

Cardiovascular Disease in Women (VII)

Pregnancy and Heart Disease

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Pregnancy and delivery are associated with substantial physiological changes that require adaptations in the cardiovascular system. These changes, well-tolerated in pregnant women without heart disease, expose women with cardiovascular disease to serious risk. In fact, heart disease is the most frequent cause of maternal death, after psychiatric disorders, and the number of pregnant women with heart disease is expected to grow in the coming years.

Preventing cardiovascular complications should be the main aim of every cardiologist involved in managing pregnant women with congenital or acquired heart disease. Unfortunately, there is a lack of data which would help in the management of these patients during pregnancy and the clinical practice guidelines are often based on assumptions regarding how a specific substrate is going to respond to the physiological changes occurring due to pregnancy.

Key words:**Embarazo y cardiopatía**

El embarazo y el parto conllevan cambios fisiológicos sustanciales que requieren la adaptación del sistema cardiovascular. Estos cambios, tolerados en las gestantes sin cardiopatía, exponen a la mujer con enfermedad cardiovascular a riesgos importantes. De hecho, la cardiopatía es la causa más frecuente de muerte materna tras los trastornos psiquiátricos, y se espera que el número de gestantes con cardiopatía crezca en los próximos años.

La prevención de las complicaciones cardiovasculares debe ser el primer objetivo de todo cardiólogo involucrado en el manejo de la gestante con cardiopatía congénita o adquirida. Desafortunadamente, faltan datos que apoyen el manejo de estas pacientes durante el embarazo y las guías de práctica clínica a menudo se basan en suposiciones acerca de cómo un sustrato específico va a responder a los cambios fisiológicos debidos al embarazo.

Palabras clave:**INTRODUCTION**

Recent progress in pediatric cardiology and heart surgery has made it possible for more than 85% of children with congenital heart disease to survive to adulthood. Half of this population is made up of women, most of whom have reached child-bearing age.¹ Pregnancy represents a new challenge in this group of patients, whose natural history has been modified by surgery.²

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The number of pregnant women with coronary disease is expected to grow due to advanced pregnancy-maternal age, the development of reproductive techniques, and increased cardiovascular risk factors in women.³

Even though rheumatic fever has decreased in developed countries in recent years,⁴ it continues to be a serious problem in developing countries. Immigrants form a risk group, especially those who, for social reasons, are unaware of the inherent risks of heart disease during pregnancy or are even unaware of the existence of heart disease.

PHYSIOLOGICAL CHANGES DURING PREGNANCY, DELIVERY, AND POSTPARTUM

The main physiological changes during pregnancy are increased blood volume, heart rate and cardiac output, and decreased peripheral vascular resistance.⁵ Thus, the increase in blood volume (30%-50%) is an adaptive process, induced by the metabolic demand of the fetus, beginning in the sixth week of pregnancy,

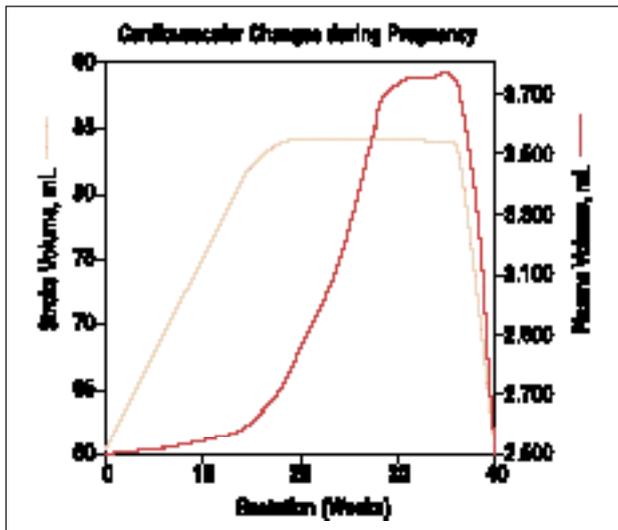


Figure.

reaching its maximum between weeks 20 and 24, and remaining so until delivery. As this blood volume increases, a parallel increase in cardiac output (CO) (30%-50%) occurs. At the beginning of pregnancy, this increase is due to stroke volume, whereas, as pregnancy progresses, increased heart rate is the main factor (Figure). Due to this hyperdynamic situation, nearly all pregnant women present a soft midsystolic murmur during auscultation. Given the increase in mammary blood flow, a continuous murmur may be heard. Even though diastolic murmurs can be physiological during pregnancy, heart disease should be ruled out if there are any.

This increase in CO is not constant, since this fluctuates according to position: the compression of the inferior vena cava by the gravid uterus in the supine decubitus position decreases venous return, thus decreasing CO.

In addition, ventricular diameters increase slightly, although remaining within normal limits. Left ventricular contractility is depressed slightly and ejection fraction is maintained, given the preload and afterload conditions.⁸ Transvalvular flow velocity increases due to the hyperdynamic situation and the presence of mild atrioventricular valve regurgitation is normal.⁹ In addition, the aortic root diameter also increases during pregnancy.¹⁰

Finally, decreased peripheral vascular resistance is around 30% and is a main factor in the physiological changes during pregnancy. This reduction in afterload is due to the fact that the placenta is a high-flow, low-resistance circuit. Pulmonary pressures remain normal during pregnancy; a decrease probably occurs in pulmonary vascular resistance that compensates for the increase in blood flow.

Very important hemodynamic changes occur during delivery due to pain, anxiety, and uterine contractions.

The first two have significant effects on heart rate and blood pressure; systolic (SBP) and diastolic (DBP) blood pressure both increase during contractions and especially during the second stage of delivery. Furthermore, uterine contractions involve an acute 50% increase in both heart rate and blood volume, as from 300 to 400 mL of blood is transferred from the uterus to the circulation during each uterine contraction and, thus, CO increases by 50% in every contraction. The magnitude of this increase rises as delivery progresses.

Despite external hemorrhage, cardiac output increases in the immediate postpartum period by 60% to 80%, due to decompression of the inferior vena cava and to the transfer of blood from the contracted uterus. Thus, the postpartum period especially involves risk in pregnant women with heart disease and it has been reported that most complications occur in this period.¹

PRE-CONCEPTION COUNSELING

In general, family planning, discussing contraceptive methods and how future pregnancies will affect the mother and fetus should begin during adolescence.¹² Such counseling should be given jointly by a gynecologist expert in high-risk pregnancies and a cardiologist with expertise in managing women with congenital heart disease. The information should include estimations of maternal mortality and morbidity during pregnancy, as well as the risk of heart failure, arrhythmias or long-term ventricular dysfunction. Parental life expectancy or the need for heart surgery should be discussed, since these are issues that obviously affect a couple's ability to care for their child.¹³

Thus, if pregnancy is suitably planned, both fetal and maternal risk can be estimated and minimized. Regarding the timing of pregnancy, for example, pregnancy is tolerated better in those with systemic right ventricle or univentricular heart if the patient is in her 20s rather than if she is older than 35. Percutaneous intervention or mitral valve replacement surgery before pregnancy should also be considered in patients with hemodynamically significant mitral valve disease. Nevertheless, the use of tissue valves should be considered regarding any surgical intervention.

Maternal Risk

Risk stratification is based on general knowledge concerning physiological changes occurring during pregnancy, on knowledge of certain conditions that involve high mortality, which have been established recently in two prospective observational studies on risk factors for cardiovascular complications during pregnancy, as well as on small studies on every

TABLE 1. Risk Factors for Maternal Complications During Pregnancy

Advanced functional class before pregnancy (NHYA class >II)
Left ventricular dysfunction (EF<40%)
Left-side obstructive lesions, mitral valvular area <2 cm ² , aortic valvular area <1.5 cm ² , and blood pressure gradient estimated via Doppler ultrasound in the left ventricular output tract >30 mm Hg
Previous history of arrhythmias with clinical impact or stroke or heart failure

specific disease, most of which were retrospective and without echocardiographic data. Generally, the following aspects should be considered:

- Diseases that involve limited cardiac output, that is, left-side obstructive lesions which will not be well-tolerated.
- The decrease in peripheral vascular resistance means that left-side valvular regurgitation and left-to-right shunts will be well-tolerated, whereas, for the same reason, right-to-left shunts will not be well-tolerated.
- It is well-established that primary pulmonary hypertension and Eisenmenger syndrome involve prohibitive risk, with 30% to 50% mortality during pregnancy.
- The need for anticoagulation therapy due to having a mechanical prosthesis involves serious maternal and fetal risk.

In the largest prospective multicenter study, done in Canada in pregnant women with heart disease (CARPREG), the frequency and predictors of cardiovascular complications were examined during pregnancy.^{14,15} Some 562 women were studied during 617 pregnancies. The study included women with congenital (75%) and acquired (25%) heart disease and excluded those with mitral valve prolapse without significant regurgitation. The frequency of cardiovascular complications during pregnancy was 13%, half during delivery, the main complications being heart failure and arrhythmias. Three deaths were recorded. Table 1 shows the predictors of cardiovascular complications during pregnancy in the CARPREG study. The estimated risk of complications during pregnancy in patients with heart disease, but without any of the risk factors described, was 5%; with 1 risk factor, 27%; and with 2 risk factors, 75%.

A prospective observational study of 90 pregnancies in 53 women has recently been published in relation to the patient population with congenital heart disease. The event rate during pregnancy was 19.4%: 16.7% due to heart failure and 2.8% due to arrhythmias, with no reported mortality. Apart from the risk factors described in the CARPREG study, right ventricular dysfunction in patients with normal ventriculo-arterial concordance and/or severe pulmonary regurgitation

TABLE 2. Risk Factors of Fetal Complications During Pregnancy

Advanced functional class prior to pregnancy (NHYA class >II)
Left ventricular dysfunction (EF<40%)
Left-side obstructive lesions, mitral valvular area <2 cm ² , aortic valvular area <1.5 cm ² , and blood pressure gradient estimated via Doppler ultrasound in the left ventricular output tract >30 mm Hg
Cyanosis
Anticoagulation therapy
Multiple pregnancy
Smoking
Maternal age <20 years or >35

were independent risk factors for cardiac complications.¹⁶

Risk to the Fetus

The risk of transmission of congenital heart disease to the children should be considered before conception. In general, there is an estimated risk of around 4%,¹⁷ whereas the risk of congenital heart disease in the general population is 0.8%.¹⁸ However, some conditions are inherited with an autosomal dominant pattern, such as DiGeorge syndrome, Marfan syndrome, hypertrophic cardiomyopathy, or Noonan syndrome, with a 50% transmission risk. In these cases, the possibility exists of carrying out a chorionic biopsy for prenatal diagnosis at the 12th week of pregnancy.

Furthermore, the incidence of fetal and neonatal complications in pregnant women with heart disease is greater than in the general population; restricted intrauterine growth, premature birth, intracranial hemorrhage, and fetal loss are the main complications reported. The prospective CARPREG study examined the incidence of adverse effects on the neonate, and risk was 18% versus 7% in pregnant women without heart disease.¹⁹ Table 2 shows the risk factors for neonatal complications. In the absence of risk factors, the incidence of neonatal complications was similar to that of women without heart disease.

Thus, monitoring should be offered to women with heart disease, including nuchal translucency at 13 weeks (the incidence of congenital heart disease is 1/1000 if nuchal translucency is normal). Fetal echocardiography can be done at 14-16 weeks of pregnancy and repeated around the 20th week if necessary, thus diagnosing the most serious congenital heart diseases.

The most frequent complication is restricted intrauterine growth. This risk is especially high if there is a maternal condition that involves limiting the increase in cardiac output, so restricting placental flow, and this worsens if it is concomitant with other obstetric risk factors.

TABLE 3. Contraception and Termination of Pregnancy

Natural methods and barrier methods have inadmissibly high failure rates in women whose pregnancy puts them at high risk
 Combined oral contraceptive pills should be avoided in patients with high risk of thromboembolism
 The minipill, which contains progesterone only, does not increase the risk of thromboembolism and has few side effects, although the failure rate is greater than that of the combined pill. Depot injections of progesterone are considered an alternative, especially in adolescents, whose therapeutic compliance is not high
 Intrauterine devices impregnated with progestagens have been an important advance in contraception in high-risk women. These are very effective and safe, with decreased rates of bleeding and low risk of infection and ectopic pregnancy
 Sterilization should be considered in women where pregnancy involves a prohibitively high risk
 The risk of termination of pregnancy is higher the more advanced the pregnancy, thus pregnancy should be terminated as soon as the decision is made, preferably in the first trimester
 The method of choice is dilation and curettage
 Abortion induced with antiprogesterins or intravaginal administration of prostaglandins is considered to be contraindicated since the cardiovascular effects are unpredictable

Biometry of the fetus is warranted in women with risk factors, as well as in patients with hypertension during pregnancy or those treated with beta-blocker (see box referring to drugs and hypertension).

See Table 3 regarding contraception and termination of pregnancy.

MANAGEMENT OF CARDIOVASCULAR COMPLICATIONS DURING PREGNANCY

The level of care and monitoring during pregnancy should be determined before pregnancy or as soon as this is confirmed. In general, it is essential that prenatal care and delivery are carefully planned. Some patients will benefit from hospitalization during the third quarter, with rest, monitoring and O₂ therapy (for example, in cyanotic patients). In view of the fact that many general obstetricians will only see a few patients with heart disease, it is important to refer them to a specialized center, since pregnant women with high-risk heart disease should be frequently assessed, including echocardiographic study.²⁰

Table 4 shows the principal heart diseases classified into low, moderate, and high risk. Each entity is specifically discussed below.

Drugs and Pregnancy

Most cardiovascular drugs cross the placenta and thus expose the fetus to their pharmacologic effects.²¹

TABLE 4. Classification of Heart Disease During Pregnancy According to Maternal Risk

High risk
 Pulmonary arterial hypertension
 Eisenmenger syndrome
 Secondary pulmonary hypertension
 Primary pulmonary hypertension
 Marfan syndrome with aortic root dilatation
 AMI during pregnancy
 Severe aortic stenosis
 Severe ventricular dysfunction
 Dilated cardiomyopathy
 Previous peripartum cardiomyopathy
 Right systemic ventricle with severe dysfunction
 Univentricular physiology with or without Fontan with severe ventricular dysfunction
 Severe mitral stenosis
 Intermediate risk: 1%-5% mortality
 Mechanical prosthesis
 Univentricular physiology (with or without Fontan) with preserved systolic function
 Unrepaired cyanotic heart disease without pulmonary hypertension
 Unrepaired aortic coarctation
 Non-severe aortic stenosis
 Severe pulmonary stenosis
 Marfan syndrome without aortic root dilatation
 Mitral stenosis
 Low risk: the risk of maternal mortality is higher than that estimated in the general population (1:1000) but lower than 1%
 Repaired congenital heart disease without defect or residual dysfunction
 Left-to-right shunt without pulmonary hypertension
 Asymptomatic moderate-to-severe mitral or aortic regurgitation without left ventricular dysfunction
 Moderate pulmonary stenosis
 Biological prostheses without residual dysfunction
 Bicuspid aortic valve

Some drugs enter the breast milk and can affect the neonate. Furthermore, during pregnancy, the pharmacokinetic properties change and the dose often requires adjustment. For all these reasons, the benefits and maternal and fetal risks should be carefully assessed before administering a given drug during pregnancy. Table 5 shows the most commonly used cardiovascular drugs.^{22,23}

Arrhythmias

Both sustained arrhythmias and extrasystole are more frequent during pregnancy. These are treated similarly but conservatively, when possible, meaning that antiarrhythmic agents should be administered, as well as any drug during pregnancy, at the lowest effective dose and with the shortest duration possible.²⁴

Paroxysmal supraventricular tachycardia (PSVT) can be treated via vagal maneuvers; if there no

TABLE 5. Drug Therapy During Pregnancy

Unsafer drugs	
ACE inhibitors	Angiotensin-converting enzyme inhibitors affect renal development in the fetus, especially during the second and third trimester of pregnancy These should be avoided throughout pregnancy
ARB-II	These have an effect similar to those of ACE inhibitors These should be avoided throughout pregnancy
Amiodarone	This causes neonatal hypothyroidism; it has also been associated with prematurity and possible neurodevelopmental problems This should be used during pregnancy only as second-line drug in case of resistance to other safer antiarrhythmic agents If used, the neonatal thyroid hormone levels should be carefully and regularly monitored
Spironolactone	This has been associated with the risk of genital anomalies, and thus should be avoided during pregnancy If potassium-sparing diuretics are required, amiloride is preferable
Acenocoumarins	These are associated with warfarin embryopathy syndrome Intracranial bleeding (see anticoagulation therapy and pregnancy)
Relatively safe drugs (without teratogenic effects)	
Aspirin	This has been used in high-risk patients to prevent preeclampsia
Diuretics	These can be used during pregnancy if necessary These cannot be used in preeclampsia; it has been reported that they could promote the appearance of preeclampsia
Beta-blockers	These have been extensively used with safety An association with intrauterine growth retardation has been described, thus, monitoring with fetal biometry is recommended
Digoxin	Its use is safe (in therapeutic concentrations) This is the treatment of choice for fetal arrhythmias Digoxin is safe during breast-feeding
Calcium antagonists	
Adenosine	Its use is safe for the treatment of PSVT
Procainamide	Treatment of maternal and fetal arrhythmias. It is not recommended for chronic treatment, given the incidence of pseudo-lupus
Lidocaine	
Flecainide	This has become the treatment of choice for fetal arrhythmias, especially in cases resistant to digoxin and complicated by fetal hydrops

response the use of intravenous adenosine may be effective. Beta-blockers are the drugs of choice for prophylaxis of supraventricular or ventricular arrhythmias during pregnancy.²⁵ Malignant ventricular arrhythmias are much less frequent and should be eliminated by electrical cardioversion (ECV), when not contraindicated, and in fact should be used in all sustained tachycardias causing hemodynamic deterioration which threaten the pregnant woman and, thus, the fetus. Fetal heart rate should be controlled and the maternal airway protected in particular. Amiodarone should only be used as a second-line drug in case of resistance to other antiarrhythmic agents.

The fact of carrying an implantable cardioverter-defibrillator (ICD) does not by itself counterindicate pregnancy. In a series of 44 pregnancies in women carrying an ICD, a greater incidence of discharges was not observed during pregnancy nor were there special maternal or fetal complications.²⁶

Finally, if strictly necessary, a pacemaker should be implanted during pregnancy. The effects of radiation can be minimized via sonography.

Cardiac Arrest

A recent document on the management of cardiocirculatory arrest during pregnancy outlines the following differential aspects²⁷:

- Place the woman 15°-30° in the lateral left decubitus position.
- Chest compression should be carried out in a position higher than the usual one.
- Drug administration via the femoral route should be avoided.
- The risk of aspiration should be minimized via previous cricoid compression and during orotracheal intubation.
- Emergency cesarean section should begin as soon as circulatory arrest is confirmed.

In these patients, it is essential to always consider the possibility of magnesium sulfate excess, eclampsia with multiorgan failure, acute myocardial infarction, aortic dissection, massive pulmonary embolism, amniotic fluid embolism, trauma, and drug overdose.

Thromboembolism

The risk of thromboembolism during pregnancy undergoes a 5-fold increase, during puerperium this risk increases 11-fold and is greater after cesarean section. This should be taken into account in women whose heart disease involves a risk of thrombosis.

Low-molecular-weight heparin (LMWH) is safe for treating deep vein thrombosis, but the dose should be initially adjusted via factor Xa-activated blood clotting time.

Prosthetic thrombosis during pregnancy has been described even with state-of-the-art prostheses in the aortic position. Thrombolysis is recommended as the treatment of choice.²⁸ Heparin can be used as first-line treatment in patients with non-obstructive thrombosis.

Finally, patients carrying a mechanical prosthesis are at particularly high risk during pregnancy, and the risks and benefits of using oral anticoagulants compared to heparin should be carefully considered.

Endocarditis

Infectious endocarditis is uncommon during pregnancy but can be difficult to manage. The need for surgical treatment should be weighed against the risk of fetal loss, but should not be delayed if the pregnant woman is in a life-threatening situation.

The American Heart Association and the European Society of Cardiology^{29,30} do not recommend the use of prophylactic antibiotics during delivery; despite this, many centers carry it out. Although the beneficial effect of such prophylaxis has not been demonstrated, their use seems reasonable in particularly high-risk women, such as those with previous episodes of bacterial endocarditis, those carrying a valvular prosthesis or pregnant women with heart disease considered as being at high risk of endocarditis undergoing operative vaginal delivery.

Heart Failure

Any pregnancy is accompanied by certain symptoms, such as fatigue, decreased capacity for exercise and dyspnea. Thus, deterioration in functional class by itself is not an indication for hospitalization, given its subjectivity; the increase in jugular venous pulse and the presence of peripheral edema could lead to an erroneous diagnosis of heart failure.

If the diagnosis of heart failure is confirmed, bed rest and a low-salt diet is recommended. Pharmacological treatment will include beta-blockers, digitalis and oral diuretics. Angiotensin-converting enzyme inhibitors (ACE inhibitors) and the angiotensin II receptor blockers (ARA-II) are

contraindicated during pregnancy, but hydralazine and nitrates can be used.

Cases of severe heart failure require hospitalization and the use of intravenous diuretics, in addition to vasodilators to reduce afterload. In life-threatening cases, the temporary use of intraaortic balloon counterpulsation, or left ventricular assistance can be indicated.⁴

Heart Surgery During Pregnancy

Although maternal mortality is similar to that outside of pregnancy, such surgery should be reserved for patients resistant to medical treatment where the delay in surgical treatment could have serious consequences. Furthermore, fetal prognosis worsens in this situation, with fetal loss reaching 30%. The complexity of the intervention and the duration of the bypass directly affect fetus viability, which means that, if gestational age allows for this, a cesarean section should be done after heparinization and cannulation. If the gestational age does not permit extrauterine viability, the fetus and uterine activity should be monitored during surgery. Whenever possible, normothermic bypass should be done and sudden changes in maternal blood flow avoided.³¹

DELIVERY AND POSTPARTUM

Delivery should be planned carefully. Intrapartum management should be supervised by a team with expertise in the care of pregnant women with heart disease (obstetricians, anesthesiologists and nurses) and a cardiologist should be available. Maternal monitoring during delivery may require electrocardiographic monitoring, pulse oxymetry and, occasionally, invasive blood pressure assessment. The main aim is to manage the effort and stress arising from delivery in such a way that the woman does not exceed her capacity to cope.

In principle, delivery should not be induced except for obstetric reasons. Spontaneous delivery is usually faster and involves fewer complications. Specifically, vaginal delivery carries half the risk of complications of an elective cesarean section for both the mother and fetus, since it involves smaller fluctuations in blood volume (lower hemorrhage rates). However, prolonged deliveries should be avoided. Thus, the assisted delivery threshold should be low to shorten the second stage of delivery.

Epidural analgesia is fundamental; drugs that cause fewer cardiovascular alterations are used to avoid abrupt hemodynamic changes. Oxytocic drugs, such as ergometrine and oxytocin, have cardiovascular effects. Continuous oxytocin perfusion, at the lowest effective dose, has minimal cardiovascular effects.

TABLE 6. Indications for Caesarean Section (Other Than Obstetric Indications)

Marfan syndrome with aortic dilatation >45 mm
In all patients treated with warfarin at the time of delivery
In cases of abrupt maternal hemodynamic deterioration where vaginal delivery is not possible ³⁶
Some authors recommend caesarean section in women with severe pulmonary hypertension

For all these reasons, spontaneous vaginal delivery with analgesia and a low threshold for forceps-assisted birth is the safest method for most cardiac conditions, since this is associated with fewer rapid hemodynamic changes than cesarean section and has less risk of infection.³² However, in some conditions (other than for obstetric reasons) cesarean section is indicated (Table 6).

Continuous monitoring during the postpartum period is necessary in high-risk patients (if necessary, in the coronary unit), particularly in women with pulmonary hypertension or cyanosis, who have a risk of maternal mortality in the first 10 postpartum days.

CONGENITAL HEART DISEASE

Left-to-Right Shunt

The effect of increased cardiac output on a right ventricle with previous volume overload in patients with atrial septal defect (ASD) is counterbalanced by the decrease in peripheral vascular resistance; thus, pregnancy is well-tolerated in these types of conditions, with few complications. Paradoxical embolism is rare in patients with ASD. Pregnancy is also well-tolerated by patients with restrictive ventricular septal defect (VSD) and small patent ductus arteriosus.

Bicuspid Aortic Valve

This is the most frequent cause of aortic stenosis (AS) among patients of child-bearing age. Furthermore, AS is a risk factor for fetal complications. Thus, all patients with symptomatic AS should postpone pregnancy until after heart surgery. Even in asymptomatic women with moderate AS, pregnancy can cause heart failure.

The first published studies included patients with critical AS and showed high maternal mortality (17%).³³ Morbidity and mortality was far less in more recent studies.³⁴ The transvalvular pressure gradient can even double during pregnancy as a consequence of the physiological changes of pregnancy. The absence of an increase in gradient during pregnancy can indicate ventricular dysfunction. If in a pregnant woman there is severe deterioration, surgery is

indicated, although cases have been published of balloon mitral valvuloplasty in critical AS during pregnancy with good results.³⁵

AORTIC COARCTATION

Maternal mortality in women with unrepaired aortic coarctation (CoA) has been estimated to be 3%. The main complications reported are associated with severe hypertension, including aortic dissection. Changes in the aortic wall during pregnancy increase the risk inherent to CoA.

In a study of 50 women with CoA, the main cardiovascular complication was hypertension which was present in 30% of the pregnancies. Maternal death occurred in one patient with Turner syndrome (type A dissection).³⁶

Although pregnancy is considered low-risk in women with previously repaired CoA, the risk of dissection is small but not eliminated, especially if there is a residual aneurysm at the repair site. In a recently published series, the incidence of hypertension was 22%, without serious cardiovascular complications being reported.³⁷

Pulmonary Stenosis

Mild or moderate pulmonary stenosis (PS) is well-tolerated during pregnancy, with good maternal and fetal prognosis. However, in patients with severe PS, pregnancy can cause severe heart failure or arrhythmias.

Balloon pulmonary valvuloplasty can be carried out during pregnancy in highly symptomatic women.³⁸

Unrepaired Cyanotic Heart Disease Without Eisenmenger Syndrome

Maternal risk due to cyanosis differs in severity depending on whether there is concomitant pulmonary hypertension or not. In patients without pulmonary hypertension, e.g., pulmonary atresia managed via Blalock Taussig shunt (BT), mortality during pregnancy is around 5%.

In a series of 96 pregnancies in 44 women with unrepaired cyanotic congenital heart disease, but without Eisenmenger syndrome, the incidence of cardiovascular complications was 32%, with 1 maternal death.

Fetal prognosis is poor in any situation associated with maternal cyanosis, and both prematurity and spontaneous abortions are frequent. In the same study, the live birth rate was only 43%. Arterial oxygen saturation less than 85% prior to pregnancy was associated with a higher rate of fetal complications. It has been suggested that fetal prognosis can be improved by bed-rest and O₂ administration.³⁹

Repaired Cyanotic Heart Disease

Tetralogy of Fallot (TF)

This is the most frequent cyanotic heart disease. Classically, patients with repaired TF have been considered a low-risk group for maternal and fetal complications, and no fatal case been described. At present, there are many patients with repaired TF who have reached reproductive age. However, it has recently been found that pregnancy can worsen right ventricular function and dilatation in these patients.

In a retrospective study including 43 pregnancies in patients with TF, most of which were repaired, the incidence of cardiovascular complications was 7%, including supraventricular arrhythmias, heart failure, and progression of right ventricular dilatation. The fetal loss rate was higher than average.⁴⁰

The children of mothers with TF have a 3% possibility of having some type of heart disease. However, it is thought that approximately 15% of patients with TF present DiGeorge syndrome. The probability of congenital heart disease will be much greater, since this condition is inherited with an autosomal dominant pattern and the prevalence of conotruncal defects in patients with DiGeorge syndrome is 75%.⁴¹

Pulmonary Atresia

A retrospective study examined pregnant women with both mitigated and repaired pulmonary atresia. Cardiovascular complications were found even in patients who had undergone repair, and especially in patients with residual systemic-pulmonary collaterals.⁴²

Systemic Right Ventricle

In the transposition of great vessels (TGA), following the Mustard or Senning procedure, and in patients with congenitally corrected transposition of great vessels (cc-TGA), the right ventricle (RV) supports the systemic circulation (systemic right ventricle).

Transposition of Great Vessels After Atrial Switch

In this the presence of case, the rate of complications depends on there being systemic right ventricular dysfunction. Pregnancy involves high risk in patients with systemic ventricular dysfunction.

In women without systemic right ventricular dysfunction and with NYHA functional class I-II, full-term pregnancy is probably well-tolerated.⁴³ However, dilatation and irreversible deterioration of systolic

function of the systemic right ventricle have been observed after pregnancy.⁴⁴

Patients undergoing arterial switch have not yet reached reproductive age, but no complications are foreseen.

Congenitally Corrected Transposition of Great Vessels

In the only series published, maternal mortality was not observed in 41 patients with 105 pregnancies. The risk is probably equal to that of TGA after the Mustard procedure.⁴⁵

Ebstein Anomaly

Most patients tolerate pregnancy well despite cardiovascular complications, particularly supraventricular arrhythmias. A high rate of fetal loss has been described. There are more maternal and fetal complications if cyanosis occurs.

Univentricular Heart With and Without Fontan Procedure

In general, the risk to patients with univentricular physiology palliated with shunt (double left ventricular outflow tract, tricuspid atresia and atrial isomerism) is high, but depends on the other risk factors they have (Table 1); risk is prohibitive in the presence of pulmonary arterial hypertension (PAH). Some successful pregnancies have been reported in these patients.

Fontan Procedure

In general, these patients present limited ability to increase cardiac output during pregnancy.

There exists little information regarding pregnancy after the Fontan procedure. In the only series published, including 21 women and 33 pregnancies, there were 15 births, 5 therapeutic abortions, and 13 spontaneous abortions. Maternal mortality was not observed in these 21 women, although this is probably indicative of a highly selected population.⁴⁶ If there is ventricular dysfunction or obstruction, risk is presumably very high.

Supraventricular arrhythmias are frequent; in a recent review of the literature on pregnant women with Fontan circulation, 25% of the patients presented sustained arrhythmias during pregnancy.⁴⁷ There is a risk of right atrial thrombus formation; a fenestrated Fontan can lead to paradoxical embolism.

A functional Fontan with a very small right atrium or after total cavopulmonary connection (TCPC) in functional class I or II with good left ventricular function probably makes it possible to complete a pregnancy.

The need for anticoagulation therapy and conversion to TCPC should be assessed before pregnancy.

Marfan Syndrome

There is cardiac involvement in 80% of patients with Marfan syndrome, particularly mitral valve prolapse, aortic root dilatation and aortic dissection. Pregnancy is a high-risk period for these patients, with a greater incidence of dissection, especially in the third trimester and postpartum.⁴⁸ Thus, every woman with Marfan syndrome should be assessed before pregnancy which involves check-ups every 6-8 weeks and in the first 6 months postpartum; treatment with beta-blockers should be maintained during pregnancy.

The risk of dissection is low in women after undergoing elective surgery of the ascending aorta. Even in women with minimal cardiac involvement, without dilated ascending aorta (<40 mm), previous dissection or mitral regurgitation, the risk of maternal mortality is around 1% during pregnancy.⁴⁹ In patients with dilated ascending aorta, the risk of dissection during pregnancy is 10%. If the aortic root diameter is 4.5 cm or more, cesarean section may be considered.

Finally, if a type A dissection occurs, emergency surgery is indicated. Type B aortic dissection should be managed medically with the same surgical indications as apply to non-pregnant women.

Hypertrophic Cardiomyopathy

The blood volume increase involved in pregnancy is generally well-tolerated in this condition, although postpartum pulmonary edema is described in all the published series. In any case, beta-blockers should not be discontinued during pregnancy, avoiding severe vasodilatation, and vaginal childbirth should be indicated.

In the largest series mentioned, with 127 patients and 271 pregnancies, no mortality was reported, with an incidence of heart failure of 2%.⁵⁰

Dilated Cardiomyopathy

Dilated cardiomyopathy is documented very rarely before pregnancy. In most cases pregnancy is counterindicated in these patients. This is known as peripartum cardiomyopathy if diagnosed in the last month of pregnancy.

Peripartum Cardiomyopathy

This is left ventricular systolic dysfunction that develops in the last month of pregnancy or postpartum, usually during the immediate postpartum period. Pathogenesis is not well-understood, although the possibility of myocarditis has been suggested.

It presents as heart failure with marked fluid retention, with mortality higher than 20%. Treatment is the same as for any form of decompensated cardiomyopathy. On some occasions it may require inotropic support, ventricular assistance, or even transplantation.

Even in those women who recover totally after pregnancy, there is a risk of recurrence in later pregnancies, higher than 20%.⁵¹

ACQUIRED HEART DISEASE

Coronary Artery Disease

Advanced maternal age and assisted reproduction techniques means that there will be an increased incidence of diseases more characteristic of other decades of life. Thus, the incidence of coronary artery disease during pregnancy is around 6.2/100 000 in the United States. The main risk factors are advanced maternal age, the presence of classic cardiovascular risk factors, severe anemia, and the need for postpartum transfusion (attributed to the use of oxytocins).⁴

Acute myocardial infarction (AMI) during pregnancy and postpartum has been associated with mortality between 5.7% and 37%.⁵² The pathogenesis of AMI during pregnancy is unrelated to that occurring in other situations. In a series of 859 cases, coronary angiography was done during pregnancy and postpartum in half the patients; atherosclerosis was only found in only 43%, thrombus in 21%, healthy coronary artery in 29%, and coronary dissection in 16%.⁵³

Coronary dissection occurs in pregnant women without cardiovascular risk factors (near term or postpartum), affecting the left anterior descending coronary artery in 80% of cases, and causes extensive AMI with mortality ranging from 30% to 40%, partly attributed to delayed diagnosis. Stent implantation is the only effective treatment to limit its extension.^{54,55}

Treatment of AMI

Delayed diagnosis and therapeutic abstention explain part of the high mortality found in AMI during pregnancy.⁵⁶ Fibrinolytic agents have been used during pregnancy without evidence of teratogeny, although there is a serious risk of maternal hemorrhage, particularly if these are administered near the time of delivery. If emergency cardiac catheterization is not available, they should be used according to the same criteria as outside pregnancy.

Given the seriousness of AMI during pregnancy, the risk of hemorrhage with thrombolytic agents and the possibility of coronary artery dissection, whose only effective treatment is emergency cardiac catheterization, primary angioplasty is considered the

treatment of choice for AMI during pregnancy, since it is the safest for the woman and, thus, for the fetus. The radial approach has been suggested in order to minimize radiation and protect the abdomen. The European Society of Cardiology consensus document recommends primary angioplasty as the treatment of choice in AMI during pregnancy.

Acquired Valvular Heart Disease: Mitral Stenosis

Rheumatic mitral stenosis (MS) is a frequent cause of valvular heart disease in pregnant woman. The limited increase in cardiac output and increased heart rate leading to decreased diastolic filling means that MS is not well tolerated during pregnancy. Thus, valvuloplasty or surgery in all symptomatic patients should be considered before pregnancy, or even in asymptomatic patients with severe mitral stenosis who are contemplating pregnancy.⁵⁷

There should be close follow-up during pregnancy among women with mitral stenosis, with echocardiographic monitoring of the transmitral gradient and pulmonary artery pressure (PAP).

Beta-blockers should be prescribed to all symptomatic woman or whose PAP test is higher than 50 mm Hg, as well as rest and a low-salt diet. Diuretics should be added if venous congestion persists.

Patients who are symptomatic despite medical treatment should be considered for balloon mitral valvuloplasty during pregnancy; a comparative study of valvuloplasty and surgery showed that valvuloplasty is a better option, since it reduces the rate of fetal complications. The results have been published of more than 250 balloon mitral valvuloplasties done during pregnancy.⁵⁸

Regurgitant Lesions

In general, the fall in peripheral vascular resistance decreases the regurgitant volume in mitral and aortic regurgitation. In aortic regurgitation, the increase in heart rate shortens diastole thus improving hemodynamics. In this situation, pregnancy tends to be well-tolerated provided there is no ventricular dysfunction.^{59,60}

Mitral Regurgitation

The most frequent cause of mitral regurgitation in young women is mitral valve prolapse.

Aortic Regurgitation

This can be due to congenital disease in young patients (bicuspid aortic valve or Marfan syndrome) or previous endocarditis.

Mechanical and Biological Prosthesis

Ideally, women of childbearing age with valvular heart disease requiring heart surgery should receive a biological prosthesis if they are contemplating pregnancy. However, a mechanical prosthesis, whatever the anticoagulation regimen, carries a low-to-moderate risk of maternal mortality during pregnancy of between 1% and 4%, mainly due to increased risk of thrombosis. Furthermore, a mechanical prosthesis, with any anticoagulation regimen, is a risk factor for the fetus. Effective anticoagulation therapy is essential in patients carrying a mechanical prosthesis and constitutes a serious problem in pregnant women, since both oral anticoagulation (OAC) and heparin are associated with maternal and fetal complications. However, the incidence of prosthetic thrombosis during pregnancy is greater with the use of heparin and involves greater maternal mortality, meaning that OAC is safer for the mother. In addition, fetal prognosis is known to be affected by the type of anticoagulation therapy, with worse fetal prognosis if OAC is used, whereas heparin does not cross the placenta and, consequently, is safer for the fetus. Thus, the anticoagulation regimen selected should be discussed with the patient, taking into account the risks inherent to all types of anticoagulation therapy. Whatever the anticoagulation regimen selected, strict monitoring is required, since this decreases the risk of complications.^{61,62}

Oral Anticoagulation Therapy

The use of OAC between weeks 1 and 12 of pregnancy, especially between weeks 6 and 12, is associated with warfarin embryopathy which is characterized by nasal hypoplasia and bone defects. In the metaanalysis of pregnant women carrying mechanical prostheses when OAC was used throughout pregnancy, the risk of embryopathy was 6.4% in contrast to the previously reported 30%. When OAC was replaced by heparin during weeks 6 to 12, risk was less than 3%.⁶³

It is known that the risk of embryopathy is dose-related, such that this risk is very low in pregnant women when the required dose is less than 5 mg.⁶⁴

The risk of prosthetic thrombosis is less than when heparin is used during pregnancy. The same metaanalysis reported a maternal mortality of 1.8% with OAC. Furthermore, the use of OAC during the second and the third trimester has been associated with neurological anomalies, but the incidence and the clinical impact of this are not clear. In any case, if OAC is used during pregnancy, it should be changed for heparin starting in week 36 (Table 7), while the International Normalized Ratio (INR) should be

TABLE 7. Delivery and Anticoagulation Therapy

Given the high incidence of premature delivery, oral anticoagulation therapy should be replaced with heparin starting in week 36 to avoid the risk of fetal intracranial hemorrhage

If delivery begins during oral anticoagulation therapy, caesarean section should be performed

Anticoagulation therapy has implications regarding analgesic administration, since epidural and spinal techniques during anticoagulation therapy increase the risk of spinal hematoma. Any anticoagulant should be replaced with unfractionated heparin, and epidural analgesia is not recommended within the first 10-12 h after LMWH

Heparin should be interrupted 4 h before elective caesarean section and at the beginning of delivery. If serious bleeding is not present, heparin can be resumed 4-6 h after delivery and oral warfarin can be administered

maintained at the same therapeutic level as outside pregnancy.

Unfractionated Heparin

The aforementioned metaanalysis found a much higher rate of thromboembolic complications (TEC) than with OAC. When heparin only was used in the first trimester, TEC were involved in 9.2% of the pregnancies and maternal mortality was 4.2%. When unfractionated heparin (UFH) was used throughout pregnancy, the incidence of TEC was 25% and maternal mortality 6.7%. It should be pointed out that half the patients in this study were carriers of first-generation mechanical prosthesis. Hence, if UFH is chosen, the level of anticoagulation should be carefully monitored, and the patient/control ratio of activated partial thromboplastin time (APTT) should be higher than 2.5. There is no risk of embryopathy when used in the first quarter, since UFH does not cross the placenta.

Low-Molecular-Weight Heparin

The advantages of low-molecular-weight heparin (LMWH) outside pregnancy (easy administration, decreased incidence of osteoporosis, and thrombocytopenia) have suggested that it could be an alternative to UFH and OAC during pregnancy. Furthermore, LMWH does not cross the placenta and the rate of spontaneous abortions seems lower than with UFH. However, its use during pregnancy is not accepted, since, in a preliminary study, high mortality was found among patients undergoing LMWH anticoagulation therapy during pregnancy.⁶⁵ Although some authors have pointed out that in most of the cases described the dose was inappropriate and there was a lack of monitoring, given the changes in intravascular volume and weight gain, the

administration of LMWH during pregnancy requires control via activated factor X to ensure correct anticoagulation. In any case, adjusting the LMWH dose every 12 h is recommended to maintain the 4-h injection level around 1 U/mL. In addition, peak levels should be maintained between 0.6 and 0.7 U/mL, if necessary administering LMWH every 8 h.⁶⁶ Given these preliminary data and the lack of studies, LMWH has not been approved by the recent European Society of Cardiology consensus document (2003) nor is it included in ACCP guidelines on valvular heart disease (1998).

Regarding the foregoing, it should be pointed out that:

- Optimal treatment in pregnant women with a mechanical prosthesis does not exist.

- European experts⁶⁷ and the ACCP guidelines (1998) recommend the use of OAC throughout pregnancy, based on the high mortality reported with heparin and on the impression that warfarin embryopathy has been overestimated.

- If the woman does not accept the risk of warfarin embryopathy, the use of heparin instead of OAC has been suggested during the first quarter.

- Any anticoagulation therapy should be replaced with UFH at the 36th week of pregnancy.

- The use of LMWH during pregnancy is not approved, since existing data is limited. The risk of thrombosis is very high if used without monitoring.

Biological Prosthetic Valves

These prosthesis eliminate the risk associated with the anticoagulation therapy required by patients carrying mechanical ones.

Deterioration of biological prosthesis during pregnancy has not been confirmed, although most published data indicate that the deterioration process accelerates during this period. Homografts probably perform better during pregnancy than porcine bioprosthesis.⁶¹

Pulmonary Hypertension, Eisenmenger Syndrome

The inability to decrease pulmonary vascular resistance, and thus counteract volume overload, exposes pregnant woman with pulmonary arterial hypertension (PAH) to the greatest risk of mortality associated with pregnancy. Despite progress in therapy, mortality associated with PAH during pregnancy has remained the same: 30% in primary PAH, 50% in PAH associated with collagen disease, and from 30% to 50% in Eisenmenger syndrome.⁶⁸ In this syndrome, the fall in peripheral resistance increases right-to-left shunt, which worsens cyanosis.

TABLE 8. Classification of Hypertensive States of Pregnancy

Chronic hypertension	Preexisting hypertension before week 20. Eclampsia occurs in 20%-25% of women with preexisting hypertension
Gestational hypertension	Hypertension that appears in the 20th week of pregnancy and is induced by pregnancy itself
Preeclampsia	Hypertension that appears after the 20th week of pregnancy, induced by pregnancy, and is accompanied by proteinuria

TABLE 9. Treatment of Preeclampsia

Methyldopa	Continues to be the drug of choice (wide experience without adverse fetal effects, even with long-term pediatric follow-up) Starting dose: 250 mg/8 h; increase progressively up to 3-4 g/day
Other drugs that can be used with safety are labetalol, nifedipine, clonidine, and hydralazine	
Hypertension crisis management	Slow IV injection hydralazine 5 mg; can be repeated Labetalol and nifedipine are also used Nitroglycerin and nitroprusside can be used
Eclampsia	Magnesium sulfate has been shown to be more effective than nifedipine for prophylaxis of eclampsia

The risk of thromboembolism and bleeding also contribute to the high mortality⁶⁹ and most deaths occur at the time of delivery or in the first week postpartum.⁷⁰

In the case of mitral stenosis with secondary PAH, the lower severity of PAH and the possibility of balloon mitral valvuloplasty lead to a significantly better prognosis.

Arterial Hypertension and Pregnancy

Preeclampsia (Table 8) is the most frequent medical complication during pregnancy and is associated with serious morbidity for both the mother and fetus. It causes abruptio placentae, disseminated intravascular coagulation, pulmonary edema, liver failure in the mother, prematurity and low weight in the fetus.⁷¹ Thus, preeclampsia should be controlled in every woman during pregnancy via monitoring blood pressure and proteinuria.

Delivery is the only definitive treatment for preeclampsia and on some occasions should be indicated. There is no evidence of that any other treatment, including the use of antihypertensive agents, alters the course of the disease or improves prognosis.⁷² During weeks 23 and 34, preeclampsia is treated via bed-rest, intravenous magnesium sulfate as seizure prophylaxis, blood pressure control, and corticoids to promote fetal lung maturity.

The main aim of antihypertensive treatment is to prevent cerebral complications, although its benefits have not been demonstrated. The drugs used are those where more experience has been acquired and where fetal side effects have not been found (Table 8). The therapeutic aim is to maintain mean BP between 105

and 126 mm Hg and DBP between 90 and 105 mm Hg, since lower figures can cause placental hypoperfusion.

CONCLUSIONS

Pre-conception counseling should be offered to all women with heart disease with the aim of avoiding risks and helping them to plan their future. Optimal care of pregnant women with heart disease during pregnancy, delivery and the postpartum period requires a multidisciplinary team including cardiologists, gynecologists, and anesthesiologists. Specific disorders, such as AMI, require prompt diagnosis and treatment, whereas others remain problematic, such as anticoagulation therapy in pregnant women carrying mechanical prosthesis. Despite this, successful pregnancy is feasible in the great majority of women with heart disease providing they receive optimal management.

REFERENCES

1. Wren C, O'Sullivan. Survival with congenital heart disease and need for follow up in adult life. *Heart*. 2001;85:438-43.
2. Uebing A, Steer P, Yentis S, Gatzoulis MA. Pregnancy and congenital heart disease. *BMJ*. 2006;332:401-6.
3. James AH, Jamison MG, Biswas MS, Brancazio LR, Swamy GK, Myers ER. Acute myocardial infarction in pregnancy. *Circulation*. 2006;113:1-8.
4. González I, Armada E, Díaz J, Gallego P, García Moll M, González A, et al. Guías de la Sociedad Española de Cardiología en la gestante con cardiopatía.
5. Elkayam U. Branwald's heart disease. In: Zipes D, Libby P, Bonow R, Branwald E, editors. 7th ed. Philadelphia: Elsevier Saunders; 1965. p. 85.
6. Poppas A, Shroff S, et al. Serial assessment of the cardiovascular system in normal pregnancy. *Circulation*. 1997;95:2407-15.

7. van Oppen A, van der Tweel I, et al. A longitudinal study of maternal hemodynamics during normal pregnancy. *Obstet Gynecol.* 1996;88:40-6.
8. Campos O. Doppler echocardiography during pregnancy. *Echocardiography.* 1996;13:135-46.
9. Campos O, Andrade JL, Bocanegra J, Ambrose JA, Carvalho AC, Harada K, et al. Physiologic multivalvular regurgitation during pregnancy: a longitudinal Doppler echocardiographic. *Int J Cardiol.* 1992;40:265-72.
10. Meijboom L, Frederiek E, et al. Pregnancy and aortic root growth in the Marfan syndrome: a prospective study. *Eur Heart J.* 2005;26:914-20.
11. Clapp III JF, Capeless E. Cardiovascular function before, during and after the first and subsequent pregnancies. *Am J Cardiol.* 1997;80:1469-73.
12. Stout K. Pregnancy in women with congenital heart disease: the importance of evaluation and counseling. *Heart.* 2005;91:713-4.
13. Thorne S. Pregnancy and heart disease. *Heart.* 2004;90:450-6.
14. Siu S, Sermer M, Harrison D, Grigoriadis E, Liu G, Sorensen S, et al. Risk and predictors for pregnancy-related complications in women with heart disease. *Circulation.* 1997;96:2789-94.
15. Siu S, Sermer S, Colman J, Álvarez N, Mercier L, Morton B, et al. Prospective multicenter study of pregnancy outcomes in women with heart disease. *Circulation.* 2001;104:515-21.
16. Khairy P, Ouyang D, Fernandes S, Lee-Parritz A, Economy K, Landzberg J. Pregnancy outcomes in women with congenital heart disease. *Circulation.* 2006;113:517-24.
17. Swan L, Lupton M, Anthonhy J, Yentis S, Steer P, Gatzoulis M. Controversies in pregnancy and congenital heart disease. *Congenit Heart Dis.* 2006;1:27-34.
18. Burn J, Brennan P, Little J, Holloway S, Coffey R, Somerville J, et al. Recurrence risks in offspring of adults with major heart defects: results from first cohort of British collaborative study. *Lancet.* 1998;351:311-6.
19. Siu S, Colman J, Sorensen S, Smallhorn J, Farine D, Amankwah K, et al. Adverse neonatal and cardiac outcomes are more common in pregnant women with cardiac disease. *Circulation.* 2002;105:2179-84.
20. Steer P. Embarazo y anticoncepción. In: Gatzoulis MA, Swan L, Therrien J, Pantely G, editors. *Cardiopatías congénitas en el adulto.* Barcelona: J&C Ediciones médicas. p. 16-35.
21. Wood A, Pastuszak A, Ito S. Drugs in pregnancy. *N Engl J Med.* 1998;338:1128-37.
22. Qasqas S, McPherson C, Frishman W, Elkayam U. Cardiovascular pharmacotherapeutic considerations during pregnancy and lactation. *Cardiol Rev.* 2004;2:
23. Qasqas S, McPherson C, Frishman W, Elkayam U. Cardiovascular pharmacotherapeutic considerations during pregnancy and lactation. *Cardiol Rev.* 2004;2:201-21.
24. Tan H, Lie K. Treatment of tachyarrhythmias during pregnancy and lactation. *Eur Heart J.* 2001;22:458-64.
25. Meijboom L, Vos F, Timmermans J, Leffler G, Johnson DR. Adenosine use in pregnancy. *Am J Emerg Med.* 1992;10:548-9.
26. Natale A, Davidson T, Geiger M, Newby K. Implantable cardioverter-defibrillators and pregnancy. *Circulation.* 1997;96:2808-12.
27. Cardiac arrest associated with pregnancy. *Circulation.* 2005;112 Suppl IV:1503.
28. Lengyel M, Horstkotter D, Voller H, Mistiaen W. Recommendations for the management of prosthetic valve thrombosis. *J Heart Valve Dis.* 2005;14:567-75.
29. Horstkotte D, Follath F, Gutschik E, Lengyel M, Oto A, Pavie A, et al. Guidelines on prevention, diagnosis and treatment of infective endocarditis. *Eur Heart J.* 2004;25:267-76.
30. Dajani A, Taubert K, Wilson W, Bolger A, Bayer A, Ferrieri P, et al. Prevention of Bacterial Endocarditis: Recommendations by the American Heart Association. *Circulation.* 1997;96:358-66.
31. Souza MH, Elias D. Guidelines for cardiopulmonary bypass during pregnancy. Available from: www.perfliye.com.
32. Connolly H, Warnes C. Pregnancy and contraception. In: Gatzoulis MA, Webb G, editors. *Adult congenital heart disease.* London: Churchill Livingstone. p. 135-45.
33. Arias F, Pineda J. Aortic stenosis and pregnancy. *J Reprod Med.* 1978;20:229-32.
34. Silversides CK, Colman JM, Sermer M, Farine D, Siu SC. Early and intermediate-term outcomes of pregnancy with congenital aortic stenosis. *Am J Cardiol.* 2003;91:1386-9.
35. Presbitero P, Prever S, Brusca A. Interventional cardiology in pregnancy. *Eur Heart J.* 1996;17:182-8.
36. Beauchesne L, Connolly H, Ammash N, Warnes C. Coartation of the aorta: outcome of pregnancy. *J Am Coll Cardiol.* 2001;38:1728-33.
37. Vriend J, Drenthen W, Pieper P, Roos-Hesselink J, Zwiderman A, van Veidhuisen D, et al. Outcome of pregnancy in patients after repair of aortic coarctation. *Eur Heart J.* 2005;26:2173-8.
38. Siu S, Colman J. Congenital heart disease in pregnancy. *Heart.* 2001;85:710-5.
39. Presbitero P, Somerville J, Stone S, Aruta E, Spiegelhalter D, Rabajoli F. Pregnancy in cyanotic congenital heart disease. Outcome of mother and fetus. *Circulation.* 1994;89:2673-6.
40. Vedtman G, Connolly H, Grogan M, Ammash N, Warnes C. Outcomes of pregnancy in women with Tetralogy of Fallot. *J Am Coll Cardiol.* 2004;44:174-80.
41. Meijer J, Pieper P, Drenthen W, Voors A, Roos-Hesselink J, van Dijk A, et al. Pregnancy, fertility, and recurrence risk in corrected tetralogy of Fallot. *Heart.* 2005;91:801-5.
42. Neumayer U, Somerville J. Outcome of pregnancies in patients with complex pulmonary atresia. *Heart.* 1997;78:16-21.
43. Guédès A, Mercier L, Leduc L, Bérubé L, Marcotte F, Dore A. Impact of pregnancy on the systemic right ventricle after a Mustard operation for transposition of the great arteries. *J Am Coll Cardiol.* 2004;44:433-7.
44. Drenthen W, Pieper P, Ploeg M, Voors A, Roos-Hesselink W, Mulder B, et al. Risk of complications during pregnancy after Senning or Mustard repair of complete transposition of the great arteries. *Eur Heart J.* 2005;26:2588-95.
45. Connolly H, Grogan M, Warnes C. Pregnancy among women with congenitally corrected transposition of great arteries. *J Am Coll Cardiol.* 1999;33:1692-5.
46. Cannobio M, Douglas R, Mair D, Van der Velde M. Pregnancy outcomes after the Fontan repair. *J Am Coll Cardiol.* 1996;28:763-7.
47. Drenthen W, Pieper P, Roos-Hesselink J, van Lottum W, Voors A, Mulder B. *Heart.* 2006; doi:10.1136/hrt.2005.085407.
48. Boers, Zwiderman AH, Mulder BJM. Pregnancy and aortic root growth in the Marfan syndrome: a prospective study. *Eur Heart J.* 2005;26:914-20.
49. Milewicz M, Dietz H, Miller C. Treatment of aortic disease in patients with Marfan syndrome. *Circulation.* 2005;111:e150-7.
50. Thaman R, Varnava V, Hamid MS, Firozzi S, Saxhdev B, Condon M, et al. Pregnancy related complications in women with hypertrophic cardiomyopathy. *Heart.* 2003;89:752-6.
51. Elkayam U, Tummala P, Rao K, Akhter M, Karaalp I, Wani O, et al. Maternal and fetal outcomes of subsequent pregnancies in women with peripartum cardiomyopathy. *N Engl J Med.* 2001;344:1567-71.
52. Ladner H, Danielsen B, Gilbert W. Acute myocardial infarction in pregnancy and the puerperium: a population-based study. *Obstet Gynecol.* 2005;105:480-4.
53. Roth A, Elkayam U. Acute myocardial infarction associated with pregnancy. *Ann Intern Med.* 1996;125:751-62.
54. Dwyer B, Taylor L, Fuller A, Brummel C, Lyell D. Percutaneous transluminal coronary angioplasty and stent placement in pregnancy. *Obstet Gynecol.* 2005;106:1162-4.
55. Koul A, Hollander G, Moskovits N, Franker R, Herrera L, Shani J. Coronary artery dissection during pregnancy and the postpartum period: two case reports and review of literature. *Catheterization and cardiovascular interventions.* 2001;52:88-94.

56. Nallamothu B, Saint M, Saint S, Mukherjee D. Double jeopardy. *N Engl J Med*. 2005;353:75-80.
57. Mangione J, Monteiro R, Souza E, Shigheyuki A, Zuliani, Bavaresco S, et al. Long term follow-up of pregnant women after percutaneous mitral valvuloplasty.
58. Souza JA, Martínez E, Ambrose J, Alves C, Born D, Buffolo E, et al. Percutaneous balloon mitral valvuloplasty in comparison with open mitral valve commissurotomy for mitral stenosis during pregnancy. *J Am Coll Cardiol*. 2001;37:900-3.
59. Elkayam U, Bitar F. Valvular heart disease and pregnancy, part I. *J Am Coll Cardiol*. 2005;46:403-10.
60. Reimold S, Rutherford J. Valvular heart disease in pregnancy. *N Engl J Med*. 2003;349:52-9.
61. Elkayam U, Bitar F. Valvular heart disease and pregnancy, part II. *J Am Coll Cardiol*. 2005;46:403-10.
62. Hung L, Rahimtoole S. Prosthetic heart valves and pregnancy. *Circulation*. 2003;107:1240-6.
63. Chan W, Anand S, Ginsberg J. Anticoagulation of pregnant women with mechanical heart valves. *Arch Intern Med*. 2000;160:191-6.
64. Vitale N, Feo MD, DeSanto LS. Dose-dependent fetal complications of Warfarin in pregnant women with mechanical heart valves. *J Am Coll Cardiol*. 1999;33 1637-41.
65. Seshadri N, Goldhaber S, Elkayam U, Grimm R, Groce J, Heit J, et al. The clinical challenge of bridging anticoagulation with low-molecular-weight heparin in patients with mechanical prosthetic heart valves. *Am Heart J*. 2005;150:27-34.
66. Bates M, Greer I, Hirsh J, Ginsberg J. Use of antithrombotic agents during pregnancy. The seventh ACCP conference on antithrombotic and thrombolytic therapy. *Chest*. 2004;126:627-44.
67. Oakley C, Child A, Jung B, Presbitero P, Tornos P, Klein W, et al. Expert consensus document on management of cardiovascular diseases during pregnancy. *Eur Heart J*. 2003;24:561-781.
68. Weiss B, Hess O. Pulmonary vascular disease and pregnancy: current controversies, management strategies, and perspectives. *Eur Heart J*. 2000;21:104-15.
69. Bouzas B, Gatzoulis MA. Pulmonary artery hypertension in adults with congenital heart disease. *Rev Esp Cardiol*. 2005;58:465-9.
70. Avila W, Grinberg M, Snitcowsy R, Faccioli R, da Luz P, Bellotti G, et al. Maternal and fetal outcome in pregnant women with Eisenmenger syndrome. *Eur Heart J*. 1995;16:460-4.
71. James R, Nelson-Piercy. Management of hypertension before, during and after pregnancy. *Heart*. 2004;90:1499-504.
72. Duley L, Meher S, Abalos E. Management of preeclampsia. *BMJ*. 2006;332:463-8.