the first time in pregnancy by echocardiography. The most common substrates for complications are diastolic dysfunction due to the hypertrophied non-compliant myocardium, severe LVOTO, and arrhythmias.

The symptoms are typical for heart failure, with pulmonary congestion due to the increased end-diastolic pressure or syncope during physical activity as a response to outflow tract obstruction. Echocardiography is the diagnostic tool of choice. Supraventricular and ventricular arrhythmias are common.

Maternal and offspring risk

Women with HCM usually tolerate pregnancy well. Risk is increased in women who are symptomatic before pregnancy and in those with a high outflow tract gradient. Patients with a high risk clinical profile before pregnancy are at higher risk and need specialized obstetric care.[34,190] Low risk cases may have a spontaneous labour and vaginal delivery.

Management

β-Blockers should be considered in those patients with more than mild LVOTO and/or maximal wall thickness >15 mm to prevent sudden pulmonary congestion during exertion or emotional stress.[189] β-Blockers can be used for rate control in AF and to suppress ventricular arrhythmias. Verapamil can be used as a second choice when β-blockers are not tolerated (be aware of causing AV block in the fetus). Cardioversion should be considered for persistent arrhythmia because AF is poorly tolerated. Therapeutic anticoagulation with LMWH or vitamin K antagonists according to stage of pregnancy is recommended for those with paroxysmal or persistent AF. Patients with a past history or family history of sudden death need close surveillance with prompt investigation if symptoms of palpitations or pre-syncope are reported.

Delivery

Low risk cases may have a spontaneous labour and vaginal delivery. Nevertheless, complications may occur; therefore, a planned delivery is recommended in all others. The severity of LVOTO will determine if regional anaesthesia is acceptable. Epidural anaesthesia causes systemic vasodilation and hypotension, and therefore must be used with caution in patients with severe LVOTO. I.v. fluids must be given judiciously and volume overload must be avoided as it is poorly tolerated in the presence of diastolic dysfunction. Syntocinon may cause hypotension, arrhythmias, and tachycardia, and should only be given as a slow infusion.

7.4 Recommendations for the management of heart failure

Table 14 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.	I	A[174]
Women with HF during pregnancy should be treated according to current guidelines for non-pregnant patients, respecting contraindications for some drugs in pregnancy—see Section 11 *Table 21*.	I	B[168]
Women with DCM should be informed about the risk of deterioration of the condition during gestation and peripartum.	I	C
In patients with a past history or family history of sudden death close surveillance with prompt investigation is recommended if symptoms of palpitations or presyncope are reported.	I	C
Therapeutic anticoagulation with LMWH or vitamin K antagonists according to stage of pregnancy is recommended for patients with atrial fibrillation.	I	C
Delivery should be performed with β-blocker protection in women with HCM.	IIa	C
β-blockers should be considered in all patients with HCM and more than mild LVOTO or maximal wall thickness >15mm to prevent sudden pulmonary congestion.	IIa	C
In HCM, cardioversion should be considered for persistent atrial fibrillation.	IIa	C
Due to high metabolic demands of lactation and breastfeeding, preventing lactation may be considered in PPCM.	IIb	C
Subsequent pregnancy is not recommended if LVEF does not normalize in women with PPCM.	III	C

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

8. Arrhythmias

Both premature extra beats and sustained tachyarrhythmias become more frequent and may even manifest for the first time during pregnancy. Symptomatic exacerbation of paroxysmal supraventricular tachycardia (SVT) occurs during pregnancy in ~20–44% of cases.[60] Even though most palpitations are benign, new onset of VT is of concern and the patients should be investigated for the presence of underlying structural heart disease.

The major concern regarding the use of antiarrhythmic drugs during pregnancy is their potential adverse effects on the fetus. All antiarrhythmic drugs should be regarded as potentially toxic to the fetus. While the first trimester is associated with the greatest teratogenic risk, drug exposure later in pregnancy may confer adverse effects on fetal growth and development as well as increase the risk of proarrhythmia. Major controlled studies of antiarrhythmic drugs during pregnancy are lacking. Antiarrhythmic drugs are listed in Section 11.

The risk and benefit of continuing vs. stopping medication must be given careful consideration because of the potential problem of recurring tachyarrhythmia during pregnancy. These decisions are individualized and based on the nature of the arrhythmia and the underlying heart disease. It is important that symptomatic tachyarrhythmia is treated by catheter ablation prior to pregnancy where possible.

8.1 Arrhythmias associated with structural and congenital heart disease

Supraventricular and ventricular arrhythmias requiring treatment develop in up to 15% (mean 5%) of patients with congenital heart diseases during pregnancy.[56] Episodes of sustained tachycardia, particularly atrial flutter, are not well tolerated and can cause fetal hypoperfusion in structural heart disease. Direct current conversion should be performed to restore sinus rhythm. Digoxin can be used to control ventricular rate, but has no prophylactic antiarrhythmic effect. β-Blocking agents, class I antiarrhythmic drugs, and sotalol should be used with caution if the LV or RV function is impaired (see Section 11). Amiodarone should be used only when other therapy has failed and then at the lowest effective dose (see Section 11).

8.2 Specific arrhythmias

8.2.1 Supraventricular tachycardia

Atrioventricular nodal re-entry tachycardia and atrioventricular re-entry tachycardia

AV nodal re-entry tachycardia or AV re-entry tachycardia involving an accessory pathway can be terminated by vagal manoeuvres or, if that fails, by i.v. adenosine.[191] I.v. adenosine is the first drug of choice if vagal manoeuvres fail to terminate an episode of paroxysmal SVT.[191] I.v. metoprolol is recommended if adenosine fails to terminate a tachycardia. Prophylactic antiarrhythmic drug therapy should be used only if symptoms are intolerable or if the tachycardia causes haemodynamic compromise (*Table 15*). Then digoxin or a selective β-blocking agent (metoprolol) are the first-line agents, followed by sotalol, flecainide, or propafenone.[192] AV nodal blocking agents should not be used in patients with manifest pre-excitation on resting ECG. Catheter ablation should be considered only in special cases if necessary during pregnancy.

Focal atrial tachycardia

Treatment of cases of atrial tachycardia during pregnancy is generally more challenging with respect to their drug-resistant nature, tendency to be persistent, and their association with structural heart disease. Rate control, using β-blocking agents and/or digitalis, should be used to avoid tachycardia-induced cardiomyopathy. Prophylactic antiarrhythmic drug therapy includes flecainide, propafenone, or sotalol for patients with definite symptoms. Amiodarone should be used only if the arrhythmia cannot be controlled with other agents.

Electrical cardioversion is in general not recommended due to recurrence of tachycardia. Approximately 30% of atrial tachycardias may be terminated by adenosine. Catheter ablation should be considered in drug-resistant and poorly tolerated cases.

8.2.2 Atrial flutter and atrial fibrillation

Atrial flutter and AF are very rare during pregnancy unless structural heart disease or hyperthyroidism is present. A rapid ventricular response to these arrhythmias can lead to serious haemodynamic consequences for both the mother and the fetus. Diagnosis and treatment of the underlying condition are therefore the first priorities. Electrical cardioversion should be performed in the case of haemodynamic instability.

In haemodynamically stable patients with structurally normal hearts, pharmacological termination of atrial flutter and AF should be considered. I.v. ibutilide or flecainide is usually effective, and may be considered, but the experience during pregnancy is very limited.[193] Since there is even less or no experience of i.v. propafenone and the new class III antiarrhythmic drug, vernacalant, i.v. for pharmacological conversion of AF during pregnancy, these drugs may only be considered if all other attempts at cardioversion fail. Amiodarone is not recommended, unless other options fail, due to its fetotoxic effects.

Cardioversion of atrial flutter and AF, whether conducted electrically or by drugs, does require prior anticoagulation therapy and/or transoesophageal echocardiographic examination to exclude left atrial thrombus formation.[182] Anticoagulation (warfarin, substituted with UFH or LMWH in the first and last trimester) is considered mandatory for at least 3 weeks before elective cardioversion for AF or atrial flutter of 48 h duration or longer, or when the duration of AF is unknown,[182] and should be continued for at least 4 weeks after cardioversion because of the risk of thrombo-embolism related to so-called 'atrial stunning'.

For patients with AF duration $<$48 h and no thrombo-embolic risk factors, i.v. heparin or weight-adjusted therapeutic dose LMWH may be considered pericardioversion, without the need for post-cardioversion oral anticoagulation. Indications for prophylactic antiarrhythmic drugs and anticoagulation relate to the presence of symptoms and the presence of risk factors for thrombo-embolism, respectively.[182] In patients with risk factors for stroke or AF recurrence, antithrombotic treatment should continue lifelong irrespective of apparent maintenance of sinus rhythm following cardioversion.[182]

Anticoagulation in atrial fibrillation

The thrombo-embolic risk in AF depends upon the presence of risk factors. Patients without structural heart disease or risk factors ('lone atrial fibrillation') have the lowest risk of thrombo-embolic events and do not require anticoagulation or antiplatelet therapy outside of or during pregnancy; however, studies during pregnancy are not available. An increase in thrombo-embolic risk in non-valvular AF is assessed with the CHADS2 criteria[182] and the CHA_2DS_2VASC score[142] in non-pregnant patients. In these, a benefit of oral anticoagulation is documented when the thrombo-embolic risk is $\geq$4.0 events per 100 patient years (correlates to $\geq$2 risk points with the CHADS2 score or 2 risk points with the CHA_2DS_2VASC score). Therefore, also in pregnant patients, thromboprophylaxis is recommended in high risk patients. The choice of the anticoagulant is made according to the stage of pregnancy. Vitamin K antagonists are recommended in most cases from the second trimester until 1 month before expected delivery.[142] Subcutaneous administration of weight-adjusted therapeutic doses of LMWH is recommended during the first trimester and during the last month of pregnancy. The new oral thrombin antagonists such as dabigatran have shown fetotoxicity with high doses and should not be used. Either single or dual antiplatelet therapy (clopidogrel and acetylsalicylic acid) were not as effective as warfarin in high risk patients with atrial fibrillation.[142,194]

Studies in non-pregnant older patients show that LMWH is effective and can be used if appropriate monitoring is available. Subcutaneous administration of weight-adjusted therapeutic doses is recommended during the first trimester and during the last month of pregnancy.

Rate control

Controlling the ventricular rate with AV nodal blocking drugs including digoxin, β-blocking agents, and non-dihydropyridine calcium channel antagonists (verapamil, diltiazem) should be considered.[182] For heart rate control of AF, β-blockers are recommended as first choice. Digoxin can also be used but is less effective during strenuous exercise.[195] Digoxin blood concentrations are unreliable in pregnancy because of interference with immunoreactive serum components.[196] Verapamil should be the drug of second choice.

Prophylactic antiarrhythmic drugs (sotalol, flecainide, or propafenone) may be considered in the case of severe symptoms despite rate-controlling drugs.[182] Flecainide and propafenone should be combined with AV nodal blocking agents. Dronedarone, a new antiarrhythmic drug, should not be used during pregnancy.

8.2.3 Ventricular tachycardia

Life-threatening ventricular arrhythmias during pregnancy are rare. The presence of inherited arrhythmogenic disorders should always be considered by family history and appropriate diagnostic tests during or after pregnancy.[61]

In healthy patients idiopathic right ventricular outflow tract tachycardia is the most frequent type, and should be treated according to established guidelines using either verapamil or a β-blocking agent as prophylaxis if associated with severe

symptoms or haemodynamic compromise.[61,197] Catheter ablation of idiopathic RV outflow tract tachycardia may be considered if associated with haemodynamic compromise and if drug treatment fails.

VT associated with structural heart disease is associated with an increased risk of sudden cardiac death for the mother.[198] PPCM should always be ruled out in women presenting with new-onset ventricular tachycardia during the last 6 weeks of pregnancy or in the early post-partum period.

For acute treatment of VT with haemodynamic instability, immediate cardioversion, which seems safe in all phases of pregnancy, is recommended. Timely restoration of sinus rhythm is desirable even if VT is well tolerated, and can be achieved with cardioversion, anti-arrhythmic medication, or, in selected cases, overdrive pacing. In women with non-long QT-related sustained VT and a stable haemodynamic situation, i.v. sotalol acutely can be considered to terminate the tachycardia. In patients with stable monomorphic VT, i.v. procainamide, although not available in many countries, may be considered. I.v. amiodarone should be considered for patients with sustained monomorphic VT that is haemodynamically unstable, refractory to conversion with countershock, or recurrent despite other agents. I.v. amiodarone is not ideal for early conversion of stable monomorphic VT. Close monitoring of BP is recommended in the presence of LV dysfunction.

Prophylactic therapy with a cardioselective β-blocking agent, such as metoprolol, may be effective. Sotalol or class IC anti-arrhythmic drugs may be considered in the absence of structural heart disease if β-blocking agents are ineffective. Amiodarone and/or ICD implantation should be considered to treat therapy-resistant VT if necessary also during pregnancy for protection of maternal life.[61,199]

In women with the congenital long QT syndrome, the risk of cardiac arrest is greater during the post-partum period compared with before or during pregnancy.[200] β-Blocking agents have a major benefit post-partum but are also recommended during pregnancy in these women.

8.3 Interventional therapy: catheter ablation

Catheter ablation may be necessary in the case of drug-refractory and poorly tolerated tachycardias. Due to the high radiation exposure, ablation should be postponed to the second trimester if possible, and it should be performed at an experienced ablation centre with suitable lead shielding and maximal use of echo- and electro-anatomic mapping systems. Fetal radiation dose and risk from catheter ablation procedures during pregnancy have been calculated[25] (see Section 2.5).

8.4 Implantable cardioverter-defibrillator

The presence of an ICD does not itself contraindicate future pregnancy. Treatment with an ICD should also be considered during pregnancy to protect the mother's life.[61,199] In general, if pregnancy is planned, the implantation of an ICD should be considered in patients with high risk factors for sudden cardiac death.[199]

8.5 Bradyarrhythmias

Bradyarrhythmias and conduction disturbances are rare during pregnancy. Asymptomatic bradyarrhythmias may become symptomatic due to demands of higher heart rate and CO in patients with structural heart disease.[201] However, bradyarrhythmias usually have a favourable outcome in the absence of underlying heart disease.

8.5.1 Sinus node dysfunction

Sinus bradycardia may appear as a reflex cardiac slowing (Valsalva manoeuvre) during delivery. Rare cases of sinus bradycardia have been attributed to the supine hypotensive syndrome of pregnancy, caused by uterine compression of the inferior vena cava blood return with paradoxical sinus slowing. In the rare instance that symptomatic bradycardia occurs, it 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.

8.5.2 Atrioventricular blocks

First-degree AV block can be observed during pregnancy in the absence of underlying heart disease. The site of AV delay is usually located above the bundle of His and does not progress to complete heart block. Second-degree AV block occurs rarely, and is usually associated with structural heart disease or drug therapy. The majority of cases are second-degree type I Wenckebach block, unassociated with symptomatic bradycardias. In patients with congenital heart disease, second-degree block most commonly occurs in cases of repaired tetralogy of Fallot and less often after repair of VSDs.

Acquired complete heart block, most often seen in congenital heart disease after corrective surgery, is rare during pregnancy. Thirty per cent of congenital AV blocks remain undiscovered until adulthood, and may present during pregnancy.[201] Isolated congenital complete heart block has a favourable outcome during pregnancy, especially when the escape rhythm has a narrow QRS complex. Supportive pacing during pregnancy is usually not necessary. Vaginal delivery carries no extra risks in a mother with congenital complete heart block, unless contraindicated for obstetric reasons.

8.5.3 Pacing in pregnancy

Temporary pacing during delivery is recommended in selected women with complete heart block and symptoms due to the risk of bradycardia and syncope.

The risks of permanent pacemaker implantation (preferably one chamber) are generally low. Implantation can be performed safely, especially if the fetus is beyond 8 weeks gestation. Echo guidance may be helpful for implantation.[202]

8.6 Recommendations for the management of arrhythmias

Table 15 Recommendations for the management of arrhythmias

Recommendations	Class[a]	Level[b]
Management of supraventricular tachycardia (SVT)		
For acute conversion of paroxysmal SVT, vagal manoeuvre followed by i.v. adenosine is recommended.	I	C
Immediate electrical cardioversion is recommended for acute treatment of any tachycardia with haemodynamic instability.	I	C
For long-term management of SVT oral digoxin[c] or metoprolol/propranolol[c,d], is recommended.	I	C
For acute conversion of paroxysmal SVT, i.v. metoprolol or propranolol should be considered.	IIa	C
For long-term management of SVT, oral sotalol[e] or flecainide[f] should be considered if digoxin or a β-blocking agent fails.	IIa	C
For acute conversion of paroxysmal SVT, i.v. verapamil may be considered.	IIb	C
For long-term management of SVT, oral propafenone[f], or procainamide may be considered as a last option if other suggested agents fail and before amiodarone[e] is used.	IIb	C
For long-term management of SVT, oral verapamil[c] may be considered for rate regulation if the other AV nodal-blocking agents fail.	IIb	C
Atenolol[d] should not be used for any arrhythmia.	III	C
Management of ventricular tachycardia (VT)		
The implantation of an ICD, if clinically indicated, is recommended prior to pregnancy but is also recommended whenever indicated, during pregnancy.	I	C
For long-term management of the congenital long QT syndrome, β-blocking agents are recommended during pregnancy and also postpartum when they have a major benefit.	I	C
For long-term management of idiopathic sustained VT oral metoprolol[c,d], propranolol[c,d] or verapamil[c,f] is recommended.	I	C
Immediate electrical cardioversion of VT is recommended for sustained, unstable, and stable VT.	I	C
For acute conversion of VT that is sustained, haemodynamically stable, and monomorphic, i.v. sotalol[e] or procainamide should be considered.	IIa	C
Implantation of permanent pacemakers or ICDs (preferably one chamber) should be considered with echocardiographical guidance, especially if the fetus is beyond 8 weeks gestation.	IIa	C
For acute conversion of VT that is sustained, monomorphic, haemodynamically unstable, refractory to electrical cardioversion or not responding to other drugs, i.v. amiodarone[e] should be considered.	IIa	C
For long-term management of idiopathic sustained VT oral sotalol[e], flecainide[f], propafenone[f] should be considered if other drugs fail.	IIa	C
Catheter ablation may be considered in the case of drug-refractory and poorly tolerated tachycardias.	IIb	C

For drug dosing information, please refer to three published guidelines on the management of patients with atrial fibrillation, supraventricular arrhythmias, and ventricular arrhythmias.[61,142,192]
[a]Class of recommendation.
[b]Level of evidence.
[c]AV nodal blocking agents should not be used in patients with pre-excitation on resting ECG.
[d]β-Blocking agents should be used with caution in the first trimester; see Section 11.
[e]Class III drugs should not be used in cases with prolonged QTc.
[f]Consider AV nodal blocking agents in conjunction with flecainide and propafenone for certain atrial tachycardias.
AV = atrioventricular; ECG, electrocardiogram; ICD = implantable cardioverter-defibrillator; i.v. = intravenous; SVT = supraventricular tachycardia; VT = ventricular tachycardia.

9. Hypertensive disorders

Hypertensive disorders in pregnancy remain a major cause of maternal, fetal, and neonatal morbidity and mortality in developing and in developed countries. These women are at higher risk for severe complications such as abruptio placentae, cerebrovascular accident, organ failure, and disseminated intravascular coagulation. The fetus is at risk for intrauterine growth retardation, prematurity, and intrauterine death. Hypertension is the most common medical problem in pregnancy, complicating up to 15% of pregnancies and accounting for about a quarter of all antenatal admissions.[203]

9.1 Diagnosis and risk assessment

High BP readings should be confirmed on two occasions,[204] using mercury sphygmomanometry (Korotkoff V for reading DBP) in the sitting position, or an aneroid device. BP measurements in the left lateral recumbency are a reasonable alternative. Only validated measuring devices and validated ambulatory BP monitoring (ABPM) devices should be used (see: www.dableducational.org). Hypertension in pregnancy, as diagnosed by ABPM, is superior to the office measurement of BP in predicting outcomes.[205,206]

Basic laboratory investigations recommended for monitoring pregnant patients with hypertension include urinalysis, blood count, haematocrit, liver enzymes, serum creatinine, and serum uric acid. Proteinuria should be standardized in 24 h urine collection (if >2 g/day, close monitoring is warranted; if >3 g/day, delivery should be considered). Ultrasound investigation of the adrenals and urine metanephrine and normetanephrine assays may be considered in pregnant women with hypertension to exclude pheochromocytoma which may be asymptomatic and, if not diagnosed before labour, fatal.[207] Doppler ultrasound of uterine arteries, performed during the second trimester (>16 weeks), is useful to detect uteroplacental hypoperfusion, which is associated with a higher risk of pre-eclampsia and intrauterine growth retardation, in both high risk and low risk women.[208]

9.2 Definition and classification of hypertension in pregnancy

The definition of hypertension in pregnancy is based on absolute BP values (SBP ≥140 mmHg or DBP ≥90 mmHg).[209,210] and distinguishes mildly (140–159/90–109 mmHg) or severely (≥160/110 mmHg) elevated BP, in contrast to the grades used by the European Society of Hypertension (ESH)/ESC,[210] or others.[211]

Hypertension in pregnancy is not a single entity but comprises:[212]

- pre-existing hypertension
- gestational hypertension
- pre-existing hypertension plus superimposed gestational hypertension with proteinuria
- antenatally unclassifiable hypertension.

9.2.1 Pre-existing hypertension

Pre-existing hypertension complicates 1–5% of pregnancies and is defined as BP ≥140/90 mmHg that either precedes pregnancy or develops before 20 weeks of gestation. Hypertension usually persists >42 days post-partum. It may be associated with proteinuria.

Undiagnosed hypertensive women may appear normotensive in early pregnancy because of the physiological BP fall commencing in the first trimester. This may mask the pre-existing hypertension and, when hypertension is recorded later in pregnancy, it may be interpreted as gestational.

9.2.2 Gestational hypertension

Gestational hypertension is pregnancy-induced hypertension with or without proteinuria, and complicates 6–7% of pregnancies. It is associated with clinically significant proteinuria (≥0.3 g/day in a 24 h urine collection or ≥30 mg/mmol urinary creatinine in a spot random urine sample) and is then known as pre-eclampsia. Gestational hypertension develops after 20 weeks gestation and resolves in most cases within 42 days post-partum. It is characterized by poor organ perfusion.

Pre-eclampsia is a pregnancy-specific syndrome that occurs after mid-gestation, defined by the *de novo* appearance of hypertension, accompanied by new-onset of significant proteinuria >0.3 g/24 h. It is a systemic disorder with both maternal and fetal manifestations. Oedema is no longer considered part of the diagnostic criteria, as it occurs in up to 60% of normal pregnancies. Overall, pre-eclampsia complicates 5–7% of pregnancies,[213] but increases to 25% in women with pre-existing hypertension. Pre-eclampsia occurs more frequently during the first pregnancy, in multiple fetuses, hydatidiform mole, or diabetes. It is associated with placental insufficiency, often resulting in fetal growth restriction. Additionally, pre-eclampsia is one of the most common causes of prematurity, accounting for 25% of all infants with very low birth weight (<1500 g).[214]

Symptoms and signs of severe pre-eclampsia include:

- right upper quadrant/epigastric pain due to liver oedema ± hepatic haemorrhage
- headache ± visual disturbance (cerebral oedema)
- occipital lobe blindness
- hyperreflexia ± clonus
- convulsions (cerebral oedema)
- HELLP syndrome: haemolysis, elevated liver enzymes, low platelet count.

Management of pre-eclampsia focuses essentially on recognition of the condition and, ultimately, delivery of the placenta, which is curative.

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 platelet count and abnormal liver enzymes; it is recommended to treat such patients as having pre-eclampsia.

9.2.3 Pre-existing hypertension plus superimposed gestational hypertension with proteinuria

When pre-existing hypertension is associated with further worsening of BP and protein excretion ≥3 g/day in 24 h urine collection after 20 weeks gestation, it is classified as 'pre-existing hypertension plus superimposed gestational hypertension with proteinuria'.

9.2.4 Antenatally unclassifiable hypertension

When BP is first recorded after 20 weeks gestation and hypertension (with or without systemic manifestation) is diagnosed, it is antenatally unclassifiable hypertension. Re-assessment is necessary at or after 42 days post-partum.

9.3 Management of hypertension in pregnancy

The majority of women with pre-existing hypertension in pregnancy have mild to moderate hypertension (140–160/90–

109 mmHg), and are at low risk for cardiovascular complications within the short time frame of pregnancy. Women with essential hypertension and normal renal function have good maternal and neonatal outcomes and are candidates for non-drug therapy because there is no evidence that pharmacological treatment results in improved neonatal outcome. Some women with treated pre-existing hypertension are able to stop their medication in the first half of pregnancy because of the physiological fall in BP during this period. However, close monitoring and, if necessary, resumption of treatment is necessary.

The only trial of treatment of hypertension in pregnancy with adequate infant follow-up (7.5 years) was performed >30 years ago with α-methyldopa.[215,216]

9.4 Non-pharmacological management and prevention of hypertension in pregnancy

Non-pharmacological management should be considered for pregnant women with SBP of 140–150 mmHg or DBP of 90–99 mmHg, or both. A short-term hospital stay may be required for confirming the diagnosis of and ruling out severe gestational hypertension (pre-eclampsia), in which the only effective treatment is delivery. Management depends on BP, gestational age, and the presence of associated maternal and fetal risk factors, and includes close supervision, limitation of activities, and some bed rest in the left lateral position. A normal diet without salt restriction is advised, particularly close to delivery, as salt restriction may induce low intravascular volume. Calcium supplementation of at least 1 g daily during pregnancy almost halved the risk of pre-eclampsia without causing any harm. The effect was greatest for high risk women.[217] However, the evidence for added calcium in the prevention of hypertensive disorders is conflicting. Fish oil supplementation[218] as well as vitamin and nutrient supplements have no role in the prevention of hypertensive disorders. Low dose acetylsalicylic acid (75–100 mg/day) is used prophylactically in women with a history of early-onset (<28 weeks) pre-eclampsia.[219] It should be administered at bedtime, starting pre-pregnancy or from diagnosis of pregnancy, but before 16 weeks gestation, and should be continued until delivery. Weight reduction is not recommended during pregnancy in obese women, because it can lead to reduced neonatal weight and slower subsequent growth in infants of dieting obese mothers. However, as maternal obesity can result in negative outcomes for both women and fetuses, guidelines for healthy ranges of weight gain in pregnancy have been established. In pregnant women with normal body mass index (BMI <25 kg/m^2), the recommended weight gain is 11.2–15.9 kg; for overweight pregnant women (BMI 25.0–29.9 kg/m^2) it is 6.8–11.2 kg; and for obese pregnant women (BMI ≥30 kg/m^2) the recommended weight gain is <6.8 kg.[220]

9.5 Pharmacological management of hypertension in pregnancy

Drug treatment of severe hypertension in pregnancy is required and beneficial, yet treatment of less severe hypertension is controversial. Although it might be beneficial for the mother with hypertension to reduce her BP, a lower BP may impair uteroplacental perfusion and thereby jeopardize fetal development.

Women with pre-existing hypertension may continue their current medication except for ACE inhibitors, ARBs, and direct renin inhibitors, which are strictly contraindicated in pregnancy because of severe fetotoxicity, particularly in the second and third trimesters (*Table 21*). If taken inadvertently during the first trimester, switching to another medication and close monitoring including fetal ultrasound are advisable and usually are sufficient.

α-Methyldopa is the drug of choice for long-term treatment of hypertension during pregnancy.[216] The α-/β-blocker labetalol has efficacy comparable with methyldopa. If there is severe hypertension it can be given i.v. Metoprolol is also recommended.[221] Calcium channel blockers such as nifedipine (oral) or isradipine (i.v.) are drugs of second choice for hypertension treatment.[222] These drugs can be administered in hypertensive emergencies or in hypertension caused by pre-eclampsia. Potential synergism with magnesium sulfate may induce maternal hypotension and fetal hypoxia. Urapidil can also be selected for hypertensive emergencies. Magnesium sulfate i.v. is the drug of choice for treatment of seizures and prevention of eclampsia. Diuretics should be avoided for treatment of hypertension because they may decrease blood flow in the placenta. They are not recommended in pre-eclampsia.

9.5.1 Treatment of mild to moderate hypertension

The benefits and risks of antihypertensive therapy for mild to moderate hypertension (defined as SBP of 140–169 mmHg and DBP of 90–109 mmHg) are still controversially discussed. Current ESH/ESC guidelines[210] recommend as the thresholds for antihypertensive treatment an SBP of 140 mmHg or a DBP of 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.

In any other circumstances, the ESH/ESC thresholds are an SBP of 150 mmHg and a DBP of 95 mmHg. This Task Force recommends following these guidelines.

9.5.2 Treatment of severe hypertension

There is also no agreement on the definition of severe hypertension, with values ranging between 160 and 180 mmHg/> 110 mmHg. This Task Force recommends considering an SBP ≥170 mmHg or DBP ≥110 mmHg in a pregnant woman as an emergency, and hospitalization is indicated. The selection of the antihypertensive drug and its route of administration depend on the expected time of delivery. Pharmacological treatment with i.v. labetalol, or 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. The drug of choice in hypertensive crises is sodium nitroprusside given as an i.v. infusion at 0.25–5.0 μg/kg/min. Prolonged treatment with sodium nitroprusside is associated with an increased risk of fetal cyanide poisoning as nitroprusside is

metabolized into thiocyanate and excreted into urine.[223] The drug of choice in pre-eclampsia associated with pulmonary oedema is nitroglycerine (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.

Delivery

Induction of delivery is indicated in gestational hypertension with proteinuria with adverse conditions such as visual disturbances, coagulation abnormalities, or fetal distress.

Breastfeeding

Breastfeeding does not increase BP in the nursing mother. Bromocriptine, which is used to suppress lactation, may induce hypertension.[224] All antihypertensive agents taken by the nursing mother are excreted into breast milk. Most of the antihypertensive drugs are present at very low concentrations, except for propranolol and nifedipine, whose concentrations in breast milk are similar to those in maternal plasma.

9.6 Prognosis after pregnancy

9.6.1 Blood pressure post-partum

Post-partum hypertension is common. BP usually rises after delivery over the first 5 days. Hypertensive women during pregnancy may be normotensive after birth but then become hypertensive again in the first postnatal week. Methyldopa should be avoided post-partum because of the risk of post-natal depression.

9.6.2 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.[225] The earlier the onset of hypertension in the first pregnancy, the greater the risk of recurrence.[226]

9.6.3 Long-term cardiovascular consequences in pregnancy-induced hypertension

Women who develop gestational hypertension or pre-eclampsia are at increased risk of hypertension and stroke in later adult life.[227] as well as of ischaemic heart disease.[228,229] The relative risk of developing ischaemic heart disease after pre-eclampsia is more than twice as high compared with women with normal pregnancies, and the risk of developing hypertension is almost fourfold.[229] Women with early-onset pre-eclampsia (delivery before 32 weeks of gestation), with stillbirth, or fetal growth retardation are considered to be at highest risk.[229] Risk factors before pregnancy for the development of hypertensive disorders are high maternal age, elevated BP, dyslipidaemia, obesity, positive family history, antiphospholipid syndrome, and glucose intolerance. Hypertensive disorders in pregnancy have been recognized as an important risk factor for CVD in women.[230] Therefore, lifestyle modifications, regular BP control, and control of metabolic factors are recommended after delivery, to avoid complications in subsequent pregnancies and to reduce maternal cardiovascular risk in the future.

9.7 Recommendations for the management of hypertension

Table 16 Recommendations for the management of hypertension

Recommendations	Class[a]	Level[b]
Non-pharmacological management for pregnant women with SBP of 140-150 mmHg or DBP of 90-99 mmHg is recommended.	I	C
In women with gestational hypertension or pre-existing hypertension superimposed by gestational hypertension or with hypertension and subclinical organ damage or symptoms at any time during pregnancy, initiation of drug treatment is recommended at a BP of 140/90 mmHg. In any other circumstances, initiation of drug treatment is recommended if SBP ≥150 mmHg or DBP ≥95 mmHg.	I	C
SBP ≥170 mmHg or DBP ≥110 mmHg in a pregnant woman is an emergency, and hospitalization is recommended.	I	C
Induction of delivery is recommended in gestational hypertension with proteinuria with adverse conditions such as visual disturbances, coagulation abnormalities, or fetal distress.	I	C
In pre-eclampsia associated with pulmonary oedema, nitroglycerine given as an intravenous infusion, is recommended.	I	C
In severe hypertension, drug treatment with intravenous labetalol or oral methyldopa or nifedipine is recommended.	I	C
Women with pre-existing hypertension should be considered to continue their current medication except for ACE inhibitors, ARBs, and direct renin inhibitors under close BP-monitoring	IIa	C

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

10. Venous thrombo-embolism during pregnancy and the puerperium

10.1 Epidemiology and maternal risk

Pregnancy and the puerperium are associated with an increased incidence of venous thrombo-embolism (VTE), occurring in ~0.05–0.20% of all pregnancies.[231–235] VTE encompassing pulmonary embolism and deep vein thrombosis (DVT) represents a significant cause of pregnancy-related morbidity and mortality. Pulmonary embolism is the most common cause of direct maternal death in the UK, with an incidence of 1.56 deaths per 100 000 pregnancies, and the second most common cause of maternal death overall.[9] The case fatality rate

is 3.5%.[236] The risk of VTE is highest in the immediate post-partum period,[232] particularly after caesarean section,[235] and returns to the non-pregnant level after the sixth week post-partum.[231,232]

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

Table 17 Check list for risk factors for venous thrombo-embolism modified according to the Royal College of Obstetricians and Gynaecologists[238]

Pre-existing risk factors
Previous recurrent VTE[a]
Previous VTE—unprovoked or oestrogen related[b]
Previous VTE—provoked
Family history of VTE
Known thrombophilia[c]
Medical co-morbidities, e.g. heart or lung diseases, SLE, cancer, inflammatory conditions, nephritic syndrome, sickle cell disease, i.v. drug use
Age >35 years
Obesity, BMI >30 kg/m^2 [d]
Parity ≥3
Smoker
Gross varicous veins
Obstetric risk factors
Pre-eclampsia
Dyhydration/hyperemesis/ovarian hyperstimulation syndrome
Multiple pregnancy or assisted reproductive therapy
Emergency caesarean section
Elective caesarean section
Mid-cavity or rotational forceps
Prolonged labour (>24 hours)
Peripartum haemorrhage (>1 L or transfusion)
Transient risk factors
Current systemic infection
Immobility
Surgical procedure in pregnancy or <6 weeks post-partum

[a]Patients with previous recurrent VTEs (>1), or those with [b]a previous unprovoked or oestrogen-related VTE belong to the high risk group (see *Table 19*).
[c]See *Table 18*.
[d]Obesity based on booking weight.
Example: in a pregnant woman with a family history of VTE, age >35 years, and obesity (BMI > 30 kg/m^2, the total number of risk factors is 3. This patient belongs to the intermediate risk group and requires VTE prophylaxis accordingly (see *Table 19*).
BMI = body mass index; i.v. = intravenous; SLE = systemic lupus erythematosus; VTE = venous trombo-embolism.

Table 18 Prevalence of congenital thrombophilia and the associated risk of venous thrombo-embolism during pregnancy in a European population based on Marik and Plante[239]

Risk factor	Prevalence (%)	Odds ratio (confidence interval)
Factor V Leiden mutation		
Heterozygous	2.0–7.0	8.32 (5.44,12,70)
Homozygous	0.2–0.5	34.40 (9.86, 120.05)
Prothrombin G20210A mutation		
Heterozygous	2.0	6.80 (2.46, 18.77)
Homozygous	Rare	26.36 (1.24, 559.29)
Antithrombin deficiency (<80% activity)	<0.1–0.6	4.76 (2.15, 10.57)
Protein C deficiency (<75% activity)	0.2–0.3	4.76 (2.15, 10.57)
Protein S deficiency (<65% activity)	<0.1–0.1	2.19 (1.48, 6.00)

The presence of risk factors (see *Tables 17* and *18*) contributes to the increased risk of VTE during pregnancy and the puerperium. Seventy nine percent of women dying from an antenatal pulmonary embolism in the UK had identifiable risk factors.[9,236] The most significant risk factors for VTE in pregnancy are a prior history of unprovoked DVT or pulmonary embolism[237] and thrombophilias (*Table 18*). From 15% to 25% of VTEs are recurrent events. Half of the women who develop a thrombotic event during pregnancy have either a thrombophilic disorder or a previous idiopathic VTE.

Therefore, identification of risk factors in the individual patient is important for risk assessment and choice of preventive strategies. All women should undergo a documented assessment of risk factors for VTE before pregnancy or in early pregnancy. *Table 17* provides a suggested checklist for documentation of this risk assessment.[238] On the basis of the type and the total number of risk factors present in the individual patient, three risk groups can be identified (high, intermediate, and low risk groups) and preventive measures applied accordingly (see *Table 19*).[238] Previous recurrent VTEs and previous VTE—unprovoked or oestrogen related—are considered high risk factors. The exact influence of the other single risk factors or the summation of several risk factors on total VTE risk is not known.

10.3 Prevention of venous thrombo-embolism

Prospective, non-randomized studies showed that in women with risk factors not receiving anticoagulation the recurrence rate of

VTE ranged from 2.4% to 12.2%, in comparison with 0–2.4% in patients who did receive anticoagulation.[241]

LMWH has become the drug of choice for the prophylaxis and treatment of VTE in pregnant patients.[242] It causes less bone loss than UFH, and the osteoporotic fracture rate is lower (0.04% of pregnant women treated with LMWH).[242]

The dose of LMWH for thromboprophylaxis is based on the booking weight. There are no data to guide appropriate doses of LMWH for pregnant women who are obese or puerperal. It is agreed that women of higher weights should receive higher doses, but there are no studies available on the optimal dose and weight ranges. Patients at high risk for VTE (see *Table 19*) should receive the usual prophylactic dose of 0.5 IU /kg body weight of enoxaparin or 50 IU/kg body weight dalteparin twice daily.

10.4 Management of acute venous thrombo-embolism

10.4.1 Pulmonary embolism

Clinical presentation

The clinical symptoms and signs of pulmonary embolism during pregnancy are the same as in the non-pregnant state (dyspnoea, chest pain, tachycardia, haemoptysis, and collapse). Subjective clinical assessment of pulmonary embolism is, however, more difficult, because dyspnoea and tachycardia are not uncommon in normal pregnancy.

Diagnosis

Clinical prediction rules for assigning pre-test probabilities of VTE have been validated in the non-pregnant patient, as well as the use of D-dimer testing, compression ultrasonography, and computed tomographic pulmonary angiography (CTPA) and ventilation perfusion lung scanning for pulmonary embolism diagnosis.[243] This is not the case in pregnant women.[244] Also the diagnostic algorithms which are well established for the diagnosis of VTE in the general population have not been validated in the pregnant patient. This complicates recommendations and calls urgently for multicentre, prospective studies. A high index of suspicion is important for the timely diagnosis of VTE. All pregnant women with signs and symptoms suggestive of VTE, particularly dyspnoea of acute onset or worsening, should have objective testing performed expeditiously as in non-pregnant patients.

D-Dimer and compression ultrasonography. D-Dimer levels increase physiologically with each trimester. In one study the mean pre-conception D-dimer concentration was 0.43 (SD 0.49) mg/L, and rose in the first, second, and third trimester to 0.58 mg/L (SD 0.36), 0.83 (SD 0.46) mg/L, and 1.16 (SD 0.57) mg/L, respectively, indicating a 39% relative increase in D-dimer concentration for each trimester compared with the previous one.[245] Thus a positive D-dimer test based on the conventional cut-off level is not necessarily indicative of VTE and new cut-off levels are needed. Further objective testing is required.

Table 19 Risk groups according to risk factors, definition and preventive measures modified according to the Royal College of Obstetricians and Gynaecologists[238]

Risk groups	Definition according to risk factors listed in *Table 17*	Preventive measures according to risk group
High risk	Patients with: (i) Previous recurrent VTE (>1) or (ii) VTE unprovoked / oestrogen–related or (iii) Single previous VTE + thrombophilia or family history	High risk patients should receive antenatal prophylaxis with LMWH as well as post-partum for the duration of 6 weeks. Graduated compression stockings are also recommended during pregnancy and post-partum.
Intermediate risk	Patients with: (i) 3 or more risk factors other than listed above as high risk (ii) 2 or more risk factors other than listed as high risk if patient is admitted to hospital	In intermediate risk patients antenatal prophylaxis with LMWH should be considered. Prophylaxis is recommended postpartum for at least 7 days or longer, if >3 risk factors persist. Graduated compression stockings should be considered during pregnancy and postpartum.
Low risk	Patients with: <3 risk factors.	In low risk patients early mobilization and avoidance of dehydration is recommended.

Several risk scores for identification of patients at different risk levels have been developed,[240] yet all risk scores, including the above, still need validation in prospective studies.
LMWH = low molecular weight heparin; VTE, venous thrombo-embolism.

However, a negative D-dimer test is helpful to exclude VTE, although there are a few cases of VTE reported with normal D-dimer concentrations.[246] The recommendation to measure D-dimer levels in all pregnant women with the clinical suspicion of VTE is still controversial.[243] Yet it is the consensus of this Task Force that the D-dimer concentration should be measured in patients with suspected pulmonary embolism, followed by bilateral compression ultrasonography. If this is normal in the presence of negative D-dimer levels, then pulmonary embolism is unlikely and anticoagulation with LMWH is not warranted.

In patients with suspected pulmonary embolism, positive D-dimer levels and positive compression ultrasonography, anticoagulation treatment is indicated. If D-dimer levels are elevated and compression ultrasonography is negative in patients with suspected pulmonary embolism, further testing is required. MRI does not involve radiation exposure, is probably not harmful to the fetus, and has a high sensitivity and specificity for the diagnosis of iliac vein thrombosis. CT pulmonary angiography should be performed, when the diagnosis cannot be confirmed or excluded with the above-discussed tools. In these patients it is preferred over ventilation–perfusion lung scanning for the diagnosis of pulmonary embolism[243]; both are associated with fetal radiation exposure, with ventilation–perfusion lung scanning delivering a higher fetal dose of radiation than CT pulmonary angiography (see *Table 3* in Secion 2). However, radiation doses are below the limit that is regarded as dangerous for the fetus.[243,247]

Treatment

LMWH. LMWH has also become the drug of choice for the treatment of VTE in pregnancy and puerperium. The efficacy and safety of several LMWH preparations was shown in a review of 2777 pregnant women, treated for DVT or pulmonary embolism. The risk of recurrent VTE with treatment 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%).[242] In clinically suspected DVT or pulmonary embolism, treatment with LMWH should be given until the diagnosis is excluded by objective testing.

Dosage. The recommended therapeutic dose is calculated on body weight (e.g. enoxaparin 1 mg/kg body weight twice daily, Dalteparin 100 IU/kg body weight twice daily) aiming for 4–6 h peak anti-Xa values of 0.6–1.2 IU/mL.[248]

Monitoring. The necessity to monitor anti-Xa values regularly in patients with VTE is still controversial. Whereas it is considered necessary in patients with mechanical valves in whom LMWH is used (see Section 5), this is not so clear in patients with VTE. Given the need for dose increase as pregnancy progresses to maintain a certain therapeutic anti-Xa level,[153,154] it seems reasonable to determine anti-Xa levels also during pregnancy in patients with VTE. This appears particularly justified in view of the fact that pulmonary embolism occurred in women receiving preventive doses of LMWH.[236] This topic also requires further studies. A simple guide is dose adjustment according to increasing weight during pregnancy.

UFH. UFH also does not cross the placenta, but is associated with more thrombocytopenia, osteoporosis, and more frequent dosing when given subcutaneously compared with LMWH. It is favoured in patients with renal failure and when urgent reversal of anticoagulation by protamine is needed, as well as in the acute treatment of massive pulmonary emboli.

Dosage. In patients with acute pulmonary embolism with haemodynamic compromise, i.v. administration of UFH is recommended (loading dose of 80 U/kg, followed by a continuous i.v infusion of 18 U/kg/h).

Monitoring. The aPTT has to be determined 4–6 h after the loading dose, 6 h after any dose change, and then at least daily when in the therapeutic range. The therapeutic target aPTT ratio is usually 1.5–2.5 times the average laboratory control value. The dose is then titrated to achieve a therapeutic aPTT, defined as the aPTT that corresponds to an anti-Xa level of 0.3–0.7 IU/mL. When haemodynamics are improved and the patient is stabilized, UFH can be switched to LMWH in therapeutic doses and maintained during pregnancy. LMWH should be switched to i.v. UFH at least 36 h before the induction of labour or caesarean delivery. UFH should be discontinued 4–6 h before anticipated delivery, and restarted 6 h after delivery if there are no bleeding complications. Neither UFH nor LWMH is found in breast milk in any significant amount and they do not represent a contraindication to breastfeeding.

Thrombolysis. 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.[243] The risk of haemorrhage, mostly from the genital tract, is ~8%.[249] In ~200 reported patients, mostly streptokinase was used and, more recently, recombinant tissue plasminogen activator. Both thrombolytics do not cross the placenta in significant amounts. Fetal loss of 6% and 6% pre-term delivery were reported.[250] 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 for the residual duration of pregnancy.

Fondaparinux. There are very few studies on fondaparinux in pregnancy; one has shown minor transplacental passage of fondaparinux.[251] Because of the scarce data, the drug should not be used in pregnancy (see Section 11).

Rivaroxaban. Rivaroxaban crosses the placental barrier and has therefore not been evaluated, and is not recommended in pregnant patients.

Vena cava filters. Indications for vena cava filters are the same as in non-pregnant patients. However, the risk associated with the procedure may be increased.[243,250]

Post-partum management

In patients with recent pulmonary embolism, pre-partum 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 vitamin K antagonists for at least 5 days. Vitamin K antagonists may be started on the second day after delivery and continued for at least 3 months or for 6 months if pulmonary embolism occurred late in pregnancy. The INR should be between 2 and 3 and needs regular monitoring, ideally once every 1–2 weeks. Vitamin K antagonists do not enter the breast milk in active forms and are safe for nursing mothers.

10.4.2 Acute deep vein thrombosis

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 right iliac artery and the gravid uterus, specifically swelling of the left leg is suspicious. Isolated iliac vein thrombosis may manifest with isolated pain in the buttock, groin, flank, or abdomen. A clinical decision rule, considering three 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.[86] This clinical decision rule needs validation in prospective studies.

Diagnosis

D-Dimer. See diagnosis of pulmonary embolism.

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, yet less for distal DVT and DVT in the vasculature of the pelvis. Serial compression ultrasound evaluations at days 0, 3, and 7 in pregnancy gives a high negative predictive value of 99.5% (95% CI 97–99% %).[240]

All women with suspected DVT in pregnancy should be assessed for pre-test probability, have D-dimer testing, and then undergo compression ultrasonography.

If a proximal DVT is detected, treatment should be continued. In women with a high pre-test probability, a positive D-dimer and a normal initial compression ultrasound magnetic resonance venography may be considered to exclude isolated pelvic DVT. Women with low pre-test probability and normal D-dimer should undergo serial compression ultrasonography on day 3 and after 1 week without anticoagulation. When compression ultrasonography remains negative, DVT can be excluded.

Treatment

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

10.5 Recommendations for the prevention and management of venous thrombo-embolism in pregnancy and puerperium

Table 20 Recommendations for the prevention and management of venous thrombo-embolism in pregnancy and puerperium

Recommendations	Class[a]	Level[b]
In all women who are pregnant or consider pregnancy, assessment of risk factors for VTE is recommended.	I	C
Mothers should be informed about the signs and symptoms of VTE in pregnancy and the necessity to contact the physicians if they occur.	I	C
High risk patients[c] should receive antenatal prophylaxis with LMWH as well as post-partum for the duration of 6 weeks.	I	C
In intermediate risk patients[d] post-partum prophylaxis with LMWH should be given for at least 7 days or longer, if >3 risk factors persist.	I	C
In low risk patients[e] early mobilization and avoidance of dehydration is recommended.	I	C
Graduated compression stockings are recommended antepartum and post-partum in all women at high risk.	I	C
D-Dimer measurement and compression ultrasonography is recommended in patients with suspected VTE during pregnancy.	I	C
For treatment of acute VTE during pregnancy, UFH is recommended in high-risk and LMWH in non-high risk patients.	I	C
Graduated compression stockings should be considered in women with intermediate risk during pregnancy and post-partum.	IIa	C
In intermediate risk patients, antenatal prophylaxis with LMWH should be considered.	IIa	C
Routine screening for thrombophilia should not be performed.	III	C

[a]Class of recommendation.
[b]Level of evidence.
LMWH = low molecular weight heparin; UFH, unfractionated heparin; VTE = venous thrombo-embolism.
For definitions of high risk[c], intermediate risk[d], and low risk[e], see *Table 19*.

11. Drugs during pregnancy and breastfeeding

11.1 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 selection of

medications. As drug treatment in pregnancy concerns the mother and the fetus, 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 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.

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

11.1.1 US Food and Drug Administration classification

This classification has been published by the US Department of Health and Human Services. (Source: Drug Information for the Health Care Professional; USDPI Vol 1, Micromedex 23rd edn., 01.01.2003). Adapted and modified from Bonow *et al.*[46]

The classification consists of category A (safest) to X (known danger—do not use!). The following categories are used for drugs during pregnancy and breastfeeding.

Category B: either animal reproduction studies have not demonstrated a fetal 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 fetus 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 fetus.

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

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

11.1.2 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 opinions, mainly based on observational data, and personal experiences of women during pregnancy and the time of breastfeeding.

The English database www.safefetus.com is arranged quite similarly to the German database.

11.1.3 Pharmaceutical industry

The 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.

11.2 Recommendations for drug use

Table 21 Recommendations for drug use

Drugs	Classification (Vaughan Williams for AA drugs)	FDA category	Placenta permeable	Transfer to breast milk (fetal dose)	Adverse effects
Abciximab	Monoclonal antibody with antithrombotic effects	C	Unknown	Unknown	Inadequate human studies; should be given only if the potential benefit outweighs the potential risk to the fetus.
Acenocoumarol[a]	Vitamin K antagonist	D	Yes	Yes (no adverse effects reported)	Embryopathy (mainly first trimester), bleeding (see further discussion in Section 5 for use during pregnancy).
Acetylsalicylic acid (low dose)	Antiplatelet drug	B	Yes	Well-tolerated	No teratogenic effects known (large datasets).
Adenosine[b]	Antiarrhythmic	C	No	No	No fetal adverse effects reported (limited human data).
Aliskiren	Renin inhibitor	D	Unknown	Unknown	Unknown (limited experience).
Amiodarone	Antiarrhythmic (Class III)	D	Yes	Yes	Thyroid insufficiency (9%), hyperthyroidism, goitre, bradycardia, growth retardation, premature birth.
Ampicillin, amoxicillin, cephalosporins, erythromycin, mezlocillin, penicillin	Antibiotics	B	Yes	Yes	No fetal adverse effects reported.

Continued

Table 21 *Continued*

Drugs	Classification (Vaughan Williams for AA drugs)	FDA category	Placenta permeable	Transfer to breast milk (fetal dose)	Adverse effects
Imipenem, rifampicin, teicoplanin, vancomycin	Antibiotics	C	Unknown	Unknown	Risk cannot be excluded (limited human data).
Aminoglycosides, quinolones tetracyclines	Antibiotics	D	Unknown	Unknown	Risk to the fetus exists (reserved for vital indications).
Atenolol[c]	β-blocker (class II)	D	Yes	Yes	Hypospadias (first trimester); birth defects, low birth weight, bradycardia and hypoglycaemia in fetus (second and third trimester).
Benazepril[d]	ACE inhibitor	D	Yes	Yes[e] (maximum 1.6%)	Renal or tubular dysplasia, oligohydramnion, growth retardation, ossification disorders of skull, lung hypoplasia, contractures, large joints, anaemia, intrauterine fetal death.
Bisoprolol	β-blocker (class II)	C	Yes	Yes	Bradycardia and hypoglycaemia in fetus.
Candesartan	Angiotensin II receptor blocker	D	Unknown	Unknown; not recommended	Renal or tubular dysplasia, oligohydramnion, growth retardation, ossification disorders of skull, lung hypoplasia, contractures, large joints, anaemia, intrauterine fetal death.
Captopril[d]	ACE inhibitor	D	Yes	Yes[e] (maximum 1.6%)	Renal or tubular dysplasia, oligohydramnion, growth retardation, ossification disorders of skull, lung hypoplasia, contractures, large joints, anaemia, intrauterine fetal death.
Clopidogrel	Antiplatelet drug	C	Unknown	Unknown	No information during pregnancy available.
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).
Danaparoid	Anticoagulant	B	No	No	No side effects (limited human data).
Digoxin[f]	Cardiac glycoside	C	Yes	Yes[e]	Serum levels unreliable, safe.
Diltiazem	Calcium channel blocker (class IV)	C	No	Yes[e]	Possible teratogenic effects.
Disopyramide	Antiarrhythmic (class IA)	C	Yes	Yes[e]	Uterus contraction.
Enalapril[d]	ACE inhibitor	D	Yes	Yes[e] (maximum 1.6%)	Renal or tubular dysplasia, oligohydramnion, growth retardation, ossification disorders of skull, lung hypoplasia, contractures, large joints, anaemia, intrauterine fetal death.
Eplerenone	Aldosterone antagonist	-	Unknown	Unknown	Unknown (limited experience).
Fenofibrate	Lipid-lowering drug	C	Yes	Yes	No adequate human data.
Flecainide	Antiarrhythmic (class IC)	C	Yes	Yes[e]	Unknown (limited experience).
Fondaparinux	Anticoagulant	-	Yes (maximum 10%)	No	New drug, (limited experience).
Furosemide	Diuretic	C	Yes	Well tolerated; milk production can be reduced	Oligohydramnion.
Gemfibrozil	Lipid-lowering drug	C	Yes	Unknown	No adequate human data.
Glyceryl trinitrate	Nitrate	B	Unknown	Unknown	Bradycardia, tocolytic.
Heparin (low molecular weight)	Anticoagulant	B	No	No	Long-term application: seldom osteoporosis and markedly less thrombocytopenia than UF heparin.

Continued

Table 21 *Continued*

Drugs	Classification (Vaughan Williams for AA drugs)	FDA category	Placenta permeable	Transfer to breast milk (fetal dose)	Adverse effects
Heparin (unfractionated)	Anticoagulant	B	No	No	Long-term application: osteoporosis and thrombocytopenia.
Hydralazine	Vasodilator	C	Yes	Yes[e] (maximum 1%)	Maternal side effect: lupus-like symptoms; fetal tachyarrhythmias (maternal use).
Hydrochlorothiazide	Diuretic	B	Yes	Yes; milk production can be reduced	Oligohydramnion.
Irbesartan[d]	Angiotensin II receptor blocker	D	Unknown	Unknown	Renal or tubular dysplasia, oligohydramnion, growth retardation, ossification disorders of skull, lung hypoplasia, contractures, large joints, anaemia, intrauterine fetal death.
Isosorbide dinitrate	Nitrate	B	Unknown	Unknown	Bradycardia.
Isradipine	Calcium channel blocker	C	Yes	Unknown	Potential synergism with magnesium sulfate may induce hypotension.
Labetalol	α-/ β-blocker	C	Yes	Yes[e]	Intrauterine growth retardation (second and third trimester), neonatal bradycardia and hypotension (used near term).
Lidocaine	Antiarrhythmic (class IB)	C	Yes	Yes[e]	Fetal bradycardia, acidosis, central nervous system toxicity.
Methyldopa	Central α-agonist	B	Yes	Yes[e]	Mild neonatal hypotension.
Metoprolol	β-blocker (class II)	C	Yes	Yes[e]	Bradycardia and hypoglycaemia in fetus.
Mexiletine	Antiarrhythmic (class IB)	C	Yes	Yes[e]	Fetal bradycardia.
Nifedipine	Calcium channel blocker	C	Yes	Yes[e] (maximum 1.8%)	Tocolytic; s.l. application and potential synergism with magnesium sulfate may induce hypotension (mother) and fetal hypoxia.
Phenprocoumon[a]	Vitamin K antagonist	D	Yes	Yes (maximum 10%), well tolerated as inactive metabolite	Coumarin-embryopathy, bleeding (see further discussion in Section 5 for use during pregnancy).
Procainamide	Antiarrhythmic (class IA)	C	Yes	Yes	Unknown (limited experience).
Propafenone	Antiarrhythmic (class IC)	C	Yes	Unknown	Unknown (limited experience).
Propranolol	β-blocker (class II)	C	Yes	Yes[e]	Bradycardia and hypoglycaemia in fetus.
Quinidine	Antiarrhythmic (class IA)	C	Yes	Yes[e]	Thrombopenia, premature birth, VIII th nerve toxicity.
Ramipril[d]	ACE inhibitor	D	Yes	Yes (maximum 1.6%)	Renal or tubular dysplasia, oligohydramnion, growth retardation, ossification disorders of skull, lung hypoplasia, contractures, large joints, anaemia, intrauterine fetal death.
Sotalol	Antiarrhythmic (class III)	B	Yes	Yes[e]	Bradycardia and hypoglycaemia in fetus (limited experience).
Spironolactone	Aldosterone antagonist	D	Yes	Yes[e] (maximum 1.2%); milk production can be reduced	Antiandrogenic effects, oral clefts (first trimester).
Statins[g]	Lipid-lowering drugs	X	Yes	Unknown	Congenital anomalies.
Ticlopidine	Antiplatelet	C	Unknown	Unknown	Unknown (limited experience).

Continued

Table 21 *Continued*

Drugs	Classification (Vaughan Williams for AA drugs)	FDA category	Placenta permeable	Transfer to breast milk (fetal dose)	Adverse effects
Valsartan[d]	Angiotensin II receptor blocker	D	Unknown	Unknown	Renal or tubular dysplasia, oligohydramnion, growth retardation, ossification disorders of skull, lung hypoplasia, contractures, large joints, anaemia, intrauterine fetal death.
Verapamil oral	Calcium channel blocker (class IV)	C	Yes	Yes[e]	Well tolerated (limited experience during pregnancy).
Verapamil i.v.	Calcium channel blocker (class IV)	C	Yes	Yes[e]	Intravenously use is may be associated with a greater risk of hypotension and subsequent fetal hypoperfusion.
Vernakalant	Antiarrhythmic (class III)	-	Unknown	Unknown	No experience of use in pregnancy.
Warfarin[a]	Vitamin K antagonist	D	Yes	Yes (maximum 10%), well tolerated as inactive metabolite	Coumarin-embryopathy, bleeding (see further discussion in Section 5 for use during pregnancy).

[a]The Guideline Committee added acenocoumarol and phenprocoumon in analogy to warfarin to this list. The necessity for risk assessment also applies to these two OAC. Previously the risk category X was attributed to warfarin.[46] In the opinion of the Task Force available evidence suggests that risk category D is more appropriate for warfarin and other vitamin K antagonists (see references and discussion in Section 5.5).
[b]Adenosine: most of the experiences with this drug are in the second and third trimesters. Its short half-life may prevent it from reaching the fetus
[c]Atenolol is classified D by FDA,[252] nevertheless some authors classify as C.[253]
[d]The available data on first-trimester use do not strongly support teratogenic potential.[178,179] Because ACE inhibitors, angiotensin II receptor blockers, 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.
[e]Breastfeeding is possible if the mother is treated with the drug.[254]
[f]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.
[g]Statins: should not be prescribed in pregnancy and during breastfeeding since their harmlessness is not proven and disadvantages to the mother are not to be expected by a temporary interruption of the therapy for the time period of pregnancy.
ACE = angiotensin-converting enzyme; UF = unfractionated.

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