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Consensus Document of the Italian Association of Hospital Cardiologists (ANMCO), Italian Society of Pediatric Cardiology (SICP), and Italian Society of Gynaecologists and Obstetrics (SIGO): pregnancy and congenital heart diseases

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KEYWORDS
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The success of cardiac surgery over the past 50 years has increased numbers and median age of survivors with congenital heart disease (CHD). Adults now represent two-thirds of patients with CHD; in the USA alone the number is estimated to exceed 1 million.
In this population, many affected women reach reproductive age and wish to have children. While in many CHD patients pregnancy can be accomplished successfully, some special situations with complex anatomy, iatrogenic or residual pathology are associated with an increased risk of severe maternal and fetal complications.
Pre-conception counselling allows women to come to truly informed choices. Risk stratification tools can also help high-risk women to eventually renounce to pregnancy and to adopt safe contraception options. Once pregnant, women identified as intermediate or high risk should receive multidisciplinary care involving a cardiologist, an obstetrician and an anesthesiologist with specific expertise in managing this peculiar medical challenge.

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Introduction

The number of adult patients with congenital heart disease (CHD) has increased during the last few decades as a result of significant improvement in diagnosis and treatment, and will certainly increase further over time.[1] Women with CHD are therefore more likely to live to childbearing age, and to decide to have children.

The management of pregnancy in a woman with a CHD must necessarily be multidisciplinary, in order to minimize the maternal mortality and morbidity risk and ensure the health of the foetus.

This document is not intended to replace the existing Guidelines, but originates from the idea of supplying practicing cardiologists and gynecologists with a reliable but practical tool which will help them to identify the problem, to stratify the risk of maternal, obstetric and neonatal complication and to plan the best care plan when faced with a CHD patient who is or intends to become pregnant.

Moreover, the present version of the document is to be intended as an executive summary of the more detailed paper recently published in Italian in the Giornale Italiano di Cardiologia.

Physiological adaptations of the cardiovascular system during pregnancy

During pregnancy, the biggest adaptations occur in the mother's cardiovascular system and may lead to the emergence of a previously unidentified cardiovascular defect, causing significant increase in morbidity and mortality rates. [2-12]

Dynamic changes of major cardiovascular and clinical variables during pregnancy are reported in *Figure 1*.

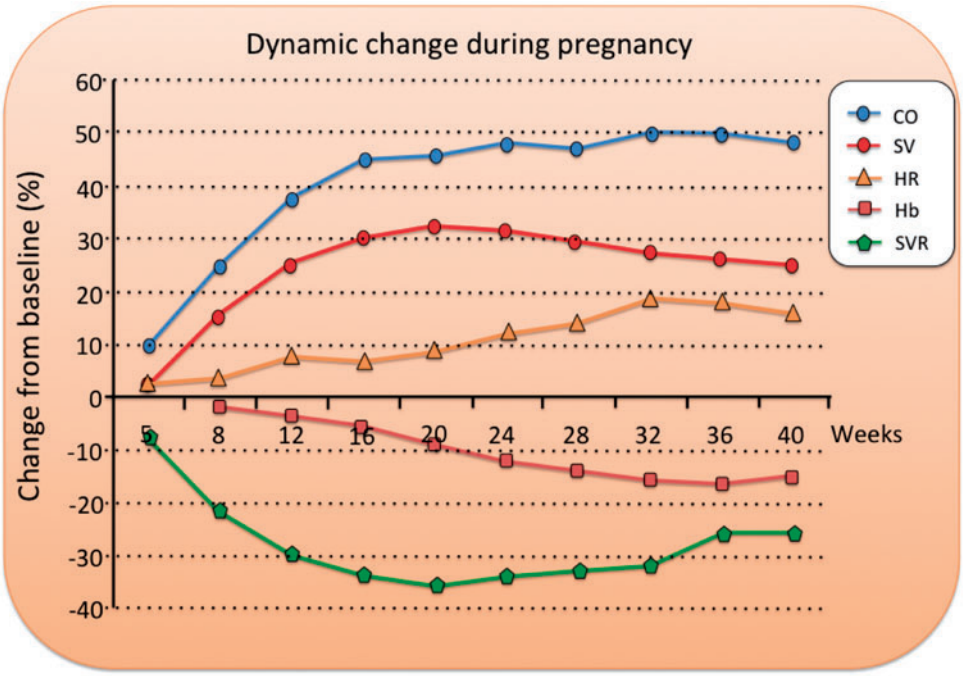

Figure 1 Cardiovascular adaptation during pregnancy.

Counselling

Counselling is pivotal in the management of a woman with a CHD who is or wishes to become pregnant.[13] The importance and complexity of pre-conceptional counselling is due to the fact that it must be performed considering three different aspect of maternal cardiovascular disease (cardiological, genetic, and obstetric), it must focus on the implications of the pregnancy for the mother and foetus in the context of the specific heart defect, and it should help the woman to identify the best strategy to be pursued in that specific condition.

Genetic counselling

Congenital heart diseases are the most common congenital defects, with a prevalence of about 5–10/1000 live births (0.8%).[14-22]

Prenatal genetic counselling offered to women with CHDs is intended:

- to assess whether the CHD is part of a syndromic complex, and/or a specific genetic syndrome;
- to genetically classify the CHD if it is present in isolation.

The first approach requires the reconstruction of the family tree, working back at least three generations, to obtain information about any known congenital defects and/or genetic diseases, age, and cause of death and miscarriages.

The next step is to examine the woman's personal medical history and assess any existing medical documentation.

This is followed by an objective examination for any signs of malformations and/or other congenital defect, which may suggest known genetic diseases.

Potential for genetic analysis (cytogenetic or molecular typing, array-comparative genomic hybridization (CGH) should be considered on a case-by-case scenario.

For non-syndromic CHDs, sequencing of the causal genes, if known, or array-CGH to check for genomic micro-imbalances, will be performed.

Genetic investigations take a varying amount of time depending upon the types of tests performed: it is therefore advisable for women with CHDs to undertake genetic counselling before conception. For women who are already pregnant, the consultation with the geneticist should take place in the early weeks of pregnancy.

If a genetic origin is identified for the CHD, the risk of recurrence is assessed: if a risk of transmission of the genetic defect is identified, the woman is offered the opportunity of invasive prenatal testing (villocentesis or amniocentesis) for the genetic disorder.

If no specific genetic defect is identified, only an empirical risk of recurrence can be provided on the basis of the type of CHD and the number of family members, apart from the mother, with the same congenital defect, and a foetal ultrasound examination is recommended (*Figure 2*).

In case of mothers with isolated CHD, the risk of recurrence in children is about 3–5%, with a higher risk for left outflow obstruction syndromes, including hypoplastic left heart syndrome.

Cardiological counselling

According to some authors,[23] pre-conceptional counselling should start as early as adolescence, especially where the risk in case of pregnancy is not negligibile, and should include advice on contraception.[24-42]

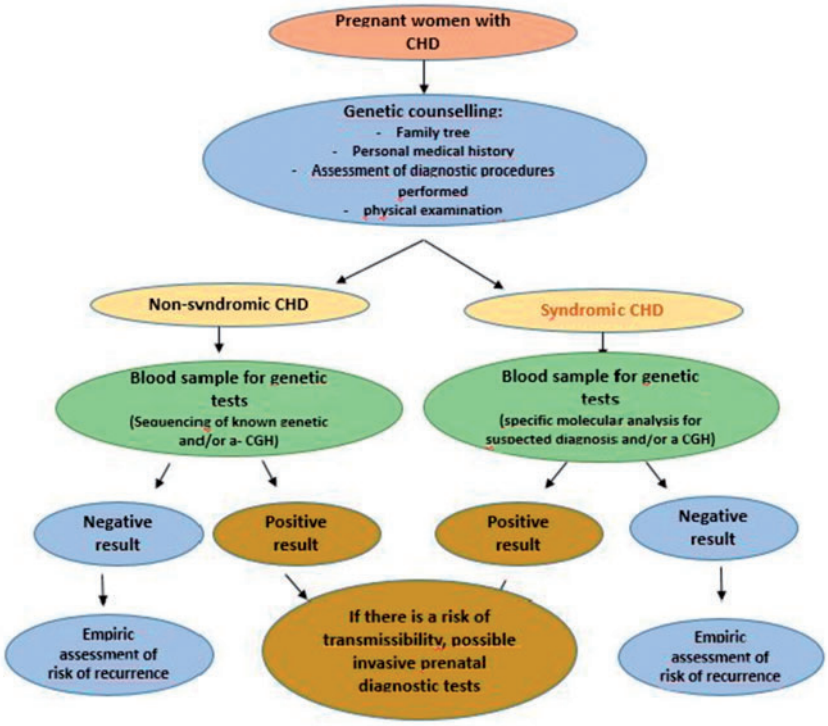

Figure 2 Clinical approach to genetic counselling in women with congenital heart disease.

It is quite common for a woman with a congenital heart defect to experience no or only mild symptoms, leading her to believe that is no reason why she should not plan pregnancy. However, the physical and pathological responses of many heart malformations to the haemodynamic changes due to pregnancy vary widely. Therefore, cardiological counselling is extremely important and should focus on planning, especially about the timing of pregnancy as appropriate to the type of CHD involved.

More specific, detailed recommendations are provided later in this document, in the sections referring to the specific congenital heart defects.

Obstetric counselling

Obestric complications (pre-term labour, non-planned cesarean section, and post-partum haemorrhage) and neonatal complications (prematurity, intra-uterine fetal growth restriction, fetal demise, or neonatal mortality) are increased in pregnant women with cardiovascular disease compared with the general parturients and it is associated with higher World Health Organization (WHO) class.[43-46] Accordingly, multidisciplinary evaluation including gynceologist–obstetrician, cardiologist, anesthesiologist, neonatologist, and others is fundamental to optimize delivery of care (*Table 1*).

Table 1 Obstetric counselling

(Pre-conceptional or early pregnancy)
WHO class definition
WHO class-based assessment of: • Foetal and neonatal risk • Maternal risk • Intensity of obstetrical follow-up
- CLASSE WHO I: every 4–5 weeks, Regional Centre - CLASSE WHO II, every 4 weeks, Referral Centre - CLASSE WHO III, every 2–3 weeks, Referral Centre - CLASSE WHO IV, every 1–2 weeks, Referral Centre, considering for termination
In women with congenital heart disease: foetal echocardiography at 21-21 weeks of gestation
In women on beta-blocker therapy: foetal evaluation and uterine Doppler assessment around 28-30 weeks of gestation
Medical therapy: to assess for need of drug-replacement, dose adjustment, drug-interruption. Counsel against self-interruption.

WHO, World Health Organization.

Maternal cardiovascular risk

In the presence of a CHD, the haemodynamic changes arising from pregnancy may increase the risk of cardiovascular complications for the mother, foetus or newborn.[47-56]

The probability that this may occur depends on the type of heart defect and the patient's clinical condition. The risk of complication is broadly related to the complexity of the heart malformation, status of repair, and specific risk factors.

Prospective and retrospective cohort studies have led to development of risk scoring systems, which all have strengths and limitations related to case mix variation, outcome and predictor definition, selection bias.

Table 2 CARPREG risk score—predictive factors

(1) Previous cardiac event:
- Cardiac insufficiency
- Transient ischaemic attack
- Stroke
- Arrhythmia

2. Basic NYHA functional class >II or cyanosis
3. Left ventricular obstruction
- On echocardiogram:
  - Mitral valve area< 2 cm^2
  - Aortic valve area< 1.5 cm^2
  - Peak left outflow gradient>30 mmHg
4. Reduced systemic ventricular function (EF < 40%)

NYHA, New York Heart Association; EF, ejection fraction.

Table 3 CARPREG risk score—score

Percentage risk of maternal cardiovascular complications	
0 Points	5%
1 Point	27%
> 1 Point	75%

Table 4 ZAHARA risk score

Predictive factors	Score
History of arrhythmia	1.50
Functional class NYHA≥ II	0.75
Use of cardiovascular medication before pregnancy	1.50
Severe left ventricular obstruction (peak aortic gradient> 50 mmHg, aortic valve area< 1.0 cm^2)	2.5
Moderate/severe systemic atrioventricular valve defect	0.75
Moderate/severe systemic subpulmonary atrioventricular valve defect	0.75
Mechanical valve prosthesis	4.5
Cyanotic heart disease (treated or untreated)	1.0

Total number of points: 0–13.
NYHA, New York Heart Association.

Table 5 ZAHARA risk score

Percentage maternal heart complications	
Total score	Percentage of risk
0–0.50	2.9
0.51–1.50	7.5
1.51–2.50	17.5
2.51–3.50	43.1
>3.51	70.0

Table 6 Modified WHO classification: general principles

I	No detectable increase in maternal mortality risk. No/minimal increase in morbidity.
II	Slight increase in maternal mortality risk or moderate increase in morbidity.
III	Significant increase in maternal mortality risk or severe increase in morbidity. Expert counselling is required. If the patient still goes ahead with the pregnancy, intensive specialist cardiological and obstetric monitoring is required throughout pregnancy, labour and the puerperal period.
IV	Extremely high-maternal mortality risk or severe risk of increase in morbidity. Pregnancy is contraindicated. If a pregnancy still occurs, the advisability of termination should be discussed. If the pregnancy still continues, intensive monitoring as in class III is necessary.

WHO, World Health Organization.

The *CARPREG* (Cardiac Disease in Pregnancy) *RISK SCORE* derives from a Canadian multicentric prospective study which assessed the risks and outcomes of pregnant women suffering from cardiovascular diseases, 74% of whom had a CHD (but not pulmonary arterial hypertension (PAH) or aortic diseases). It has been validated by a number of studies and has proved effective for the prediction of maternal risk, although there may be some overestimation (*Tables 2* and *3*).

The *ZAHARA* score derives from a European study, which assessed the risk during pregnancy for women with CHDs only. It has been developed to a scoring system and it uses risk factors (*Tables 4* and *5*). However, it should be noted that it has not yet been validated by other studies.

The *MODIFIED WHO* CLASSIFICATION recommended by the European Society of Cardiology, combines all known maternal cardiovascular risk factors, including the underlying cardiovascular disease and the other comorbidities (*Tables 6–8*).

It is the only method that considers both *specific cardiac lesions* and *cardiological clinical condition* (e.g. systemic ventricular dysfunction) and clearly states the contraindications. It has been prospectively validated as the most reliable method for risk assessment in pregnant women with congenital heart defects.

Haemodynamic risk

Repaired or un-repaired congenital heart diseases, without haemodynamically significant sequelae

Atrial septal defect and anomalous pulmonary venous return

Atrial septal defect (ASD) accounts for 6–10% of heart malformations and is the most common congenital heart defect to be detected in adults and, in view of its prevalence amongst women, during pregnancy.[57–73]

Table 7 Modified WHO Classification: applications

Conditions in which the pregnancy can be assigned to RISK Class I
- Slight haemodynamic repercussion
• Pulmonary stenosis
• PDA
• Mitral valve prolapse
- Simple lesions effectively corrected (atrial or ventricular septal defects, PDA, anomalous pulmonary venous return)
- Isolated premature atrial or ventricular contractions
Conditions in which the pregnancy can be assigned to RISK Class II or III
WHO II (if no additional complications)
- Unoperated atrial or ventricular septal defects
- Operated Tetralogy of FallotMost arrhythmias
WHO II-III (individual assessment)
- Slight left ventricular dysfunction
- Hypertrophic cardiomyopathy
- Congenital valve defect not considered in WHO Class I or IV
- Marfan's syndrome without aortic dilation
- Aorta$<$ 45 mm in aortic disease associated with bicuspid valvular disease
- Corrected aortic coarctation
WHO III
- Mechanical prosthesis
- Systemic right ventricle
- Fontan circulation
- Cyanotic heart disease (not corrected)
- Other complex congenital heart defects
- Aortic dilation 40-45 mm in Marfan's syndrome
- Aortic dilation 45-50 mm in aortic disease associated with bicuspid valvular disease
Conditions in which the pregnancy can be assigned to RISK Class IV (pregnancy contraindicated)
- Pulmonary arterial hypertension, regardless of cause
- Severe left ventricular dysfunction (EF $<$ 30%, NYHA FC III-IV)
- Previous peripartum cardiomyopathy with residual left ventricle dysfunction
- Severe mitral stenosis, severe aortic stenosis, symptomatic
- Marfan's syndrome with aortic dilation$>$ 45 mm
- Aortic dilation$>$ 50 mm in aortic disease associated with bicuspid valvular disease
- Severe aortic coarctation, not corrected

PDA, patent ductus arteriosus; NYHA, New York Heart Association; EF, ejection fraction; WHO, World Health Organization; FC, functional class.

Table 8 Cardiological follow-up

WHO Class	Frequency of cardiological follow-up
I	1-2 cardiological checks during the pregnancy
II	Cardiological assessment every 3 months
III	Cardiological and obstetric assessment every 1-2 months
IV	Pregnancy is contraindicated: however, if a pregnancy is undertaken close follow-up (see Class III) is compulsory

WHO, World Health Organization.

The left-to-right shunt is considered significant when QP/QS is $\geq$1.5 or if it causes dilation of the right ventricle.

This heart defect, generally asymptomatic in children, may be responsible for poor resistance to physical effort and/or atrial arrhythmias (fibrillation, flutter) in the 3rd-4th decade.

A corrective operation in adults ($>$30 years) does not eliminate the risk of arrhythmic events (0.8-4.3%).

Maternal cardiovascular risk. The baseline volumetric overload of the right ventricle tends to progress during pregnancy and it is accentuated by the left-to-right shunt through the ASD (possibly associated with anomalous pulmonary venous return) although this is rarely associated with congestive symptoms.

Potential paradoxical embolization through the defect is possible, although exceedingly rare and almost always associated with other concomitant risk factors. The most important risk factors for venous thromboembolism are, first and foremost, a *past history of thrombosis* and *thrombophilia*, specific clinical conditions (heart diseases, sickle cell anaemia, systemic lupus erythematosus (SLE), obesity, anaemia, and diabetes) and obstetric conditions (multiple pregnancies, electrolytic, and acid-base balance anomalies, caesarean section, post-natal infections, post-natal haemorrhage, and transfusions).

In the presence of haemodynamically significant ASD, it is advisable to close the defect before pregnancy, although a diagnosis during pregnancy is not a contraindication for this.

The mother-child outcome of pregnant women who have undergone ASD correction is equivalent to that of the general population. An un-operated, haemodynamically significant ASD leads to a higher risk of miscarriage and slow intrauterine growth (reduced placental perfusion). The only contraindication to pregnancy for women with ASD (both repaired and un-repaired) is the presence of pulmonary hypertension (PH) or very poor systolic function of the left ventricle (*Table 9*). There are no cardiovascular contraindications to a vaginal delivery in this setting (*Table 10*).

Ventricular septal defect

Ventricular septal defect (VSD) is one of the most common congenital heart defects (about 20%).

The symptoms depend on the extent of the shunt. Depending on the pulmonary pressures, VSD is defined as *restrictive* (normal pulmonary pressures), *moderate* (below-systemic pulmonary pressures), or *non-restrictive* (pulmonary pressures systemic).

The majority of VSDs with haemodynamic repercussions are operated in childhood. Follow-up studies at age 22-34 years demonstrate the absence of symptoms over the long term, except in cases with residual PH.

Maternal cardiovascular risk. Pregnancy is tolerated well in the case of repaired or small/moderate VSDs.

A higher percentage of pre-eclampsia is noticed in unrepaired pregnant women, with intrauterine growth retardation in operated pregnant women.

Table 9 Cardiological checks—atrial septal defect ± partial anomalous pulmonary venous return

WHO I–II	
Pre-pregnancy	Pregnancy
Cardiology examination Electrocardiogram TT ± ETE echocardiogram Holter dynamic ECG Surgical/interventionist closure If shunt is haemodynamically significant (dilation of right cavity)	Individualized follow-up Cardiology examination Electrocardiogram TT echocardiogram Holter dynamic ECG Venous thromboembolism1,63([a]) • Check list for risk factors • Definition of risk group • Prevention NO routine screening for thrombophilia(Class III Level C)
Venous thromboembolism1,63 • Check list for risk factors • Definition of risk group Prevention NO routine screening for thrombophilia (Class III Level C)	

TT: transthoracic; ETE, transoesophageal echocardiogram; WHO, World Health Organization.
[a]If not performed prior to pregnancy.

Table 10 Atrial septal defect ± partial anomalous pulmonary venous return

WHO III
Contraindications to pregnancy • Pulmonary hypertension • Deterioration of the contractile function of the left ventricle

WHO, World Health Organization.

Table 11 Cardiological checks—ventricular septal defect

WHO I	
Pre-pregnancy	Pregnancy
Examination Electrocardiogram Echocardiogram	Follow-up: twice during the pregnancy Examination Electrocardiogram Echocardiogram Prophylaxis against bacteria endocarditis

WHO, World Health Organization.

Prophylaxis against bacteria endocarditis may be considered indicated in cases of un-repaired VSD and in the event of residual shunts after repair, although not currently standard treatment based on most recent guidelines.

Pregnancy is contraindicated in the case of PAH with shunt reversal (WHO Class IV: Eisenmenger syndrome).

There are no cardiological contraindications to a vaginal delivery (*Table 11*) and neonatal outcome is no different from that of the general population.

Patent ductus arteriosus

Patent ductus arteriosus (PDA) accounts for about 5–10% of all congenital heart defects.

As with VSD, the degree of the pressure gradient created between the aorta and the pulmonary artery provides the basis for classifying the PDA as *restrictive, moderate and non-restrictive* (see Section Ventricular septal defect).

The symptoms depend on the size of the shunt, as with VSD.

Maternal cardiovascular risk. Pregnancy is well tolerated for small/moderate PDAs but is contraindicated in the case of PAH with shunt reversal (WHO risk Class IV: Eisenmenger syndrome).

Prophylaxis against bacterial endocarditis may be considered in cases of un-repaired PDA or in the event of residual shunts after repair, although not currently standard treatment based on most recent guidelines. As for VSD, vaginal delivery is not contraindicated and neonatal outcome is no different from that of the general population (*Table 12*).

Pulmonary stenosis (trivial-mild)

Congenital pulmonary valve stenosis accounts for about 10% of congenital heart defects.

The severity of stenosis is assessed on the basis of the gradient across the pulmonary valve: *mild* (peak gradient <30 mmHg), *moderate (*peak gradient 30–60 mmHg), and *severe* (peak gradient >60 mmHg).

Mild or moderate stenosis may be due to mild valvular dysplasia or sequela of pulmonary valvuloplasty or valvotomy during childhood. In these cases, it is frequently associated with a certain degree of regurgitation.

Usually, mild-moderate pulmonary stenosis does not tend to deteriorate. It is compatible with a normal lifestyle in adults. Pregnancy is tolerated well and a 3-month cardiological follow-up is sufficient (*Table 13*).

A high rate of obstetric complications (pre-eclampsia and eclampsia) and premature births is recorded.

There are no cardiological contraindications for a vaginal delivery.

Mitral-aortic valve disorders

Mild-moderate mitral and aortic valve insufficiency. Defects of this kind may be post-rheumatic fever, congenital (bicuspid aortic valve, degenerative, or post-operative (percutaneous/surgical dilation).

Mild-moderate mitral or aortic insufficiency does not normally lead to a change in the volume of the left cavities, or any such change is slight.

Maternal cardiovascular risk. Mild-to-moderate mitral or aortic defects are usually considered defects with low-risk profile during pregnancy. Specific consideration should be given to the presence of severely depressed systolic ventricular function. A cardiological follow-up every trimester is considered sufficient and usually there are no cardiovascular indications to caesarean delivery (*Table 14*).

Mild-moderate mitral and aortic valve stenosis. Mitral valve stenosis with area $>1.5\,cm^2$ or aortic valve stenosis with area $>1.0\,cm^2$ and a mean gradient of ≤ 40 mmHg are considered to be mild-moderate.

Maternal cardiovascular risk. Pregnancies are considered 'low' risk. A 3-month follow-up is recommended.

There are no contraindications to a vaginal delivery.

Table 12 Cardiological checks—patent ductus arteriosus

WHO I	
Pre-pregnancy	Pregnancy
Examination	Follow-up: twice during the pregnancy
Electrocardiogram	
Echocardiogram	Examination
	Electrocardiogram
	Echocardiogram
	Prophylaxis against bacteria endocarditis

WHO, World Health Organization.

Table 13 Cardiological checks—mild-moderate pulmonary valve stenosis

WHO I–II	
Pre-pregnancy	Pregnancy
Examination	Follow-up: twice during the pregnancy
Electrocardiogram	
Echocardiogram	Examination
Stress test	Electrocardiogram
	Echocardiogram

WHO, World Health Organization.

Haemodynamic risk of repaired or un-repaired congenital heart defects with iatrogenic and/or residual defect, with low possibility of cardiocirculatory adaptation during pregnancy

Severe mitral valve stenosis (WHO IV)

. Maternal cardiovascular risk. Mitral valve stenosis in women of childbearing age is usually the consequence of rheumatic fever.[1,49,73,74–134] This disease is rare in the developed countries, but it is still relatively common in patients from developing countries. Severe valve stenosis (valve area $<1.5\,cm^2$) interacts unfavourably with the haemodynamic changes induced by pregnancy, also due to the higher propensity to atrial tachyarrhythmia (especially atrial fibrillation).

Obstetric and foetal risk. Obstetric complications are usually secondary to the haemodynamic problems. A high proportion of pre-term births (20–30%), intrauterine growth retardation (5–20%), and foetal or neonatal death are reported. The risk of foetal complications is higher in symptomatic women [New York Heart Association Functional Class (NYHA Functional Class III–IV)].

Clinical management. Severe mitral valve stenosis is a contraindication to pregnancy in western countries (*Figure 3*). Echocardiogram monitoring during pregnancy must not be based only on transvalvular gradient, which is not a reliable parameter for the haemodynamic assessment of the stenosis.

Table 14 Mitral-aortic valve defects of mild-moderate haemodynamic extent

Cardiological checks		Cardiological checks	
Mild-moderate mitral/aortic valve stenosis		Mild-moderate mitral/aortic valve insufficiency	
WHO I–II		WHO I–II	
Pre-conception	Pregnancy	Pre-conception	Pregnancy
Cardiology examination	Cardiology examination	Cardiology examination	Cardiology examination
Electrocardiogram	Electrocardiogram	Electrocardiogram	Electrocardiogram
Echocardiogram	Echocardiogram	Echocardiogram	Echocardiogram
Stress test	Holter dynamic ECG	Stress test	Holter dynamic ECG
		Do not administer	Suspend
		Ace-inhibitors	Ace-inhibitors

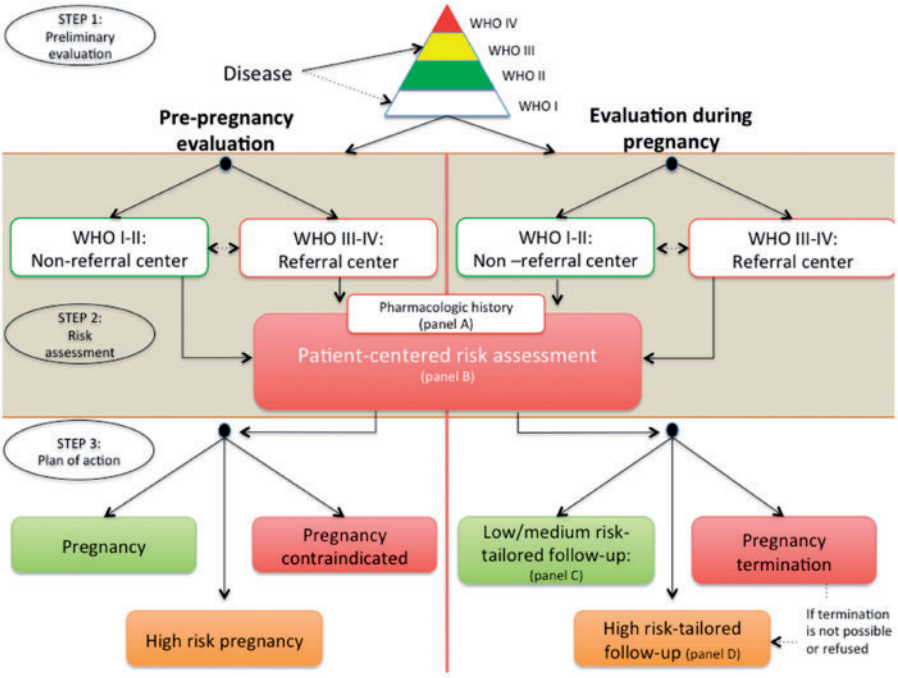

Figure 3 Stepwise approach for risk assessment in women with congenital heart disease.

During pre-conception counselling, women should be informed about the high risk of maternal and foetal complications in the event of a pregnancy, and should be encouraged to undergo corrective surgery.[4] If the anatomical characteristics allow, valvuloplasty should be considered.

For women assessed during pregnancy, therapeutic abortion should be discussed and offered if possible (*Figure 3*). If the patient refuses these options, the pregnancy must be closely monitored (Panel D).

In case of symptoms of cardiac insufficiency, patients must be confined to bed and beta-blocker therapy should be started, together with stimulation of diuresis by low doses of a diuretic. Atrial fibrillation should be promptly treated by the immediate introduction of pharmacological rate control (intravenous beta-blockers with low half-life or verapamil as second line of treatment), to be followed by electric cardioversion if necessary Electrical cardioversion should be considered as first line of treatment in patients with impaired haemodynamics. In patients with a history of atrial fibrillation, severe atrial dilation, low-cardiac output, spontaneous atrial echo contrast and serious cardiac insufficiency, the risk of cardio-embolic events is high. The need for anticoagulant therapy should therefore be considered, clearly discussing the pro and cons with the patient (*Figure 4*).

Percutaneous valvuloplasty during pregnancy is a procedure described in a number of cases; it is effective in acutely reducing transvalvular gradient and pulmonary congestion symptoms, but foetal mortality and maternal morbidity are potential drawbacks, and it is therefore usually only performed in women who are symptomatic (NYHA Class III–IV) in spite of optimized medical therapy by experienced teams.

Perinatal period. In most cases, asymptomatic patients (NYHA Class I–II) without PH can tolerate a vaginal delivery (Panel E). Caesarean section is recommended in patients with serious symptoms or PH.

Severe aortic valve stenosis (WHO III-IV)

Maternal cardiovascular risk. The vast majority of female patients of childbearing age with aortic valve stenosis has a bicuspid aortic valve. In contrast with the historical data which reported excessive mortality and morbidity in women with severe aortic valve stenosis (peak transvalvular velocity >4 m/s., average gradient >40 mmHg), more recent data point to a lower risk. The risk of complications appears to be higher in case of systolic dysfunction of the left ventricle and if symptoms are present. In some cases, the presence of aortic dilation may expose the patient to the risk of gradual aortic dilation and dissection (see Section Aortic disease). Cardiac insufficiency occurs in about 10% of patients, while the risk of arrhythmia is moderate (3–25%).

Obstetric and foetal risk. The obstetric risk is significantly increased due to the rise in the rate of cases of pregnancy-related hypertension (including pre-eclampsia), pre-term birth, and intrauterine growth retardation.

Clinical management. Seriously symptomatic women with severe stenosis are usually advised against pregnancy and encouraged to undergo a procedure to reduce the gradient (*Figure 3*). If the anatomy is favourable, percutaneous valvuloplasty is preferred, in order to reduce the risk relating to anticoagulant therapy and the need for reoperation.

In asymptomatic women, a stress test or, if possible, cardiopulmonary test will provide important prognostic guidance. In women who show arrhythmia under stress, failure

Strategy	Operational details	Recommendations	Comments
LMWH throughout pregnancy	Twice-a-day subcutaneous administration	Dosing based on anti-Xa level 4 hours after last administration	Minimal risk of embriopathy. Maternal thromboembolic events: 4.3%-16.7%.
UFH throughout pregnancy	Twice-a-day subcutaneous administration	Dosing based on aPTT level 6 hours after last administration	Minimal risk of embriopathy. Maternal thromboembolic events: 33.3%.
UFH/LMWH up to 13th week of gestation, vitamin K oral antagonist after	Target INR Aortic mechanic cardiac valve: INR 2.5 (range 2.0-3.0) Mitral mechanic cardiac valve: INR 3.0 (range 2.5-3.5)	Back-switch to UFH/ LMWH after 36th week of gestation	Risk of embriopathy: 2% Maternal thromboembolic events: 8.6-22.4%
Vitamin K oral antagonist throughout pregnancy	Target INR Aortic mechanic cardiac valve: INR 2.5 (range 2.0-3.0) Mitral mechanic cardiac valve: INR 3.0 (range 2.5-3.5)	Back-switch to UFH/ LMWH after 36th week of gestation To be considered in very high risk profile for thrombotic events. Consider low dose of aspirin.	Risk of embriopathy: 3.7-6.4% Maternal thromboembolic events: 3.9%.

LMWH= low molecular weight heparin; UFH= unfractioned heparin

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Figure 4 Anticoagulation during pregnancy.

to modulate the systemic arterial pressure, stress-induced hypotension, slow increase in heart rate, or a significant reduction in the tolerance of exercise, the risk linked to pregnancy is probably higher and thus individual assessment at a specialist centre is mandatory (*Figure 3*).

In cases of left ventricle systolic dysfunction, pregnancy is usually contraindicated.

In asymptomatic patients with no ventricular dysfunction and good tolerance of exercise, pregnancy is usually well tolerated and there is no reason to advise against it (Panel C).

The onset of signs and symptoms of cardiac insufficiency during pregnancy should generally be treated with bed rest, mild beta-blocking therapy (not recommended in case of systolic ventricular dysfunction), and low-dosage diuretic therapy (Panel D). In case of atrial tachyarrhythmias, especially atrial fibrillation, pharmacological rate control is generally effective, and should be followed by elective external electric cardioversion, with subsequent consensual foetal monitoring. Urgent electric cardioversion is indicated in cases with haemodynamic impairment

In the rare cases with cardiac insufficiency refractory to medical therapy, patients may undergo percutaneous valvuloplasty during pregnancy. The procedure is usually effective in acutely reducing the gradient and leading to symptoms improvement. If this procedure is contraindicated or not technically possible, valve replacement becomes a possible option after a Caesarean as soon as foetal maturity allows.

Dilation of the ascending aorta must be ruled out, especially in cases of aortic valve stenosis arising from bicuspid valve (see Section Aortic disease).

Perinatal period. Vaginal delivery is normally recommended for most patients, using an approach for a high risk profile (Panel E). Caesarean section is only performed on severely symptomatic patients, or those with severe systolic impairment of the left ventricle or severe aortic dilation.

Severe pulmonary valve stenosis (WHO II-III)

Maternal cardiovascular risk. Pulmonary valve stenosis is generally well tolerated during pregnancy; however, if associated with severe dysfunction and dilation of the right ventricle, very severe stenosis may be associated with the onset of arrhythmia and congestive cardiac insufficiency. In case of severe pulmonary valve stenosis (peak transvalvular velocity >4 m/s, peak instantaneous gradient >64 mmHg), women with symptoms at the pre-conception clinical evaluation usually risk a deterioration of their FC during pregnancy.

Obstetric and foetal risk. Obstetric and foetal risk is related mainly to the onset of pregnancy-related systemic arterial hypertension (including pre-eclampsia) and the risk of recurrence of the foetal congenital heart defects.

Clinical management. In asymptomatic women, pregnancy is not contraindicated but requires close monitoring (Panel C). In the event that symptoms occur, checks must become more frequent (panel D). In women who develop severe symptoms of cardiac insufficiency in spite of medical therapy (bed rest, diuretic therapy), the use of percutaneous valvuloplasty during pregnancy is a possible approach.

Women who are severely symptomatic at the pre-conception clinical evaluation should normally be advised to undergo an elective procedure to reduce the gradient (usually percutaneous valvuloplasty) before a pregnancy.

Perinatal period. Asymptomatic women can give birth by the vaginal approach. For symptomatic women (NYHA Class III–IV), a caesarean section can be considered.

Aortic disease (WHO III–IV)

The association between pregnancy and aortic dissection is reflected by the fact that more than half the cases of aortic dissection in women less than 40 years of age are associated with pregnancy. Dissection, or rupture, generally occurs during the last 3 months of pregnancy or during the perinatal period. Pre-conception assessment is extremely important for identifying women at risk of gradual aortic dilation and dissection before pregnancy; this gives the chance of advising prophylactic replacement surgery or (in rare cases), or of discouraging patients from pregnancy.

If a woman at high risk of aortic dissection undergo clinical evaluation when already pregnant, the options include therapeutic abortion or strict monitoring which includes periodical cardiovascular imaging and a balanced clinical decision considering the risk related to mother's prophylactic replacement surgery and foetal risks. These cases must be assessed at specialistic centres with a multidisciplinary team including experienced cardiac surgeons, cardiologists, interventional radiologists, anaesthetists, and a high risk maternity-foetal unit (*Figure 3*, Panel D). The surgical option, with or without consensual caesarean section, is inevitable in cases of acute dissection, especially of type A. In all these cases, maternal and foetal mortality rates are high.

From the epidemiological point of view, most women of childbearing age with significant aortic disease have one of the following conditions: systemic connective tissue disease (Marfan's syndrome, Loeys-Dietz syndrome, type IV Ehlers–Danlos syndrome), bicuspid aortic valve, Turner syndrome, or a hereditary aortic syndrome (*Figure 5*). In few cases, aortic dilation may be associated with a corrected congenital heart defect. Aortic dilation only occurs in isolation in rare cases.

In all cases where suspicion of aortic dissection in a pregnant woman is well founded, the need for swift diagnosis justifies the use of computed tomography imaging, with abdominal shielding techniques if necessary.

General risk factors for dissection during pregnancy are a family history of aortic dissection at a young age, especially during pregnancy, rapid dilation of the aorta (>5 mm/year) and the presence of aortic dilation prior to conception (with threshold values which may vary depending on specific individual clinical characteristics). The presence of hereditary connective tissue diseases or conditions associated to a greater probability of dissection during pregnancy make pre-conception assessment even more problematical and these patients should be directed to Centres with specific experience (*Figures 3* and *5*).

Marfan syndrome. Marfan syndrome (MS) is an autosomal, dominant, genetic disease with multiorgan involvement of the connective tissue, often associated with mutation of the fibrillin gene. Cardiovascular manifestations of the disease include progressive aortic dilation with risk of dissection, mitral valve prolapse, atrial, and ventricular arrhythmias. Pregnancy in women with MS has been associated with higher risk of aortic dissection (2%), which appears to be clustering during the third pregnancy trimester and in the post-partuum period. Higher risk of aortic complications is reported in patients with no pre-conceptional diagnosis of the disease, larger aorta or rapidly progressive aortic dilation.

Obstetric and fetal complications include pre-term labour, intra-uterine fetal growth restriction and MS recurrence in the offspring.

Pre-conceptional evaluation must identify women with higher risk of aortic dissection which include patients with previous dissection event, history of aortic surgery, family history of aortic dissection, large aorta, and rapidly progressive aortic dilation (>5 mm/year). Although a safe aortic diameter has not been identified, recent data suggest that aortic diameter less than 45 mm is associated with low risk of pregnancy-induced aortic dissection. Detailed aortic imaging (using cardiac magnetic resonance or computed tomography) is essential in the pre-conceptional evaluation. Clinicians have to be aware of the methodological peculiarities of the different imaging modalities in assessing aortic diameter. Standardization of aortic diameter either to body surface area or height needs to be considered in patients with marginal body dimensions.

In women with aortic diameter less than 45 mm (or equivalent adjusted for body surface area or height) without family history of aortic dissection, aortic valve disease and stable aortic dimension, pregnancy is usually possible. In the presence of severe aortic dilation, pre-pregnancy aortic surgery (with potential for valve sparing approach) is warranted. A similar approach should be considered in case of sever aortic valve disease, or rapidly progressive aortic dilation. Strong family history of aortic dissection, especially in relatives with normal or only mild dilated aorta, may increase the risk of adverse event during pregnancy and these women should be evaluated in a referral centre to undergo a thorough discussion about risk and benefit of pregnancy.

Serial imaging follow-up of aortic dimension is pivotal during pregnancy and it is usually accomplished using echocardiography. Appropriate timing is not well defined, but close follow-up every 6–8 weeks seem appropriate with closer visits in case of large aorta or progressive dilation.

Blood pressure control during pregnancy should be optimal and will include using of beta-blocker (which should be started also in patients that were not on therapy before pregnancy). Ace-inhibitor (ACEI)/angiotensin II receptor blockers (ARBs) will need to be replaced given potential teratogenic effect.

Vaginal delivery is usually reserved for low-risk patients with aortic diameter <40 mm. Epidural anaesthesia may be used, but dural ectasia should be always ruled out before. Elective Cesarean section is recommended in all the other cases. Beta-blocker should be continued also during the post-partuum period and in case of breastfeeding neonates should be screened for drug-related adverse effects.

Type IV Ehlers–Danlos syndrome. Ehlers–Danlos syndrome is a rare connective tissue disease linked to an anomaly in

A

Clinical scenario	Cardinal features	Potential pregnancy-related complications	Genetic trasmission	Threshold for pre-pregnancy aortic surgery*	Threshold for cesarean section*
Marfan syndrome	Ocular, muscolo-skeletal and cardiovascular involvement	• Aortic dissection • Severe mitral regurgitation • Systolic ventricular dysfunction • Arrhythmias	Autosomal dominant	>45 mm	>40mm
Loeys-Dietz syndrome	Dilation and arterial tortuosity, bifid uvula, aggressive vascular phenotype	• Aortic dissection	Autosomal dominant	>42 mm	Always
Familial aortic syndrome	Family history of aortic dissection, potential for overlapping features with Marfan or Loeys-Dietz syndromes	• Aortic dissection	Variable	> 40-45 mm (based on individual characteristics)	If aortic dilation
Bicuspid aortic valve	Possible family history of left heart congenital malformation, aortic coarctation	• Aortic dissection • Pregnancy-related hypertension (if aortic coarctation)	Variable	>50 mm, 27 mm/m^2	> 45 mm
Turner syndrome	Short stature, low-set ears, webbed neck, infertility, aortic coarctation,	• Aortic dissection • Pregnancy-related hypertension (if aortic coarctation)	Unclear	> 25 mm/m^2	>20 mm/m^2

* Value obtained using echocardiography at the end of systole with leading edge-to-leading edge methodology

B

Patient-centered risk assessment

First-level evaluation (to be considered in every patient):
- Physical examination
- ECG
- TTE
- Exercise test
- Holter ECG

Second-level evaluation (to be considered in selected patients):
- TEE
- Cardiac CT
- CMR
- Cardiac catheterization
- EP study
- Cardiopulmonary exercise test

Red flag for high risk (specific weight in risk assessment may vary depending upon individual characteristics, baseline cardiac disease and obstetric factors):
- Advanced NYHA class (III-IV)
- Effort-related chest pain
- Congestive symptoms
- Syncope
- Systemic oxygen saturation <90%
- III cardiac tone (before pregnancy)
- Congestive signs
- Arrhythmias
- Systemic outflow obstruction (including mitral valve stenosis)
- Systemic ventricular systolic dysfunction
- Pulmonary arterial hypertension
- Left atrial dilation
- Aortic dilation
- Mechanic cardiac valve
- ICD
- Oral anticoagulant therapy

Figure 5 (*A*) Deciding thresholds for aortic dilation in women with or without connective tissue disorder. (*B*) Individualized approach in risk assessment in women with congenital heart disease.

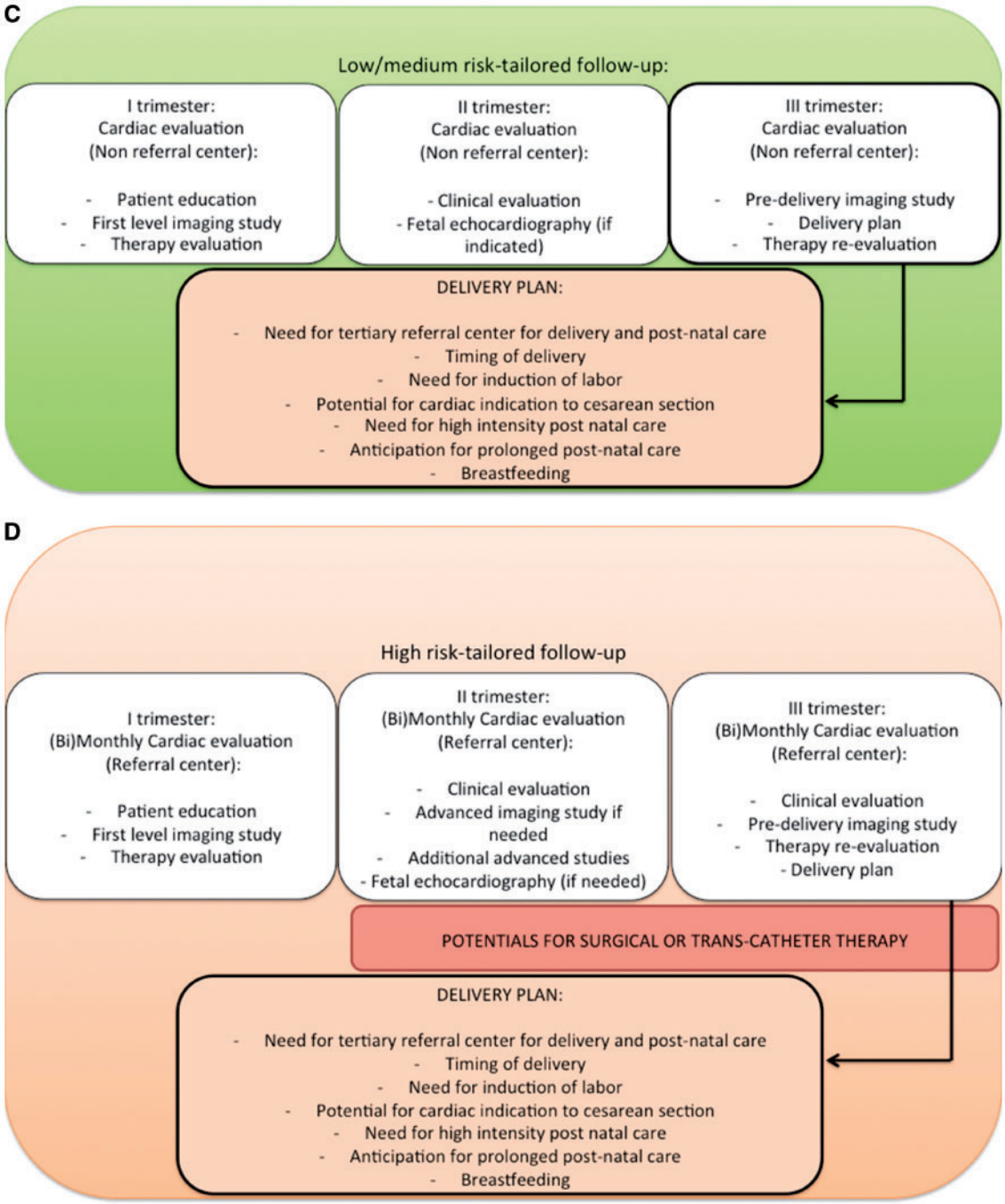

Figure 5 Continued

collagen synthesis, which systematically affects the skin, ligaments, joints, blood vessels, and organs. In Type IV (vascular), there is a high propensity to aortic and arterial dissection even with normal vessel diameters. In this disease, tissues are particularly fragile and this has been associated with spontaneous tearing of the womb during pregnancy. Moreover, tissue fragility makes both aorta replacement surgery and emergency repair in the event of aortic dissection extremely problematical. Therefore, even women with normal aortic diameter are generally advised against pregnancy.

Aortic dilation associated to operated congenital heart defects. Dilation of the aortic root and the ascending thoracic aorta occurs in a large number of adults after surgical correction of especially cono-truncal CHD (such as tetralogy of Fallot with or without pulmonary atresia or persistent truncus arteriosus), functionally univentricular heart, and after arterial switch procedures to correct transposition of the great arteries. At the moment, cases of aortic dissection are anectodal and the risk seems to be significantly lower than with other conditions associated to aortic

dilation (such as connective tissue diseases). Pregnancy is therefore low risk except for cases of very severe dilation and should not be contraindicated on the basis of aortic dilation alone.

Isolated aortic dilation. In rare cases, aortic dilation is not associated to any other anomaly and appears to be isolated. In such cases, it seems to be essential to rule out a family history of dissection or unexplained sudden death, especially amongst young relatives in the direct line, and severe systemic arterial hypertension (which should be investigated if necessary to rule out secondary forms). In cases of isolated aortic dilation the risk of dissection seems to be higher for severe dilations (aortic root diameter $>$55 mm) and prophylactic replacement surgery is then reasonable to be advised. Risks for lesser degrees of dilation appear to be low, although an individual assessment is necessary, evaluating the presence of aortic valve disorders, the progression of the dilation over time and a complete study of the aorta. Naturally, arterial pressure must be strictly controlled during pregnancy (with beta-blocker therapy if necessary), with intensive monitoring of the aorta during pregnancy.

Aortic coarctation (WHO II-III)

Maternal cardiovascular risk. Pregnancy is generally well tolerated in women with corrected aortic coarctation without residual lesions. Data indicate that the risk of pregnancy-associated hypertension, including pre-eclampsia, is higher in these patients. On the other hand, in patients with significant re-coarctation or women with un-operated coarctation there is a high risk of low placental perfusion, with possible intrauterine growth retardation and foetal death. Moreover, these patients have a higher risk of aortic dissection or intracranial haemorrhage, especially during the last 3 months or the perinatal period. The presence of aortic dilation or bicuspid aortic valve disorder increases the risk of cardiovascular complications during pregnancy.

Obstetric and foetal risk. A high rate of recurrence of congenital heart defects with left outflow obstruction (including hypoplastic left heart syndrome) is reported in the foetuses of women with aortic coarctation. Pregnancy-related hypertension disorders are more frequent than in pregnant women without coarctation, as are the risks of miscarriage or intrauterine foetal death.

Clinical management. In women with coarctation which has been corrected without residual effects, the risk associated to pregnancy is low (Panel C). An advanced imaging assessment is needed, not only of the corrected site, but of the entire aorta prior to conception (if this has not recently been done during patient follow-up). In women with significant re-coarctation or uncorrected coarctation, pregnancy should be postponed pending correction of the lesion (*Figure 3*). In pregnant women in whom un-operated coarctation or significant re-coarctation is diagnosed, percutaneous treatment is possible and should be considered, usually during the second 3 months of pregnancy.

Perinatal period. Vaginal delivery is usually recommended in all cases (unless there are foetal or obstetric contraindications). The use of epidural anaesthesia is recommended above all in patients with systemic arterial hypertension. Caesarean section is only recommended for cardiovascular reasons in cases with severe aortic dilation or uncontrolled arterial hypertension.

Ebstein's anomaly of the tricuspid valve (WHO II-III)

Maternal cardiovascular risk. Few data are available concerning cardiovascular risk in women with Ebstein's anomaly of the tricuspid valve during pregnancy. Severe tricuspid valve regurgitation associated to severe ventricular 'atrialisation', defines these patients as at risk of congestive cardiac insufficiency with central venous pressures increase. Moreover, accessory atrial-ventricular pathways often coexist, leading to the risk of arrhythmias, which may be exacerbated by the increased haemodynamic load generated by pregnancy. This condition is often associated with an ostium secondum type atrial septal defect, which may lead to right-to-left atrial shunts and systemic desaturation, often severe, especially in patients with high right atrial filling pressure.

In cases associated to left ventricular cardiomyopathies (left ventricular non-compaction), the risk of possible systolic dysfunction and mitral valve regurgitation coexists.

Obstetric and foetal risk. Some data indicate a moderate risk of pre-term birth, low-birth weight, intrauterine growth retardation and foetal death, especially in patients with severe systemic desaturation.

Clinical management. In women with no or mild symptoms (NYHA Class I-II) with no history of atrial or ventricular arrhythmias, normal haemoglobin saturation, and only moderate valvular regurgitation, pregnancy is generally free from complications, at medium–low risk.

In cases with severe desaturation combined with a serious patent atrial septum but only moderate tricuspid valve regurgitation, the percutaneous or surgical closure of the atrial septal defect can be considered prior to conception, in order to improve the level of saturation.

Women with signs or symptoms of cardiac insufficiency and severe tricuspid valve regurgitation should be advised to undergo heart surgery (valvuloplasty or replacement with a biological prosthesis) before planning pregnancy.

Moreover, patients with a history of complex arrhythmias should undergo an electrophysiological test prior to conception.

Perinatal period. Birth should be vaginal (if no obstetric or foetal contraindications) in most patients. Breastfeeding is usually possible.

Tetralogy of Fallot (WHO Class II-IV)

Maternal cardiovascular risk. Tetralogy of fallot is one of the most common cyanotic CHD in humans. The number of patients with corrected tetralogy of Fallot who reach childbearing age is steadily increasing. Although pregnancy in

women with uncorrected disease is recorded, the severe systemic desaturation associated to the right-to-left shunt is a major risk factor for maternal morbidity (including the risk of cardio-embolism events) and foetal mortality.

Conversely, in patients in whom the defect has been corrected pregnancy is usually well tolerated, although complications have been reported, both for the mother (cardiovascular: arrhythmias, congestive cardiac insufficiency, progressive aortic dilation, or thromboembolism; obstetric: miscarriage, pre-eclampsia, and premature birth) and the foetus (low-birth weight, recurrence of congenital heart defect).

Individual risk analysis can be even more complex due to the considerable anatomical variety within this category and the different correction procedure patients may have undergone. The risk of cardiovascular complications is greatest in patients with severe obstructions of the right ventricular outflow, systolic dysfunction, and severe right ventricle dilation, and moderate–severe or severe tricuspid valve regurgitation.

The propensity to arrhythmias (atrial and ventricular) usually varies with haemodynamic changes and is probably higher in women with a history of arrhythmia prior to conception.

There is currently disagreement concerning the role of pulmonary regurgitation in defining patients with tetralogy of Fallot as at high risk during pregnancy. Small studies suggest that interaction between severe pulmonary regurgitation and pregnancy in patients with corrected tetralogy of Fallot predisposes to accelerated progressive ventricular dilation.

Obstetric and foetal risk. Foetal risk is high in patients with severe desaturation ($<$85%). Obstetric and foetal complications are probably more frequent in women who require cardiovascular medical therapy before pregnancy, and in those in a high NYHA FC (III–IV) before pregnancy.

Clinical management. In patients with uncorrected heart defects and systemic arterial saturation $<$85%, pregnancy is usually contraindicated and surgical correction of the heart defect should precede pregnancy (*Figure 3*).

Women with corrected tetralogy of Fallot, normal biventricular systolic function and favourable anatomy (no right ventricular outflow obstruction, no severe pulmonary regurgitation, no severe stenosis of the peripheral pulmonary branches, no dilated ascending aorta) can be assessed at regional centres, usually tolerate pregnancy without any particular complications and only require assessment at specialistic centres in response to individual risk factors (*Figure 3*, Panel C).

In patients with more unfavourable anatomy, assessment in referral centre with experience in the care of adults with CHD is required, in order to identify patients with increased risk and provide a tailored pre-conception assessment (*Figure 3*), with second-level diagnostic procedures if necessary (including cardiopulmonary tests and cardiovascular magnetic resonance); in selected patients, these tests may reveal anatomical defects which can be corrected prior to conception to reduce the risk of complications during pregnancy (pulmonary vascular rehabilitation, surgical, or percutaneous pulmonary valve replacement).

In selected cases, a severe symptomatic left ventricle dysfunction may be a contraindication for pregnancy.

In women with tetralogy of Fallot and high-risk profile, monitoring during pregnancy will involve monthly or twice monthly clinical checks (Panel D) with the possibility of hospitalization in case of complications.

In women with severe aortic dilation ($>$55 mm), a team assessment may be necessary to consider the replacement of the ascending aorta before conception.

Perinatal period. Vaginal delivery is possible in most cases. Elective caesarean section may be considered in women with severe signs and symptoms of cardiac insufficiency, complex arrhythmias or severe aortic dilation.

Complete atrioventricular block (WHO Class II–III).

Maternal cardiovascular risk. Complete atrioventricular block in women considering pregnancy or already pregnant may be due congenital heart block in a minority of patients, or may complicate the medical history of women with repaired CHD. Implantation of a pacemaker (endocavitary or epicardial) is very common women with acquired or surgical-related heart block, women with congenital block or recent onset or undiagnosed acquired atrioventricular block may not have received an implant and are a group of patients for whom assessment prior to conception or during pregnancy is particularly complex. In fact, the lower chronotropic reserve may jeopardize physiological cardiovascular adaptation of the heart rate during pregnancy, especially during the last 3 months and the perinatal period. The patient is therefore at risk for congestive cardiac insufficiency with symptoms such as asthenia, pre-syncope, or syncope and effort dyspnoea.

Obstetric and foetal risk. None of the available data suggest an increase in obstetric complications in patients with complete atrioventricular block. Foetal complications are mostly secondary to maternal haemodynamic impairment, or to a possible maternal congenital heart defect.

Clinical management. Women with complete atrioventricular block who have already been implanted with a definitive pacemaker are not a group with a particularly high risk of complications and in general no contraindication to pregnancy is reported. Pacemaker battery lifetime should be assessed before conception in order to avoid elective replacement during pregnancy or the puerperal period (although this is not contraindicated when necessary).

In case of congenital atrioventricular block, especially without symptoms, large QRS complex, complex arrhythmias, or significant increase of the QT interval, pregnancy is usually well tolerated and the need for pacing during pregnancy is extremely rare. In women with symptoms suggesting bradycardia, particularly large QRS complex, ventricular dysfunction or bradycardia-related complex arrhythmias, it may be reasonable to proceed with definitive pacemaker implantation before conception. However,

even if temporary pacing or the implantation of a permanent pacemaker becomes necessary during pregnancy (e.g. in patients who are symptomatic or show signs of low output), this is usually low-risk for both the mother and the foetus, especially after the first 3 months. (Panel D).

Perinatal period. Vaginal delivery is not contraindicated (except for obstetric–foetal reasons), nor is breastfeeding. Temporary pacing during the perinatal period may be an emergency stabilization treatment strategy in patients who develop bradycardia arrhythmia symptoms during labour or the puerperal period.

Cardiomyopathies

Hypertrophic cardiomyopathy (WHO Class II-III)

Maternal cardiovascular risk. Hypertrophic cardiomyopathy is becoming increasingly frequent in women of childbearing age or during pregnancy; its physiological and pathological characteristics may interact unfavourably with pregnancy.[135–166] The vast majority of patients can tolerate the haemodynamic strain of pregnancy and the puerperal period. Risk factors for clinical deterioration during pregnancy are the presence of symptoms (especially dyspnoea) before pregnancy and probably the presence of a severe obstruction to left ventricular outflow. Labour and the period immediately after delivery may be a high-risk moment, especially for patients with severe ventricular outflow obstruction. The tendency to develop dangerous arrhythmias does not seem to change significantly with pregnancy, but few data are available. Paroxystic episodes of atrial fibrillation, often not well tolerated, are described.

Many patients are receiving chronic treatment with beta-blockers. Usually drugs in this class are well tolerated during pregnancy, although a low risk of foetal growth retardation is reported (especially with atenolol).

Obstetric and foetal risk. Since the disease is transmitted by dominant autosomal transmission with incomplete penetrance, this issue is to be discussed with the patient during the pre-pregnancy counselling. There are no reports of foetal morbidity and obstetric complications directly traceable to the disease.

Clinical management. Only few studies have analysed pregnancy in patients suffering from hypertrophic cardiomyopathy.

Women with few or no symptoms and without severely obstructed ventricular outflow can be reassured, and in these cases pregnancy usually involves a low risk of cardiovascular morbidity.

Women with severe symptoms of left outflow obstruction, receiving optimized medical treatment, should be encouraged to undergo non-pharmacological procedures to reduce the gradient before planning a pregnancy.

Patients with symptoms of cardiac insufficiency and without left ventricular outflow obstruction are a group at higher risk of a deterioration of FC during pregnancy, with risk of pulmonary oedema, especially during the perinatal period. In these cases, careful assessment is required, with advanced cardiovascular imaging, at a specialist centre (*Figure 3*, Panel D).

Pregnancy does not seem to be associated to an increase in the risk of sudden death. However, it is reasonable to identify patients suitable for implantation of an implantable cardioverter defibrillator (ICD) prior to conception. The presence of an ICD does not appear to be a contraindication for pregnancy, although non-fatal complications have been reported.

The need for anticoagulant therapy prior to conception (usually only affecting patients with a history of atrial fibrillation) causes clinical problems since no optimal treatment strategy is available which protects the patient from thromboembolic risks without causing a risk for the foetus. Choices should be made on a case-by-case basis in these circumstances (*Figure 4*).

Women receiving treatment with beta-blockers before pregnancy should continue this therapy.

Generally, the correct response to symptoms and signs of cardiac insufficiency is pharmacological treatment with beta-blockers and low doses of diuretic. Paroxystic episodes of atrial fibrillation, especially at high-ventricular response frequency, are often not well tolerated and should be treated by means of rate control or external electric cardioversion, especially in case of haemodynamic impairment (foetal monitoring is useful immediately after cardioversion).

In the rare cases with systolic dysfunction and progressive ventricular dilation (end-stage), the disease prognosis is extremely unfavourable, carrying the risk of death due to refractory cardiac insufficiency and the need for mechanical ventricular assistance or heart transplant during the follow-up. These patients are at very high risk of sudden death. In these rare cases, pregnancy would appear to be contraindicated.

Perinatal period. In women with unobstructed ventricular outflow and in NYHA Class I–II, vaginal delivery is generally preferable (barring obstetric or foetal indications) and is well tolerated (Panel E). In patients with major left ventricular outflow obstructions, the venous pooling effect of the Valsalva manoeuvre, associated with increased catacholaminergic tone, may cause a clinically significant reduction in cardiac output during the expulsion phase of labour. The assistance of an expert anaesthetist in these cases is absolutely essential.

There is a risk of pulmonary congestion after delivery, and therefore, especially with women with symptoms of cardiac insufficiency during the ante-natal period, clinical monitoring should be extended and diuresis aided with low doses of diuretic. Breastfeeding is generally possible.

Dilatative cardiomyopathy (WHO Class II-IV)

Maternal cardiovascular risk. Dilatative cardiomyopathy in women of childbearing age may have many different aetiologies and includes genetic or hereditary cases, can be related to treatment with cardio-toxic drugs and, more rarely, can be related to inflammation or ischaemia.

Women with dilatative cardiomyopathy are at risk of the onset of symptoms and signs of cardiac insufficiency during pregnancy and the puerperal period. Moreover, in cases with severe ventricular dysfunction or forms with left ventricular non-compaction, there is a risk of cardiogenerated thromboembolism, which appears to be exacerbated by the hyper-coagulation associated with pregnancy.

Obstetric and foetal risk. Complications for both the mother (non-cardiac death, pregnancy-induced hypertension and post-natal haemorrhage) and the foetus (pre-term birth, low birth weight, neonatal respiratory distress, intraventricular haemorrhage and intrauterine or neonatal death) are reported and may complicate the most severe forms of cardiac disease.

Almost 35% of cases of idiopathic dilatative cardiomyopathy show hereditary segregation, which may imply the risk of recurrence of in offspring.

Clinical management. The pre-conception assessment of patients with dilatative cardiomyopathy must include a thorough clinical assessment, in order to identify the risk factors related to acute events during pregnancy and the perinatal and puerperal periods (*Figure 2*, Panel B). Asymptomatic patients with fairly normal ejection fraction (EF) and no history of cardiovascular events (pulmonary oedema, complex arrhythmias or stroke) have a low risk of cardiovascular complications during pregnancy.

In the (uncommon) cases of women in NYHA Class III–IV, with EF below 45% and a history of cardiac events, the risk of even serious complications is substantially increased and, further to individual assessment, some patients may have a risk profile which makes pregnancy contraindicated (*Figure 3*, Panel B). Very high-risk cases include the presence of severe ventricular dysfunction (EF $<$20%), the need for anticoagulant therapy, severe biventricular dysfunction, PH, and a history of complex arrhythmias.

Last but not least, counselling is particularly though in the group of women with a history of *peripartum cardiomyopathy*. There are significant physiopathological and clinical differences between this condition and non-peripartum dilatative cardiomyopathy. The risk of recurrence in the event of a second pregnancy is extremely high (20–50%), especially if the systolic function of the left ventricle has not completely recovered. Therefore, especially in cases of residual left ventricle dysfunction, the risk profile appears to be extremely high, to the point where pregnancy is contraindicated. In cases of peripartum cardiomyopathy in which the systolic function has subsequently been normalized, the risk of recurrence and cardiovascular complications (including cardiac death) is definitely lower, although a complication-free pregnancy cannot be guaranteed.

In pregnant women with dilatative cardiomyopathy or in patients who are considering a pregnancy, a thorough study of the pharmacological record is essential, since some drugs used for the treatment of chronic cardiac insufficiency are contraindicated in pregnancy due to their teratogenic or toxic effects on the foetus (Panel A).

The aims of the treatment of cardiac insufficiency in pregnancy are the same as in women who are not pregnant. Since ACE inhibitors, ARBs, and aldosterone antagonists are contraindicated, alternative molecules must be used. Beta-blocker therapy is usually well tolerated and the foetal risk is low. If vasodilation therapy is required, hydralazine, nitro-derivatives, and amlodipine have been used in pregnancy, especially in women with systemic arterial hypertension. The use of diuretics is not contraindicated, although there is a theoretical risk of oligohydramnios in the case of aggressive diuresis. The risk of arrhythmias during pregnancy is higher in women with a history of arrhythmias prior to pregnancy. Beta-blockers, digoxin, and calcium antagonists can be used for acute rate control in the main supraventricular arrhythmias. In case of haemodynamically tolerated ventricular arrhythmias amiodarone can be used, although it is not usually recommended as a long-term treatment due to adverse effects on the foetus. In these cases, procainamide provides a second choice for the control of arrhythmias (in hospital, for high-intensity treatments). External electric cardioversion followed by foetal monitoring is recommended in all cases of arrhythmias with haemodynamic impairment.

In all pregnant women who require anticoagulant therapy, there is no treatment protocol that is risk-free for mother and foetus (*Figure 4*).

Perinatal period. The perinatal period is critical and its management requires a multidisciplinary assessment involving a cardiologist, gynaecologist–obstetrician, and anaesthesiologist. In high-risk cases, in patients with symptoms and in the (unusual) cases where the perinatal situation is complicated by haemodynamic impairment, a coordinated strategy for management of the high risk level is required (Panel E).

The post-natal period may be complicated by a deterioration in cardiac insufficiency due to fluctuation of the catecholaminergic tone, anaemia, and autotransfusion, with the risk of acute pulmonary oedema. Arrhythmias and cerebrovascular events are also possible. Therefore, intensive monitoring for 12–24 h, depending on the patient's individual characteristics, is generally recommended. Cases of severe anaemia should also be properly dealt with in order to reduce secondary tachycardia and an increase in the cardiac workload.

Restrictive cardiomyopathy (WHO Class III-IV)

Restrictive cardiomyopathy is a rare myocardial disease involving a severe impairment of the diastolic properties of the ventricles, restrictive filling of the ventricles with high-telediastolic ventricular pressures, normal or almost normal left ventricular systolic function, and an unfavourable prognosis. Very few data are available relating to the risk associated to pregnancy in women with restrictive cardiomyopathy. However, the disease physiopathological features interact unfavourably with natural cardiovascular changes that occur during pregnancy. In general, in the absence of sufficient evidence and on the basis of this disease unfavourable prognosis, it appears reasonable to consider these patients at high risk and thus to advise against pregnancy, especially in symptomatic patients.

'*Systemic*' right ventricle

Transposition of the great arteries after 'physiological' correction (atrial switch)

The natural history of transposition of the great arteries (TGA) dramatically changed in the 60s with the introduction of the technique pioneered by Senning and Mustard (*atrial switch*), which redirect the blood flows within the atria, leaving the morphological right ventricle to support the systemic circulation *(systemic right ventricle)*.[167–186] These techniques, subsequently replaced from the 80s onward by anatomical correction *(arterial switch)*, are still used today in particularly complex cases.

In spite of this, the long survival time provided by Senning and Mustard's technique has allowed a considerable number of operated women to reached childbearing age, although 20-year follow-ups have revealed a gradual dysfunction of the right ventricle, leading to a worsening of tricuspid valve regurgitation, and a consequent rapid deterioration of the ability to adapt to physical effort.

'Congenitally corrected' transposition of the great arteries (double discrepancy)

This malformation is rare (0.4–0.6% of all congenital heart defects) and is the embryological result of an incorrect looping of the cardiac tube, which results in a double atrioventricular and ventricular-arterial discrepancy: left atrium-right ventricle-aorta (LA-RV-AO) and right atrium-left ventricle-pulmonary artery (RA-LV-PA).

It is rare in its 'isolated' form (about 5%). Congenitally corrected TGA (TGAcc) is often associated with anomalies which lead to abnormally low or high pulmonary blood flow, atrioventricular blocks, or tricuspid valve defects which cause symptoms to appear earlier than in the 'standard' form (67% compared with 25%).

As in TGA corrected by atrial switch surgery, the right ventricle performs a 'systemic' role.

Systemic right ventricle dysfunction: pathological mechanism

The right ventricle's relative inability to cope with a 'systemic' function is due to its anatomical and physiological peculiarities (volume pump), in which it differs from the left ventricle (pressure pump). The changes in the geometrical form of the right ventricle in response to high pressures also causes a distortion of the tricuspid valve, leading to insufficiency of the valve due to failure of the leaflets to coapt.

Tricuspid valve regurgitation is a risk factor regardless of mortality in these patients, and affects the survival both of operated patients (34% vs. 90%) and those who have not been operated (60% vs. 100%).

Contractile dysfunction of the systemic right ventricle is also due in part to *unbalanced* myocardial perfusion (increase in wall stress), the end result of which (fibrosis) is reflected in EFs $<$40%. Left ventricle EF is also lower in these patients, revealing the negative influence of the right ventricle.

Systemic right ventricle and pregnancy

Having a morphological right ventricle serving the systemic circulation is associated with progressive ventricular systolic dysfunction, systemic tricuspid valve regurgitation and arrhythmias (*Table 15*).

- Right ventricular function and FC

Retrospective data on right ventricular function impairment in women (pregnant or not) who have undergone *atrial switch* surgery, reveal a similar EF in the two groups, with more evident deterioration of tricuspid regurgitation in the pregnant group and poorer EF recovery after birth in older women: these data confirm the tendency to right ventricular dysfunction in the clinical history of operated patients, and make it advisable to plan a pregnancy at a fairly young age. Generally speaking, the data available, which are not derived from large groups, confirm a deterioration in systemic RV function during pregnancy, which rarely reaches failure but which may not recover postnatally in a variable percentage of up to 70% of cases. Similarly, in some series a significant deterioration of FC is reported in pregnant compared with non-pregnant women who have undergone *atrial switch*, in a percentage varying between 20 and 40%, probably partly due to the kind of criteria used in deciding if advising for or against pregnancy in the most severe cases.

The prolonged volume overload generated by pregnancy might explain why the deterioration in FC after delivery in patients who have undergone *atrial switch* compared with the controls (non-pregnant *atrial switch* patients) is minimized during long-term follow-up, basically supporting the hypothesis that pregnancy someway accelerates the process of clinical deterioration already described in the natural history of atrial switch patients (3rd–4th decade) (*Table 16*). In addition, the post-partum period often carries high risk of significant increase of pulmonary venous pressure due to a combination of auto-trasfusion with increased ventricular pre-load and rigid intra-atrial baffles with potential for abnormal diastolic properties leading to reduce ability to handle the haemodynamic load of this phase. This may have clinical consequences, because some women (in particular in the setting of severe tricuspid regurgitation and abnormal systemic ventricular function) may present with signs of pulmonary congestion and oedema after delivery, and prolonged observation in hospital may be reasonable.

- Arrhythmias

Arrhythmic events are frequent in the follow-up of *atrial switch* patients, both pregnant and not pregnant (62% vs. 53%), due above all to the many intra-atrial suture lines.

Arrhythmias are definitely more common in women who already had a clinical history of arrhythmia before pregnancy. Due to the specific nature of its conduction tissue, TGAcc may involve the risk of complete atrioventricular block.

- Obstetric and neonatal complications

Vaginal delivery should not be ruled out for asymptomatic or slightly symptomatic women and when contractile function of the systemic right ventricle is good caesarean section is justified on obstetric grounds, or if the patient is

Table 15 Pre-pregnancy clinical approach to women with systemic right ventricle

'Systemic' right ventricle: Counselling	
WHO III	
Pre-conception	During pregnancy
Cardiology examination Electrocardiogram Transthoracic ± transoesophageal Echocardiogram Holter ECG (arrhythmias) Cardiopulmonary stress test (functional capacity) Cardiac nuclear magnetic resonance	1 month/2-month follow-up • Cardiological examination • Electrocardiogram • Transthoracic ± transoesophageal echocardiogram • Holter ECG (arrhythmias).
If: FC III-IV Systemic right ventricle EF < 40% Severe tricuspid regurgitation WHO IV ↓ Pregnancy not recommended	

Table 16 Potential complications during pregnancy in women with systemic right ventricle

Right ventricle
Risk of: • deterioration of the contractile function of the systemic right ventricle • increase in tricuspid (systemic atrioventricular valve) regurgitation • risk, during post-natal period, of failure to recover in right ventricle contractile function • arrhythmias • miscarriages, intrauterine growth retardation, premature births

Table 17 Modality of delivery in women with systemic right ventricle

Right ventricle	
Systemic right ventricle: type of delivery	
Satisfactory clinical condition SRV EF > 40% ↓ Vaginal delivery	Symptoms: FC III-IV SRV EF < 40% ↓ Caesarean section

SRV, systemic right ventricle; FC, functional class; EF, ejection fraction.

symptomatic and the contractile function of the systemic right ventricle is impaired (EF <40%) (*Table 17*).

A high rate of miscarriage (20–30%) is described and neonatal complications are common in terms of both premature births (30–50%) and intrauterine growth retardation (>30%) due to the decrease in placental perfusion caused by the progressive deterioration of the contractile function of the systemic right ventricle.

Single ventricle physiology

The term *univentricular heart* covers a wide spectrum of cardiac malformations, in which the atresia of an atrioventricular valve, or the hypoplasia or absence of a ventricle, makes biventricular correction impossible.[187-210]

In *Fontan circulation*, the subpulmonary ventricular pump is absent and the caval and pulmonary pressures are the same, which explains the high risk of caval stasis and systemic hypoperfusion.

In women with *Fontan circulation*, the onset of menstruation is delayed (primary amenorrhea); oligo and polymenorrhea and low fertility are common. The possibility of a pregnancy is conditional on a careful assessment of the pregnancy-related risk.

The risk is low in the case of NYHA Class I/II, EF ≥50%, only minimal atrioventricular valve regurgitation and no arrhythmias or embolic events.

The risk increases if symptoms are present (NYHA Class II/III) together with impaired EF (<50%), significant (II/III) atrioventricular valve regurgitation, arrhythmias, and embolic events.

Pregnancy is strongly contraindicated for patients with severe symptoms (NYHA III/IV), cardiac function impaired by low-ventricular contractility (EF <40%) and serious (III/IV) atrioventricular valve regurgitation. O_2 saturation <85% and/or the presence of a protein-losing syndrome worsen the prognosis.

Maternal-foetal risks

Arrhythmias are amongst the most common complications, especially in *classic* Fontan circulation. A high-frequency arrhythmia may lead to cardiac insufficiency and must therefore be interrupted by using drugs or electric cardioversion.

Both pulmonary and systemic embolic events are frequent, especially during the post-natal period, as are

genital and uterine haemorrhages, generally due to long-term treatment with antiplatelet or anticoagulant drugs.

The single ventricle is unable to tolerate the increase in blood volume during pregnancy, especially in the case of a right single ventricle and/or if there is significant atrioventricular valve regurgitation. Pregnancy-related cardiac insufficiency may occur during pregnancy and regress after the birth as the blood volume normalizes, or may occur postnatally.

The rate of miscarriage due to the reduced placental flow may be as high as 50%.

During labour, it is important to maintain a satisfactory transpulmonary gradient, prevent an increase in pulmonary valve resistance and maintain vena cava return, in order to preserve cardiac output. Therefore, epidural is preferable to general anaesthesia.

Caesarean section may be indicated in situations such as maternal cardiac insufficiency, uncontrolled maternal arrhythmias, uncontrolled embolic events or premature rupture of the membranes.

Due the rapid increase in the preload, the post-natal period is critical, with a risk of pulmonary oedema, especially in patients with impaired cardiac function, and thromboembolism.

Foetal problems including growth retardation, low birth weight (poor uterine-placental perfusion), premature birth (69% of newborns) or even death are particularly common.

Pulmonary hypertension

Definition, classification, and epidemiology

Pulmonary hypertension (PH) is a condition characterized by an increase in mean pulmonary pressure ($\geq$25 mmHg) at rest, documented by means of right cardiac catheterization.[211-239]

Pulmonary hypertension may be a complication of a large number of diseases and its physiopathology and treatment vary depending on the cause; it can therefore be subdivided into several different classes (*Tables 18* and *19*).

Pulmonary hypertension during pregnancy implies a high risk of complications and death for both the mother and the child.

Table 18 Pulmonary hypertension. Clinical classification[217]

1 Pulmonary arterial hypertension
1.1 idiopathic
1.2 hereditary
1.2.1 BMPR2 mutation
1.2.2 Other mutations
1.3 Induced by drug-taking and toxins
1.4 Associated to
1.4.1 Connective tissue diseases
1.4.2 HIV infection
1.4.3 Portal hypertension
1.4.4 Congenital heart defects
1.4.5 Schistosomiasis
1' Pulmonary vein occlusive disease and/or pulmonary capillary haemangiomatosis
1'' Newborn persistent pulmonary hypertension
2 Pulmonary hypertension due to left heart diseases
2.1 Systolic dysfunction
2.2 Diastolic dysfunction
2.3 Valve disorders
2.4 Congenital or acquired cardiomyopathy with obstruction of inflow or outflow section of the left ventricle: congenital cardiomyopathies
2.5 Congenital or acquired pulmonary vein stenosis
3 Pulmonary hypertension due to lung disease and/or hypoxia
3.1 Chronic obstructive bronchitis
3.2 Pulmonary interstitial disease
3.3 Lung diseases with mixed obstructive and restrictive pattern
3.4 Ventilatory disorders while sleeping
3.5 Alveolar hypoventilation
3.6 Chronic exposure to high altitudes
3.7 Growth disorders
4 Pulmonary hypertension due to chronic pulmonary thromboembolism and other pulmonary artery obstructions
4.1 Pulmonary hypertension caused by chronic thromboembolism
4.2 Other obstructions of the pulmonary artery
4.2.1 Angiosarcoma
4.2.2 Other intravascular tumours
4.2.3 Arteritis
4.2.4 Congenital stenosis of the pulmonary arteries
4.2.5 Parasitosis (hydatidosis)
5 Pulmonary hypertension with unclear and/or multifactor pathogenic mechanisms
5.1 Haematological disorders: chronic haemolytic anaemia, myeloproliferative disorders, splenectomy
5.2 Systemic disorders: sarcoidosis, pulmonary histiocytosis, neurofibromatosis, lymphangioleiomyomatosis
5.3 Metabolic diseases: glycogenosis, Gaucher disease, thyroid diseases
5.4 Others: pulmonary tumoral thrombotic microangiopathy, fibrosing mediastinitis, chronic renal failure with or without dialysis, segmental pulmonary hypertension

Physiopathology

In order to understand the pregnancy-related risk for women suffering from PH, it is necessary to be familiar with the physiological changes which occur in the cardiopulmonary system throughout pregnancy (see Physiological changes to the cardiovascular system during pregnancy).

Although their physiopathological origins may differ, the various forms of PH all feature an inadequate vasodilatory response to an increase in cardiac output, with an increase in mean pulmonary artery pressure which triggers dysfunction and insufficiency of the right ventricle.

In patients with PAH, the underlying factor is a deficiency of nitric oxide and prostacyclin (which has a vasodilatory action) and increased activation of Endothelin 1 (EDN 1) (with a vasoconstrictor action) in the pulmonary vascular bed. However, the pro-proliferation function on the smooth muscle cells of the pulmonary vessels mediated by E2 (17-beta-estradiol) remains unchanged, and causes the detrimental reshaping of the pulmonary vessels.

In patients with chronic thromboembolism, it is this vascular remodelling which prevents vasodilation.

Maternal death is most common during the last 3 months and the first month after the birth, but undoubtedly the

Table 19 Type 1 pulmonary arterial hypertension (see Section Congenital heart defects) associated with congenital heart defects

Eisenmenger syndrome: this includes all systemic-pulmonary shunts due to large defects which lead to a net increase in pulmonary arterial resistances and cause a reverse (pulmonary-systemic) or bidirectional shunt.
It is characterized by cyanosis, erythrocytosis, and multiple organ involvement.
Possible complications are haemoptysis, cerebrovascular accidents, cerebral abscesses, modified coagulation, and sudden death.
Maternal mortality rates vary in the different series, from 20 to 50%[27]
In pregnancies of this kind the risk to the foetus is particularly high: if oxygen saturation is less than 85% the likelihood of a live birth is less than 12%.[216]
But the risk is high even in the event of a termination of the pregnancy[48]
The risk of thromboembolism is high but at the same time patients are exposed to a high risk of haemoptysis and thrombocytopenia and the decision to administer anticoagulant therapy must be carefully assessed.
The serious desaturation stimulates the production of erythrocytes, which increases the viscosity of the blood; therefore, great caution must be taken when using diuretics.
An iron deficiency has been recorded in 56% and has a negative prognostic value[217]
Pulmonary arterial hypertension associated to systemic-pulmonary shunt
In patients in this category with moderate or large defects, the increase in pulmonary arterial resistances is from mild to moderate, there is still a large systemic-pulmonary shunt and there is no cyanosis at rest
Pulmonary arterial hypertension with minor defects
With small defects (VSD <1 cm and ASD <2 cm in diameter, effectively documented by echocardiogram) the clinical picture is very similar to that of idiopathic PAH
Pulmonary arterial hypertension after corrective heart surgery
In these cases, the CHD has been corrected but PAH is either still present immediately after the surgery or has recurred several months or years after the operation, in the absence of significant residual post-operative congenital defects or defects which develop as a consequence of the surgery

VSD, ventricular septal defect; ASD, atrial septal defect; PAH, pulmonary arterial hypertension; CHD, congenital heart disease.

delivery itself is extremely dangerous due to the concomitance of several factors:

- the negative inotropic effect on the right ventricle mediated by testosterone,
- the vasoconstrictor effect linked to the sharp drop in the levels of oestrogens and dehydroepiandrosterone (DHEA)
- the shift in volumes arising from the shrinkage of the uterus after expulsion of the foetus
- the consequent fluctuations in endovascular pressure,
- the Valsalva manoeuvres
- the increase in the right-to-left shunt in the foramen ovale → consequent
- ↑ hypoxia → which causes acidosis
- loss of blood.

Studies performed in periods before the introduction of prostanoids reported high mortality, with values between 30 and 56%. The latest review examines women with PAH after the introduction of prostanoids and reports a mortality rate between 17 and 33%, placing them in WHO Class IV, regardless of their actual FC, and meaning that the recommendation that pregnancies should be terminated remains unchanged.

Death occurs due to PH attacks, pulmonary thrombosis or refractory right cardiac insufficiency. This may also occur in patients in WHO Classes I–II.

Pulmonary hypertension and pregnancy

Clinical problems

- Patient with diagnosis of verified or suspected PH who wishes to plan a pregnancy (see also Section Counselling)

In this case, the even serious risks related to the pregnancy for both the mother and the child should be clearly explained and the patient should be referred to a specialistic PH centre, where the functional assessment will be performed, allowing the specific risk for the patient concerned to be estimated (see *Table 20*).

- Patient who is already pregnant

Patients with PAH must be managed by a multidisciplinary team comprising a cardiologist, a pneumologist, an anaesthesiologist, a neonatologist and a gynaecologist with expertise in high-risk pregnancies; the team members must be in constant contact and ready to deal with any complications with a pre-planned strategy, decided as a team and discussed with the patient and general practitioners (*Table 21*).

Recommended treatments and procedures: see check schedule table

General principles

Specific therapy for patients in Group I (see also Section Drugs). With regard to the choice of drugs, the general principle that the therapy must consider the FC (see Table of WHO and pregnancy-modified WHO CLASSES) and comorbidities applies.

The specific therapy for PAH must be maintained and/or increased with the aim of pursuing the 'therapeutic goals'[10] (without cardiopulmonary tests and with the use of catheterization only if actually necessary):

Amongst specific PAH drugs, five phosphodiesterase inhibitors and prostanoids can be used during pregnancy (*Tables 22–24*).

Table 20 Risk stratification in patients with pulmonary hypertension

Key factors for prognosis Mortality at 1 year	LOW risk <5%	Intermediate risk 5-10%	High risk >10%
Clinical signs of right ventricular insufficiency	Absent	Absent	Present
Progression of symptoms	No	Slow	Rapid
Syncope	No	Occasional	Frequent
WHO Functional Class	I-II	II-III	IV
Walking test	>440 m	165-440 m	<165 m
Cardiopulmonary test	VO_2 peak >15 mL/min/kg (65% of predicted value) VE/VCO_2 slope <36	VO_2 Peak 11-15 mL/min/Kg (35-65% of predicted value) VE/VCO2 slope 36-44.9	VO_2 Peak <11 mL/min/kg (<35 % of predicted value) VE/VCO_2 slope ≥45
NT-proBNP	BNP <50 ng/L proBNP <300 ng/L	BNP 50-300 ng/L proBNP 300-1400 ng/L	BNP >300 ng/L proBNP >1400 ng/L
Echocardiogram or nuclear magnetic resonance	Right atrium area <18 cm^2 No pericardial effusion	Right atrium area 18-26 cm^2 No minimal pericardial effusion	Right atrium area >26 cm^2 Pericardial effusion
Haemodynamic parameters	Pressure in right atrium <8 mmHg Cardiac index > 2.5 L/min/m2 SVO_2 >65%	Pressure in right atrium 8-14 mmHg Cardiac index 2.0-2.4L/min/m^2 SVO_2 60-65%	Pressure in right atrium >14 mmHg Cardiac index < 2.0 L/min/m^2 SVO_2 <60%

Modified from LG ESC 2015[215].
BNP: brain natriuretic peptide.

Table 21 Modality of follow-up during pregnancy in women with pulmonary hypertension

Pulmonary hypertension during pregnancy		
Follow-up		
First 3 months Monthly	Middle 3 months Monthly	Last 3 months Weekly
Examination	Examination	Examination
Echocardiogram	Echocardiogram	Echocardiogram
BNP	BNP	BNP
Walking test	Walking test	Walking test
Suspend warfarin	Start low molecular weight heparin if patient is confined to bed	Start low molecular weight heparin if patient is confined to bed
Suspend etra	Optimize specific PAH therapy	Optimize specific PAH therapy
Start low molecular weight heparin if patient is confined to bed	Plan fortnightly checks in case of signs of initial insufficiency	Plan caesarean section 34th week
Optimize specific PAH therapy	Hospitalization in case of signs of right ventricle insufficiency	Plan spinal anaesthesia
Therapeutic abortion in case of signs of right ventricle insufficiency	Terminate pregnancy in case of signs of right ventricle insufficiency not responsive to maximum therapy	Plan transfer to cardiology intensive care unit For post-natal monitoring

PAH, pulmonary arterial hypertension.
BNP: brain natriuretic peptide.

Patients in FC I-II can be treated in monotherapy with a five phosphodiesterase inhibitor, but a parenterally administered prostaglandin must be added at the first signs of deterioration.

Patients in FC I-II without right ventricle impairment suffering forms of PAH responsive to *calcium-antagonists* must continue their therapy, but here again intensive checks are required as they may suddenly become non-responsive.

In patients in FC III without right ventricle impairment, a prostaglandin administered by inhalation can be used: *iloprost* is the most thoroughly investigated drug.

Patients in WHO Class IV with evidence of right ventricular dysfunction must be treated with parenteral prostaglandin; the most thoroughly investigated drug is *epoprostenol*.

In Class III patients or those with evidence of right ventricle dysfunction, treatment with prostanoids at low

Table 22 Treatment of PAH with specific drugs in relation to functional class" modify the table accordingly to avoid repeatings

Treatment of PAH with specific drugs in relation to functional class	
WHO I-II	Monotherapy 5 phosphodiesterase inhibitors
WHO I-II Responders to calcium antagonists	Calcium antagonists
WHO III with right ventricle function conserved	Prostaglandin by inhalation
WHO III with right ventricle dysfunction	Parenteral prostaglandin
WHO IV	Parenteral prostaglandin + sildenafil

PAH, pulmonary arterial hypertension; WHO, World Health Organization.

Table 23 FDA class of major PAH-specific therapy

PAH drugs	PAH drugs During pregnancy (under FDA classification)
Epoprostenol	B
Treprostinil	B
Sildenafil	B
Tadalafil	C
Nitric oxide	C
Iloprost	C
Bosentan	X contraindicated
Ambrisentan	X contraindicated
Macitentan	X contraindicated
Riociguat	X contraindicated

FDA, Food and Drug Administration.

dosage (2–4 ng/Kg/min i.v) must be started during the last 3 months in order to face the delivery in the best possible haemodynamic conditions.

Treatment with low molecular weight heparin must be replaced with unfractionated heparin during the preparation for the delivery, in order to allow immediate suspension in the event of haemorrhagic complications.

Non-dicoumarol anticoagulants are contraindicated.

Particular clinical events

Right ventricular dysfunction

The presence of signs of right ventricular dysfunction in a pregnant patient with PH is in itself a strong indication for the termination of the pregnancy.

If the signs of insufficiency are already present in the *first 3 months*, therapeutic abortion is mandatory.

However, if the problem occurs during the *last 3 months*, efforts must be concentrated on reaching a late enough stage in pregnancy to enable the survival of the child, while planning a caesarean section at the earliest possible date.

Table 24 Dosing regimen of PAH-specific drugs allowed during pregnancy

Epoprostenol i.v	2–4 ng/Kg/min→20–40 ng/Kg/min
Treprostinil subcutaneous	1–2 ng/Kg/min→20–80 ng/Kg/min
Iloprost by inhalation	6–8 inhalations/day 2.5–5 μg/inhalation, medial dose 30 μg/day
Sildenafil	cp 20–40 mg three times a day
Tadalafil	cp 40 mg in a single administration
Calcium antagonists in patients already being treated with this class of drugs	Nifedipin 120–240 mg/day Diltiazem 60 mg x3 Amlodipin 2.5 mg/day
Contraindicated in Eisenmenger syndromes	

The onset of signs of insufficiency during the *middle 3 months* is the most difficult eventuality to deal with. The option of choice must be a therapeutic abortion: in the event of refusal, these patients must be admitted to a cardiological intensive care unit (*Table 25*).

Vasovagal syncope

Vasovagal syncope is most common in pregnant women with PH and is potentially fatal. Vasovagal syncope can be triggered by a wide variety of factors: anxiety, pain, excessively quick change in posture, compression of the inferior vena cava, neck manipulation, administration of vasodilators, spinal anaesthesia, or induction of general anaesthesia.

If a potential trigger factor cannot be avoided, two venous accesses and atropine should be prepared in advance.

Delivery (see also Section Labour and delivery)

Vaginal delivery

Vaginal delivery is not recommended and is only justified by the need for an urgent delivery or the impossibility of performing a caesarean section; in this case, epidural anaesthesia must be used.

Oxytocin can be used but with caution and at low dosages, because it may increase pulmonary resistances.

Caesarean section

Planned caesarean section is the preferred type of delivery.

In haemodynamically stable patients, the caesarean section must be planned between the 34th and the 36th week. In the event of initial symptoms of haemodynamic deterioration, the delivery must be brought forward, also bearing in mind the risk to mother and child of a pre-term delivery.

Pregnancy termination

Termination of the pregnancy should be considered as the first option to be offered to women suffering from PAH,

Table 25 Treatment of right ventricular dysfunction

Reduction of right ventricle afterload in forms of hypertension belonging to Group 1	Therapy with prostanoids in infusion (epoprostenol 2–4 ng/Kg/min i.v)
Reduction of right ventricle afterload in forms of hypertension belonging to Group 2	Treatment with prostanoids is not currently recommended for class 2, but short-term and acute patient studies have revealed beneficial effects.[228,229]
Metabolic acidosis	Correction of acid–base balance with slow administration of bicarbonates (Henderson–Hasselbach formula)
Hypoxaemia	Correction with O_2 and maintenance of saturation levels of at least 92%
Reduction in diuresis: check water balance	If positive, administer diuretics (furosemide)
Reduction in diuresis during diuretic therapy	Check carefully for signs of dehydration Check acid-base balance Check peripheral arterial pressure Perform haematochemical test for kidney function
In case of peripheral signs of dehydration	Peripheral vein hydration with 1000–1500 mL/24 h
In case of hypotension	Vasoactive amine to keep arterial pressure at no less than 100 mmHg, Noradrenalin
In case of metabolic acidosis with increase in lactates	Slow correction with bicarbonates and addition of dobutamine to improve cardiac output
In the event of the onset of supraventricular arrhythmias with no haemodynamic deterioration	Acute treatment with amiodarone to achieve pharmacological cardioversion within 12 h after the onset of the arrhythmia; the drug must be suspended once the sinusoid rhythm is restored and must be stopped within 48 h in all cases due to the effects on the child's thyroid. If the arrhythmia persists, digitalis will be used for rate control Anticoagulant treatment with enoxaparin
In the event of the onset of supraventricular tachyarrhythmia with haemodynamic and/or ventricular deterioration	Electric cardioversion anticoagulant treatment with enoxaparin
Life-threatening haemoptysis (>300 mL)	Correction of anaemia with transfusions Angiotac for transcutaneous embolization of bronchial arteries

however it may carries significant risk for the mother and this should prompt extensive discussion with women affected regarding the need for effective contraception.

Cyanosis

Pregnancy in cyanotic heart diseases

There are two possible categories of cardiopulmonary disease related to cyanosis.[216]

The first include CHD with right-to-left shunt, partially corrected during childhood, in which pulmonary pressures are normally not high (e.g. atresia of the pulmonary artery with systemic collateral arteries, non-severe forms of Fallot tetralogy with or without palliative correction, single ventricular heart with palliative surgery during childhood with no further correction possible, and Fontan corrections with fenestration openings still present in the duct or associated pulmonary fistulas);

The second group consists of Eisenmenger syndrome, in which the profound anatomical changes in the pulmonary arterioles render normal gaseous exchange impossible (see Section Pulmonary hypertension)

In both cases, pregnancy involves a clearly defined risk for both mother and foetus.

Maternal-foetal risks

The maternal-foetal risk is proportional to FC and maternal desaturation.

The higher maternal desaturation, the higher the maternal-foetal risk. A maternal saturation <85% implies significant complications for the mother (15–30%) and low-foetal survival (<12%). Foetal risk is significantly reduced (10%) with maternal saturation >90%.

Cyanotic heart diseases also imply a high rate of miscarriage (35–40%), less pronounced (10%) in the case of Eisenmenger S. The rate of premature births and low weight is high (40%).

The high level of maternal-foetal risk means that patients of childbearing age with PH should consider contraception (IUDs) or, in some cases, sterilization (tying of the Fallopian tubes).

Arrhythmias

The cardiovascular adaptations and haemodynamic load imposed by pregnancy may facilitate the onset of atrial arrhythmias, favoured by surgical scars or atrial dilations or, although more rarely, ventricular arrhythmias, especially in women with congenital cyanotic heart defects.[55,240-253]

Pharmacological treatment does not always prove effective in the treatment of arrhythmias in these conditions, also because it is hampered by a high incidence of adverse events and side effects for the mother and foetus.

Arrhythmias in women with congenital heart defects during pregnancy may be:

- typical of a number of repaired or un-repaired CHD and therefore independent of the pregnancy;
- directly dependent on the pregnancy and thus the result of hypoxic and/or haemodynamic stress

Brady arrhythmias are absolutely rare and generally occur in patients with severe arrhythmias prior to the pregnancy.[245]

No particular treatment is generally required, although anecdotal cases have been described of zero radiation pacemakers implanted during the last 3 months of pregnancy.

Ventricular and supraventricular extrasystolic arrhythmias are particularly frequent during the pregnancies of patients with congenital heart defects, but no particular treatment is generally required.

Tachyarrhythmias during pregnancy are mainly due to both ventricular and atrial post-incisional re-entrant events.[246] The most frequent of these arrhythmias is re-entrant intra-atrial tachycardia: the underlying cause is the presence of a large scar-related re-entry with its circuit entirely contained within the atrium, created during palliative or radical surgical correction. The arrhythmia starts suddenly and ceases just as abruptly. Duration is extremely variable, from a few seconds to days, but it's generally less than 12 h. Episodes of syncope may occur during the arrhythmia, but the event most to be feared is cardiac insufficiency due to the increase in heart rate, especially if the ventricular function is already impaired. If the systemic ventricle is the right one, due to this ventricle's specific anatomical and physiological characteristics the stress induced by the arrhythmia is even more likely to lead to insufficiency, correlated to a significant increase in morbidity and a possible increase in the foetal mortality rate.[247-251]

Arrhythmias of this kind may be very difficult to control by pharmacological means, since the common anti-arrhythmia drugs tend to depress both the automatic response of the sinoatrial node and the systolic function of the left ventricle, often impaired further to the corrective cardiac surgery procedure itself, apart from being toxic for the foetus.

- Pharmacological therapy

When choosing *pharmacological therapy for arrhythmia* during pregnancy, it is important to consider not only the type of arrhythmia to be treated and the underlying congenital heart defect but also the level of ventricular dysfunction, the potential negative inotropic effect of the drug used, the risk of changes to conduction in the sinoatrial or atrioventricular node, any pro-arrhythmic effect of the drug to be used and last, but no less important, the potential risk for the foetus.[123] Therefore, in all cases the principle always applies that, regardless of the chosen drug and especially in the case of anti-arrhythmia therapy for non-acute conditions, the minimum effective dose should always be used. For details of pharmacological therapy, refer to the Section Therapy.

It is important to state that when the onset of a tachyarrhythmia puts the haemodynamic situation at risk, *electric cardioversion (ECV)* is required; this procedure can be used during pregnancy, generally without any particular risks for the mother and foetus; however, when ECV is the chosen strategy, careful monitoring of foetal cardiac function is always recommended.

In case of patients implanted with implantable automatic defibrillator devices, especially new-generation devices, there are no negative consequences for the foetus from any electric shock. However, with previous-generation single chamber devices, inappropriate electric treatments may occur as a consequence of misdiagnosis of repetitive ventricular arrhythmia when faced with supraventricular arrhythmia or high sinus frequencies, not uncommon during pregnancy.

Additional risks related to arrhythmias during pregnancy are those due to the need for anticoagulant therapy during atrial fibrillation[252,253] (see Section Therapy)

Therapy

Cardiological and anticoagulant drugs

Pharmacological treatment during pregnancy involves both the mother and the foetus.[251,253-294] The potential risk for the foetus must always be assessed in relation to the benefit of the therapy, considering that the mother's haemodynamic balance is a fundamental requirement for the health of the foetus.

The Food and Drug Administration has established five risk classes on the basis of methodologically sound studies and the cost-benefit ratio.

Anticoagulant therapy

During physiological pregnancy, there are changes in haemostasis which lead to a higher rate of coagulation, thus reducing the risk of bleeding during labour.

Although use of heparin is considered safe for the foetus and effective for many maternal indication for anticoagulation (pre-eclampsia, anti-phospholipid syndrome, prevention, or treatment of venous thromboembolism, arrhythmias), major concern and source of confusion still remain for the optimal treatment of women with non-biological valvular prosthesis. Oral vitamin K antagonists are the most effective therapy for the prevention of thrombotic and embolic maternal complications in this setting, but are associated with a high risk of foetal complications ('warfarin embryopathy'): Between the 6th and 9th weeks of gestation, warfarin adversely affects bone development in particular, causing nasal hypoplasia and punctate chondrodysplasia; from the 4th month it may cause atrophy of the optic nerve, mental retardation and microcephaly, the consequence of multiple haemorrhages. An increased risk of miscarriage, premature births, and maternal haemorrhage is also reported. Maternal and foetal complications are probably significantly reduced if the dose of warfarin required for effective anticoagulation is $\leq$5 mg daily of warfarin-equivalent.

There are no data on the use of the new oral anticoagulants during pregnancy.

Non-fractionated heparin (NFH) does not cross the placenta and does not involve risks of foetal embryopathy, but

the use of NFH at any time during pregnancy is correlated with an increase in the risk of stillbirths and prematurity, a high incidence of thrombosis on prostheses and, in the case of prolonged use, osteoporosis and maternal thrombocytopenia. Low molecular weight heparin (LMWH) has fewer side effects; subcutaneous administration is easiest and increases the drug's bio-availability, but its effectiveness for the prevention of thrombosis on prostheses during pregnancy is still under dispute.

The dosage of LMWH must be established by means of regular checks on activated X factor (X_a) levels. Assessment of the mean value of X_a, 4 h after administration, is probably useful for determining the optimal dosage of LMWH, some authors suggest monitoring of trough level, although this recommendation is not universally accepted.

When choosing the type of therapeutic protocol, consideration must be given to the type of prosthesis (the risk of thrombosis is lower for new-generation prostheses); the risk/benefit ratio should always be discussed with the pregnant woman and her partner.

The possible strategies which can be used if anticoagulant therapy is necessary during pregnancy are set out in (*Figure 4*). In the presence of new valvular prosthesis (in particular in aortic position), the use of uninterrupted LMWH with frequent X_a monitoring and emphasis and optimal patient compliance may be considered. In case of older valve types, depending upon the dose of warfarin required for obtaining therapeutic INR, first trimester LMWH with X_a monitoring may be considered, along with reverse to warfarin therapy during second and third trimester. The use of uninterrupted warfarin throughout pregnancy may be considered in those women with old valve types and need for less than 5 mg daily of warfarin-equivalent, although this strategy may expose the foetus to the potential risk of major congenital abnormalities.

With natural deliveries, the risk of haemorrhage is not significantly increased, although this is not the case with caesarean section. In the event of pre-term deliveries with patients still receiving warfarin therapy, it may be useful to administer vitamin K, even though normal coagulative function is recovered after about 24 h, or frozen fresh plasma, to both the mother and the child. Moreover, in this event a caesarean section is to be preferred, in order to reduce the risk of foetal haemorrhage. Heparin can be restarted 6 h after the birth.

Warfarin is not secreted with maternal milk and can therefore be administered during breast feeding.

The drug normally recommended for the treatment of acute thrombo-embolic complications during pregnancy is LMWH, with the dosage established on the basis of X_a levels. The therapy must be continued for at least 6 weeks after delivery.

Systemic arterial hypertension therapy

Systemic arterial hypertension is a complication in 5–10% of all pregnancies and is a major cause of maternal and foetal morbidity and mortality.

Pharmacological therapy is indicated if the hypertension is at least moderate in degree: systolic arterial pressure (AP) $>$ 150 mmHg, diastolic AP $>$ 95 mmHg.

The threshold for the indication of treatment falls to 140/90 mmHg in the following conditions: (i) gestational hypertension; (ii) pre-existing hypertension with superimposed gestational hypertension; and (iii) hypertension with subclinical signs of organ damage or with symptoms, at any stage of pregnancy.

The ESC Guidelines recommend α *methyldopa* as drug of first choice for the treatment of AH during pregnancy, but its use is not recommended during breastfeeding due to a potential aggravation of maternal post-natal depression.

The alternative drugs are labetalol and nifedipine. They are probably equivalent in terms of therapeutic efficacy, while many studies report the absence of negative effects for the foetus.

The drug of first choice for the treatment of hypertension crises is *sodium nitroprusside*, in i.v. infusion (0.25–5 μg/kg/mi).

ACEIs and ARBs are probably moderately teratogenic and significantly toxic for the foetus. Their use is therefore contraindicated throughout pregnancy. There are no contraindications to the administration of ACEIs or ARBs during breastfeeding.

Hydrochlorothiazide is contraindicated due to a possible teratogenic action and possible foetal toxicity (with the onset of foetal tachyarrhythmias).

Amongst beta-blocker drugs, the use of atenolol is not recommended due to its possible teratogenic action (hypospadias) and the risk of foetal hypoglycaemia and bradycardia and low birth weight.

A detrimental effect on foetal growth and low birth weight are also reported for the other beta-blockers.

Pharmacological therapy for arrhythmias

In women with a structural heart defect, a persistent arrhythmia often modifies the maternal haemodynamics, with repercussions for foetal health. However, since all the commonly used arrhythmia drugs cross the placenta, their use must consider the potential negative effects for the foetus.

The use of digoxin and beta-blockers, especially β1 selective drugs such as metoprolol, is considered safe during pregnancy; these drugs have been used both to restore the sinus rhythm and for ventricular rate control during supraventricular arrhythmias.

Amiodarone is contraindicated during pregnancy due to the frequency and severity of the maternal and foetal side-effects. Its possible use is limited to arrhythmias which may be resistant to other pharmacological treatments (such as focal atrial tachycardia) and in any case as last option if the previous steps fail. Finally, the changes in drugs' metabolism during pregnancy and thus the advisability of checking blood concentrations during treatment should be considered.

Re-entrant supraventricular (atrioventricular or intranodal) arrhythmias are the types of arrhythmia most frequently reported. The drug of first choice, also during pregnancy, is i.v. adenosine in rapid bolus; the data in the literature are not plentiful but there are no reports of adverse events in the foetus. If success is not achieved, metoprolol can be used. Prophylaxis against recurrences is

only advisable for symptomatic cases or when the arrhythmia rapidly impairs the haemodynamics. *Focal atrial tachycardia* is rare during pregnancy but is more resistant to pharmacological therapy. Here again, digitalis and metoprolol are the first choice drugs, with sotalol, flecainide and propafenone as second choice.

Atrial fibrillation and atrial flutter are rare during pregnancy but may occur in some subgroups of patients with congenital heart defects. Intravenous flecainide has been used but experience with this drug in pregnancy is very limited. External electrical cardioversion is safe for the mother and foetus; if the arrhythmia persists for at least 48 h anticoagulant therapy must first be administered for at least three weeks.

Persistent ventricular tachycardia (VT) must be promptly treated with ECV due to the risk of haemodynamic instability. The drug of first choice for prophylaxis against recurrences is metoprolol; if unsuccessful, the alternative drug is sotalol, or a Class I C anti-arrhythmia drug. Amiodarone should only be used where other drugs have failed.

In pregnant women with long QT syndrome, the risk of arrhythmia is higher during the 9 months after delivery than prior to conception and during pregnancy. Prophylaxis with β blockers must therefore be continued during breastfeeding.

Pharmacological therapy for heart failure

Heart failure (HF) in pregnancy may have a variety of causes, which partially affect the indications for therapy.

One particular condition is peripartum cardiomyopathy, which occurs in the last month of pregnancy or during the 5 months after the delivery.

In women with CHD, HF has particular characteristics depending on the anatomical-functional context, which must be assessed on a case-by-case basis. A medical history of HF and a low NYHA FC before pregnancy are factors indicating a higher risk of adverse events.

HF during pregnancy should be treated in accordance with the guidelines currently used for acute and chronic HF, with the necessary consideration of the drugs' potential negative effects on the foetus.

ACEIs and ARBs are contraindicated in pregnancy due to their foetal toxicity and must be discontinued as soon as possible in women already under treatment.

Loop diuretics (such as furosemide) must be used with caution during pregnancy, only in cases with pulmonary congestion, since they reduce the placental flow. The amniotic fluid must be regularly checked during diuretic treatment due to the risk of correlated oligohydramnios.

Spironolactone must be avoided due to its tetragenic effects (risk of cleft lip) and possible antiandrogenic effects, recorded in animal testing.

Beta-blockers (metoprolol, bisoprolol, carvedilol) can be used for treatment of chronic HF, if tolerated; selective β1 drugs such as metoprolol are preferred. Atenolol is contraindicated due to its potential teratogenic and toxic effects for the foetus (see previous points).

Anticoagulant therapy must be considered

- In case of severely impaired ventricular function (EF $<35\%$), especially in cases of peripartum cardiomyopathy, in which there is a higher risk of thromboembolic complications
- If the echocardiogram reveals intracardiac thrombosis
- In patients with previous thromboembolic episodes
- In the presence of atrial tachyarrhythmias

In acute HF, dopamine and levosimendan can be used if treatment with inotropes is necessary. The effectiveness of levosimendan in pregnancy is not defined.

Pharmacological therapy for pulmonary arterial hypertension

Women suffering from PH should be advised against pregnancy, and if it occurs they should be given the option of termination.

If the couple decide to go ahead in spite of the risks, the pregnancy must be managed by level III specialist centres.

The therapeutic indications are summarized in *Tables 22–24*.

Ca-antagonists (nifedipine) used in patients who are responders to the vasoreactivity test may be continued during pregnancy.

The five phosphodiesterase inhibitor sildenafil has been used in pregnancy; no teratogenic or toxic effects for the foetus are reported.

Endothelin inhibitors (bosentan, macitentan, and ambrisentan), used for the treatment of PAH, are potentially teratogenic and must be suspended.

Prostanoids (prostacyclin and iloprost by inhalation) have been used both during pregnancy and during delivery and the post-natal period.

Interventional cardiological procedures during pregnancy

The use of catheterization in women with congenital heart defects during pregnancy[295–319]

Managing an interventional cardiological problem during pregnancy in a woman with a congenital heart defect may have complex implications.

The physicians involved have to assume the responsibility for two patients, balancing the needs of the sick mother against those of her foetus.

As in all patients, interventional procedures in pregnant patients require appropriate imaging, general anaesthesia/sedation and other drugs including antibiotics and antiemetics.

The physiological changes caused by pregnancy and the presence of the foetus definitely make the choice of drugs and the use of ionising radiation more problematical.

In this section, we will discuss the risks of radiological exposure and the management of specific pathological conditions.

The ESC Guidelines suggest that interventional procedures can be considered for a variety of pathologies, with very precise indications, timings and protective systems for radiation exposure (Class II recommendation, Evidence level C).

Foetal monitoring should be scheduled immediately before and immediately after the procedure, to document the foetus's state of health.

In particularly high-risk conditions, continual monitoring throughout the procedure can be considered.

Exposure to radiation

Cardiac catheterization in pregnant women involves risks to the foetus due to exposure to radiation. The effects of radiation on the foetus depend on both the radiation dose and the gestational age at which the exposure occurs (*Table 26*).

The best period for a procedure is after the 4th month of pregnancy: from this time onward, organogenesis is complete, the foetal thyroid is still inactive and the uterus is still small in volume, leaving plenty of space between the foetus and the mother's chest.

There is no clear evidence that exposing a pregnant woman to .Fifty mGy involves a higher risk of congenital malformations, learning disabilities, growth retardation, or miscarriage for the foetus.

The potential effects of radiation are mainly of two types; determinist and stochastic. Deterministic effects are observed above a cumulative limit dose and the severity is therefore dose-dependent. Examples of deterministic effects on the foetus are miscarriage and teratogenicity, irrespective of the gestational age at which the exposure occurs.

The highest prenatal risk and the highest rate of deterministic effects are observed at gestational age 8-15 weeks, when the growing sensitive cortical cells of the encephalon are exposed to an amount of radiation in excess of 300 mGy. This may have an effect on normal neuro-development and it has been associated with mental retardation.

The stochastic effects are the result of damage to individual cells, sufficient to cause a mutation while retaining the capacity for subdivision.

Carcinogenesis is an example of a stochastic effect. There is no level of exposure to radiation below which the stochastic effect is non-existent.

During cardiac catheterization of a pregnant woman, precautions must be taken to minimize the risks to the foetus. The womb must be screened from the direct source of the radiation using a specific barrier, which completely surrounds the mother's abdomen from the diaphragm to the pubic symphysis. The fluoroscopy time should be as short as possible and cineangiographic acquisitions avoided to reduce the amount of radiation produced.

With regard to contrast media, it is important to know that the iodine medium is not teratogenic.[9,10]. Previous experiences with the injection of large doses into the amniotic sac have led to the development of hypothyroidism in the newborn, although this was not observed after intravenous injection into a pregnant woman or during animal pregnancies.

However, the use of iodine contrast medium during the first 3 weeks of pregnancy should be avoided.

Valve defects

Pregnancy in a woman with a valve defect can be associated with complications for both the mother and the foetus.

Aortic stenosis

Percutaneous valvuloplasty is the preferred technique since it involves a low risk of losing the foetus; it is contraindicated in women with severe aortic insufficiency or in case of calcified valves.

Aortic valvuloplasty should be considered as a palliative procedure which allows the pregnancy to be brought to term.

Mitral stenosis

Mitral stenosis is not well tolerated during pregnancy and therefore if the valve area is less than 1.5 cm^2 treatment prior to conception is preferable.

When, in spite of optimal medical therapies, the pregnant woman is still in NYHA FC III-IV or systolic pulmonary pressure remains >50 mmHg, valvuloplasty must be considered.

Pulmonary stenosis

Isolated pulmonary valve stenosis is rarely associated with complications during pregnancy.

Percutaneous valvuloplasty can be performed if necessary, with the sole technical precaution of suitable protection for the mother's abdomen.

Atrial septal defect

The closure of an atrial septal defect during pregnancy is hardly ever necessary. One possible indication for closure is the risk of paradoxical thromboembolism in spite of complete treatment with heparin as already described in the literature.

Table 26 Effects of radiation and limit dose for pregnant women

Gestational age	Foetal development	Effects of radiation
1-2 weeks	Implantation in the womb	Miscarriage (>50 mGy)
2-8 weeks	Organogenesis	Teratogenicity (>100 mGy)
2-15 weeks	Neuronal development	Microcephaly and mental retardation (>100 mGy)
2-40 weeks	Genetic mutation	Tumours <15 years (0.06% risk for every 10 mGy of exposure)
		Tumours > 15 years (0.4% risk for every 10 mGy of exposure)

Table 27 Comparative features of potential contraception modalities in women with congenital heart disease

Method	To be recommended yes/no	Remarks
Condom	No	Poor safety profile
Hormonal methods containing oestrogens	No	Risk of thrombosis
Progestin pill (Desogestrel 75 mcg)	Yes (pending choice of definitive method)	Possible risk of venous thromboembolism
IUDs ('coils')	Yes (reversible long-term methods)	Antibiotic prophylaxis before fitting and removal in women at risk of infectious endocarditis
S.C. device with slow release of Etonogestrel 68 mg		
Tube sterilization	Yes (irreversible method)	

Table 28 Termination of pregnancy

Period of pregnancy	Type of hospitalization	Method	Remarks
1st 3 months	OUTPATIENT (LEVEL III)	SURGICAL METHOD (HYSTEROSUCTION AND CURETTAGE)	I.v. anaesthesia (Diprivan) Routine i.v. antibiotic prophylaxis
		PHARMACOLOGICAL METHOD (MIFEPRISTONE 600 MG BY MOUTH + INTRAVAGINAL PROSTAGLANDIN)	Initial stages of pregnancy. Surgery required in 5% of cases
2nd 3 months (deterioration in mother's clinical condition/foetal death/patient's decision under Law 194)	Hospitalization (LEVEL III)	Pharmacological method (Mifepristone 600 mg by mouth- + intravaginal prostaglandin)	

The procedure for the percutaneous closure of an ASD can be performed with monitoring by means of an intracardiac probe, minimizing fluoroscopic exposure.

Aortic coarctation

The diagnosis of aortic coarctation during pregnancy is rare.

If necessary, percutaneous treatment is possible; aortography can be performed using a low-osmolarity contrast medium. A coated stent should be used since it reduces the risk of any complications on the aortic wall, which occur with higher incidence during pregnancy.

Contraception

Contraception should be discussed with women with congenital heart defects in adolescence (in order to prevent a pregnancy, a potential risk for the woman's health) and discussed again at the end of the first pregnancy, if any (to guarantee sufficient time for haemodynamic conditions to be restored).[320–324]

Contraceptive efficacy, safety in terms of cardiovascular risk and the woman's compliance must be assessed for each method (*Table 27*).

Table 29 General principles for labour and delivery in women with congenital heart disease

Labour, delivery, and post-natal period
- Do not allow the pregnancy to continue after term (gestational age 40 weeks)
- Spontaneous delivery is preferable
- Absolute indications for caesarean section:

- onset of labour in patient still undergoing treatment with dicoumarols
- dilation of aortic root in excess of 4 cm in women with Marfan's syndrome
- aortic dissection
- serious aortic stenosis
- Eisenmenger syndrome

- Continuous monitoring of mother's condition during labour
- Use of epidural pain relief is strongly recommended
- Encourage breastfeeding
- Critical nature of post-natal period (risk of pulmonary oedema)
- Critical nature of puerperal period (increased risk of thrombosis, risk of cardiac insufficiency and arrhythmias)

Termination of pregnancy

Women in the highest risk class (WHO IV) who present for observation already pregnant must be dissuaded from continuing with the pregnancy in view of the serious maternal mortality risk (up to 50%).[325-327]

Labour and delivery[46,328-330]

Table 29 summarizes principal recommendation for labor and delivery.

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