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THE PRESENT AND FUTURE

STATE-OF-THE-ART REVIEW

High-Risk Cardiac Disease in Pregnancy

Part I

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ABSTRACT

The incidence of pregnancy in women with cardiovascular disease is rising, primarily due to the increased number of women with congenital heart disease reaching childbearing age and the changing demographics associated with advancing maternal age. Although most cardiac conditions are well tolerated during pregnancy and women can deliver safely with favorable outcomes, there are some cardiac conditions that have significant maternal and fetal morbidity and mortality. The purpose of this paper is to review the available published reports and provide recommendations on the management of women with high-risk cardiovascular conditions during pregnancy. (J Am Coll Cardiol 2016;68:396–410)

Cardiovascular disease has been estimated to be present in 1% to 4% of pregnancies. The incidence of pregnancies in women with heart disease is rising, mainly due to an increased number of women with congenital heart disease (CHD) reaching childbearing age; advancing maternal age; and increased incidence of risk factors, including diabetes mellitus, hypertension, pre-eclampsia, and multifetal pregnancies.

Although the majority of women with cardiac disease can become pregnant and, with early diagnosis and appropriate management, can be brought to term safely, there are high-risk cardiac conditions that may be associated with important morbidity, and even mortality. With increased numbers of pregnancies in women with cardiac problems, heart disease has emerged as the leading cause of nonobstetric maternal mortality. This state-of-the-art review is focused on the approach to pregnancy in women with cardiac conditions associated with high maternal and fetal risks (**Central Illustration**).

NORMAL CARDIAC PHYSIOLOGY OF PREGNANCY

Blood volume increases substantially during pregnancy, starting as early as the sixth week and rising rapidly until midpregnancy, when the rise continues at a slower rate, with an average maximum increase of 50% (1,2) (**Figure 1**). Because the red blood cell mass increases less rapidly, the hemoglobin concentration falls, causing the "physiological anemia of pregnancy." Cardiac output (CO) during pregnancy increases by about 50%, predominantly due to augmentation of stroke volume during early pregnancy and increased heart rate in the third trimester. Systemic blood pressure (BP) falls during the first trimester, reaching a nadir in midpregnancy and returning toward pre-gestational levels before term. This change results from a decline in systemic vascular resistance due to reduced vascular tone. Hemodynamics are altered substantially during labor and delivery, secondary to anxiety, pain, and uterine

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contractions. Oxygen consumption increases 3-fold, and systolic and diastolic BP rise during contractions. Reduction of pain and apprehension with analgesia and anesthesia may limit hemodynamic changes and the rise in oxygen consumption. Cesarean delivery is frequently recommended in women with cardiac disease; however, it can be also associated with considerable hemodynamic changes related to intubation and drugs used for anesthesia. A temporary increase in intracardiac pressures may occur immediately after delivery due to relief of caval compression and blood shift from the contracting uterus into the systemic circulation, which may lead to clinical deterioration.

PREGNANCY RISK ASSESSMENT

Assessment of pregnancy risk is an important aspect of the care of women with heart disease who are of childbearing age (3). All women with cardiac disease can benefit from pre-conception counseling, which should include a detailed discussion of the risk of pregnancy. Some women may require optimization of cardiac status prior to pregnancy, and for those women considering pregnancy, cardiac medications that are teratogenic, such as warfarin and angiotensin-converting enzyme inhibitors, can be switched to safer medications when necessary. Increasing numbers of women with heart disease are considering fertility therapy, and in this circumstance, pre-conception risk stratification and safety of fertility therapy should be addressed. A discussion of safe contraception choices is relevant for those who decide not to become pregnant. It is important that this information is communicated effectively to patients; a number of groups have shown that many women do not fully understand pregnancy and contraception risks (3–5).

Cardiologists with expertise in pregnancy and heart disease should perform pre-conception counseling and risk stratification. Issues to address at the time of pre-conception counseling are shown in **Table 1**. Risk assessment should include a complete history and physical examination, a 12-lead electrocardiogram (ECG), and a transthoracic echocardiogram. In women who are pregnant, signs and symptoms of pregnancy can mimic heart disease, and should be interpreted accordingly. Risk stratification may be further defined by incorporating other clinical and imaging information, including disease activity, cardiac computed tomography (CT), or cardiac magnetic resonance. Cardiac magnetic resonance and CT findings should be reviewed and incorporated into risk assessment, especially in women with aortopathies and complex congenital lesions. Exercise stress testing to measure functional capacity and BP response to exercise is useful for risk stratification in women with valve lesions, such as aortic stenosis (AS) (6,7). Cardiopulmonary testing, with measurements of oxygen saturation, functional capacity, peak VO_2, and chronotropic index, provides helpful information in women with complex CHD (8). Baseline and serial serum B-type natriuretic peptide levels during pregnancy can be incorporated into pregnancy assessment in women with the potential to develop heart failure (HF) during pregnancy due to myocardial disease, valvular heart disease, and CHD. In specific cases, women with arrhythmias may benefit from continuous ECG monitoring, exercise testing, or electrophysiology studies. Women with inherited cardiac conditions should have a formal genetic evaluation to discuss transmission of disease to offspring (6,9). Autosomal-dominant cardiac conditions include Marfan, Noonan, William, Holt-Oram, and 22q11 deletion syndromes, as well as some of the inherited arrhythmias (long-QT syndrome) and cardiomyopathies (hypertrophic cardiomyopathy). Women with inherited cardiac conditions who have an identified genetic mutation may wish to explore the option of pre-implantation genetic screening. Assessment with maternal fetal medicine specialists (high-risk obstetricians) to discuss obstetric risk is an important part of pre-conception assessment.

To estimate pregnancy risk, it is important to consider general and lesion-specific risk predictors. General risk predictors are relevant for all women with heart disease and include factors such as cardiac history, functional capacity, and ventricular function. Lesion-specific risks are known for many, but not all, cardiac conditions and are discussed later, in the corresponding sections.

For women with pre-existing heart disease, the most common cardiac complications during pregnancy are arrhythmias, HF, and thromboembolic events (TEs). Early studies on pregnancy risk predictors identified functional class and cyanosis as important determinants of adverse outcomes during pregnancy (10–12). Subsequently, large pregnancy cohorts were assembled, and pregnancy risk indexes were developed (13–19), which are shown in **Table 2**. The first prospective risk index was developed by the CARPREG (Cardiac Disease in Pregnancy) investigators. The CARPREG study examined outcomes in women with congenital and acquired heart disease and identified 4 predictors of adverse maternal

ABBREVIATIONS AND ACRONYMS

AC = anticoagulation

BPHV = bioprosthetic heart valve

CHD = congenital heart disease

HF = heart failure

LMWH = low molecular weight heparin

MPHV = mechanical prosthetic heart valve

PHV = prosthetic heart valve

SCAD = spontaneous coronary artery disease

TT = thrombolytic therapy

UFH = unfractionated heparin

CENTRAL ILLUSTRATION **High-Risk Heart Disease in Pregnancy**

HIGH-RISK HEART DISEASE (HRHD) IN PREGNANCY

Pre-conception counseling and pregnancy risk stratification for all women with HRHD of childbearing age

In women considering pregnancy: Switch to safer cardiac medications and emphasize importance of close monitoring

In women avoiding pregnancy: Discuss safe and effective contraception choices or termination in early pregnancy

Valve disease	Complex congenital heart disease	Pulmonary hypertension	Aortopathy	Dilated cardiomyopathy
Pregnancy not advised in women with: • Severe mitral and aortic valve disease • Mechanical prosthetic valves if effective anticoagulation not possible	**Pregnancy not advised in women with:** • Significant ventricular dysfunction • Severe atrioventricular valve dysfunction • Failing Fontan circulation • O_2 saturation <85%	**Pregnancy not advised for:** • All women with established pulmonary arterial hypertension	**Pregnancy not advised in some women with:** • Marfan syndrome (MFS) • Bicuspid aortic valve (BAV) • Turner syndrome • Rapid growth of aortic diameter or family history of premature aortic dissection	**Pregnancy not advised in women with:** • Left ventricular ejection fraction <40% • History of peripartum cardiomyopathy
Pregnancy management: • Close follow-up • Drug therapy for heart failure or arrhythmias • Balloon valvuloplasty or surgical valve replacement in refractory cases	**Pregnancy management:** • Close follow-up	**Pregnancy management:** • Close follow-up • Early institution of pulmonary vasodilators	**Pregnancy management:** • Treat hypertension • Beta-blockers to reduce heart rate • Frequent echo assessment • Surgery during pregnancy or after C-section if large increase in aortic dimension	**Pregnancy management:** • Close follow-up • Beta-blockers • Diuretic agents for volume overload • Vasodilators for hemodynamic and symptomatic improvement
Delivery: • Vaginal delivery preferred • C-section in case of fetal or maternal instability • Early delivery for clinical and hemodynamic deterioration • Consider hemodynamic monitoring during labor and delivery	**Delivery:** • Vaginal delivery preferred • C-section in case of fetal or maternal instability • Consider hemodynamic monitoring during labor and delivery	**Delivery:** • Vaginal delivery preferred • C-section in case of fetal or maternal instability • Timing of delivery depends on clinical condition and right ventricular function • Early delivery advisable • Diuresis after delivery to prevent RV volume overload • Extended hospital stay after delivery	**Delivery:** • C-section in cases of significant aortic dilation MFS >40 mm BAV >45 mm Turner: ASI >20 mm/m^2	**Delivery:** • Vaginal delivery preferred • C-section in case of fetal or maternal instability • Consider hemodynamic monitoring during labor and delivery • Early delivery for clinical and hemodynamic deterioration

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Management strategies for women who have valve disease, complex congenital heart disease, pulmonary hypertension, aortopathy, and dilated cardiomyopathy.
ASI = aortic size index; BAV = bicuspid aortic valve; echo = echocardiographic; HRHD = high-risk heart disease; MFS = Marfan syndrome; RV = right ventricular.

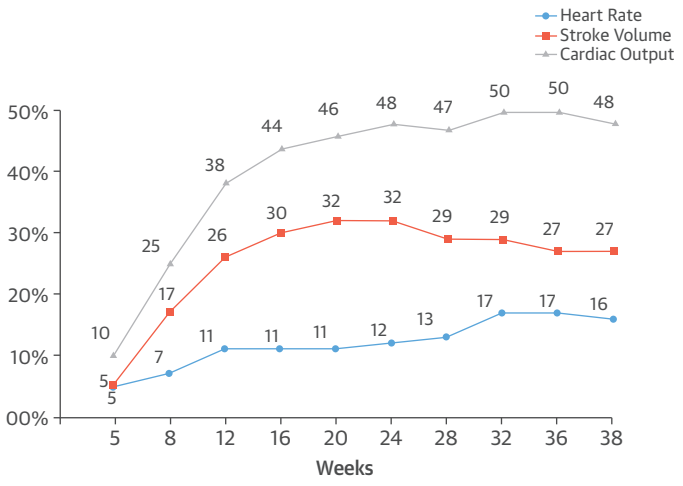
events: prior cardiac events; poor functional status (New York Heart Association [NYHA] functional class >II) or cyanosis; left heart obstruction; and systemic (subaortic) ventricular systolic dysfunction (14). The BACH (Boston Adult Congenital Heart) group studied predictors of outcomes in women with congenital heart disease and, in addition to the CARPREG risk factors, identified smoking history and reduced subpulmonary ventricular function and/or severe pulmonic regurgitation as important determinants of adverse outcomes during pregnancy (16). The ZAHARA (Zwangerschap bij vrouwen met een Aangeboren HARtAfwijking-II [translated as "Pregnancy in women with CHD II risk index"]) risk score was on

the basis of pregnancy outcomes in women with CHD. It is a weighted risk score that contains 8 risk predictors, which are shown in **Table 2** (17). In 2006, a British working group created a lesion-specific risk classification using a modified World Health Organization (WHO) classification. This is now widely used. The WHO classification categorizes cardiac lesions as low risk (WHO I), medium risk (WHO II), high risk (WHO III), and lesions in which pregnancies are contraindicated (WHO IV) (20). The European Society of Cardiology (ESC) guidelines on the management of cardiovascular diseases made minor modifications to the WHO classification (6). The modified WHO risk classification appeared to be the most reliable system for risk prediction in several studies (21).

Obstetric and perinatal outcomes risks also need to be considered. Women with heart disease are at risk for obstetric complications (22,23). In 1 study of women with CHD, adverse obstetric events (pre-term delivery, premature rupture of the membranes, postpartum hemorrhage) occurred in 32% of pregnancies (21). Miscarriages are common in women with cyanotic heart disease or Eisenmenger syndrome. Live birth rates are low in women with cyanotic heart disease, occurring in only 43% of pregnancies overall and 12% of pregnancies in women with oxygen saturations ≤85% (24). Women with coarctation of the aorta are at increased risk for hypertension, preeclampsia, and HF (25). Bleeding at the time of delivery is more common in women with cyanotic heart disease and in women taking anticoagulants. Fetal and neonatal deaths, premature births and associated complications (respiratory distress syndrome or intraventricular hemorrhage), and small-for-gestational-age birth weight babies are more common in women with heart disease compared with "healthy" women (14,15,17). Risk factors for perinatal complications include: poor maternal functional class, left heart obstruction, maternal age <20 or >35 years, multiple gestations, smoking during pregnancy, and anticoagulant therapy. Perinatal complications are further increased in women with concomitant obstetric risk factors, such as a history of premature delivery or rupture of membranes, incompetent cervix or cesarean delivery, intrauterine growth retardation, antepartum bleeding >12 weeks gestation, febrile illness, or uterine/placental abnormalities during present pregnancy (15).

Despite significant advances in our understanding of pregnancy risk with the development of risk indexes and a large number of studies on lesion-specific outcomes, clinical judgment remains a very important aspect of risk stratification. There are variables with an effect on outcomes that are neither captured in current risk scores nor described in papers on lesion-specific outcomes. Therefore, assessment by cardiologists and obstetricians with experience in pregnancy care is crucial.

FIGURE 1 Hemodynamic Changes During Pregnancy



Percent changes in heart rate, stroke volume, and cardiac output measured in the lateral position throughout pregnancy compared with pre-pregnancy values. Adapted from Elkayam and Gleicher (1) and Robson et al. (103).

NATIVE VALVE DISEASE

Valvular heart disease is a common cardiac condition in young women considering pregnancy. In the CARPREG and the ROPAC (Registry of Pregnancy and Cardiac Disease) study cohorts, a significant portion of women had either acquired or congenital valve

TABLE 1 Pre-Conception Counseling Considerations: Issues to Address With the Patient

Pregnancy risk stratification • Maternal cardiac risk • Maternal obstetric risk • Fetal and neonatal risks
Long-term effects of pregnancy on the heart
Maternal life expectancy
Genetic consultation
Contraception safety and efficacy
Modification of cardiac medications
Optimization of cardiac status
Planning for pregnancy*

*For women who are pregnant, follow-up during pregnancy should be discussed. The European Society of Cardiology guidelines on the management of cardiovascular diseases during pregnancy suggest that women with World Health Organization (WHO) I lesions should have 1 to 2 cardiac visits during pregnancy, WHO II lesions should have cardiac follow-up every trimester, WHO III lesions should have monthly or bimonthly cardiac follow-up, and WHO IV lesions (who do not elect to terminate the pregnancy) should have monthly or bimonthly follow-up (4).

TABLE 2 Risk Factors Associated With Adverse Maternal Cardiac Outcomes in Pregnant Women With Heart Disease

CARPREG study (14)
- Poor functional class (NYHA functional class III or IV) or cyanosis
- Systemic ventricular ejection fraction <40%
- Left heart obstruction
- Cardiac event prior to pregnancy

ZAHARA study (17)
- History of arrhythmias (weighted score 1.5)
- Cardiac medications before pregnancy (weighted score 1.5)
- NYHA functional class prior to pregnancy ≥II, left heart obstruction (weighted score 0.75)
- Left heart obstruction (weighted score 2.5)
- Systemic atrioventricular valve regurgitation (weighted score 0.75)
- Pulmonary atrioventricular valve regurgitation (weighted score 0.75)
- Mechanical valve prosthesis (weighted score 4.25)
- Cyanotic heart disease (weighted score 1.0)

Modified WHO classification (6)

WHO classification I
- Uncomplicated small or mild pulmonary stenosis
- Patent ductus arteriosus
- Mitral valve prolapse
- Successfully repaired simple lesions (atrial or ventricular septal defect, patent ductus arteriosus, anomalous pulmonary venous connection)

WHO classification II (if otherwise well and uncomplicated)
- Unrepaired atrial or ventricular septal defect
- Unrepaired tetralogy of Fallot

WHO classification II–III (depending on individual)
- Mild left ventricular impairment
- Native or tissue valvular heart disease not considered WHO I or IV
- Marfan syndrome without aortic dilation
- Aorta <45 mm in association with bicuspid aortic valve disease
  Repaired coarctation

WHO classification III
- Mechanical valve
- Systemic right ventricle
- Fontan circulation
- Unrepaired cyanotic heart disease
- Other complex congenital heart disease
- Aortic dilation 40–45 mm in Marfan syndrome
- Aortic dilation 45–50 mm in bicuspid aortic valve disease

WHO classification IV (pregnancy contraindicated)
- Pulmonary arterial hypertension from any cause
- Severe systemic ventricular dysfunction (LVEF <30%, NYHA functional class III–IV)
- Severe mitral stenosis; severe symptomatic aortic stenosis
- Marfan syndrome with aorta dilated >45 mm
- Aortic dilation >50 mm in aortic disease associated with bicuspid aortic valve
- Native severe coarctation of the aorta

a. CARPREG (Cardiac Disease in Pregnancy): Each risk factor is worth 1 point. Women with risk scores of 0, 1, or >1 had event rates during pregnancy of 5%, 25%, or 75%, respectively.

b. ZAHARA (Zwangerschap bij vrouwen met een Aangeboren HARtAfwijking-II): Weighted risk score. Weights shown in parenthesis. Women with risk scores of 0–0.50, 0.51–1.5, 1.51–2.5, 2.51–3.5, and >3.51 had event rates of 2.9%, 7.5%, 17.5%, 43.1%, and 70.0%, respectively.

c. World Health Organization (WHO) classification:
- WHO classification I: no detectable increased risk of maternal mortality and no/mild increase in morbidity.
- WHO classification II: small increase in maternal risk mortality or moderate increase in morbidity.
- WHO classification III: significantly increased risk of maternal mortality or severe morbidity. Expert counseling required. If pregnancy is decided upon, intensive specialist cardiac and obstetric monitoring needed throughout pregnancy, childbirth and the puerperium.
- WHO classification IV: extremely high risk of maternal mortality or severe morbidity; pregnancy contraindicated. If pregnancy occurs, termination should be discussed. If pregnancy continues, care as for WHO class III.

LVEF = left ventricular ejection fraction; NYHA = New York Heart Association.

lesions (14,26). Although most women are aware of their diagnosis prior to pregnancy, some present for the first time during pregnancy. Occasionally, women come to attention when a murmur is detected. Although many women with valve disease, especially less severe valve disease, do well throughout pregnancy, there are some valve lesions in which the risk of pregnancy is considered prohibitive, including severe mitral stenosis (MS), severe symptomatic AS, and valve lesions associated with severe left ventricular (LV) dysfunction or significant pulmonary hypertension (6). These women should receive appropriate pre-conception counseling and, when possible, be offered valve intervention prior to pregnancy (6,7).

For women who become pregnant, serial clinical and transthoracic echocardiographic monitoring during pregnancy is required. The frequency of cardiac monitoring during pregnancy needs to be individualized (**Table 1**). The hemodynamic changes of pregnancy can lead to increased mitral and aortic valve gradients on transthoracic echocardiograms, with overestimation of the severity of the valve lesion. When possible, the degree of stenosis can be estimated by tracing the valve area. If this is not possible, the valve area can be estimated by the pressure half-time method for MS or by the continuity equation for AS (27,28). Bed rest and medical therapy should be initiated if clinical decompensation occurs during pregnancy. Percutaneous balloon valvuloplasty for stenotic lesions is the preferred treatment in women with refractory symptoms (6,7). When possible, balloon valvuloplasty should be performed after the first trimester to avoid radiation exposure to the fetus during organogenesis. Only experienced operators should perform valvuloplasty. Abdominal shielding can be used to minimize fetal radiation exposure. Valve surgery is only considered if other therapies have failed because it is associated with a significant fetal mortality risk of 20% to 30% (29–31).

All women with significant valve disease should have joint care with a maternal fetal medicine specialist or high-risk obstetrician. Women should also be seen by obstetric anesthesia to plan for delivery. For women who remain stable throughout pregnancy, a delivery at term is optimal. A planned induction is usually advised in women with severe stenotic lesions, in whom telemetry monitoring for arrhythmias and arterial line insertion for accurate measurement of BP are recommended. Hemodynamic monitoring during labor and delivery, and for 12 to 24 h post-partum, is used to ensure that hemodynamics and volume status are optimized and that complications are prevented, when possible. A vaginal delivery with good pain management is the preferred mode of delivery for most women with valve disease. Some experts advise consideration of a cesarean delivery for women with severe AS (6). For

women with moderate or severe stenotic valve lesions who have a vaginal delivery, an assisted second stage of labor is used to minimize maternal expulsive effort. Tocolytic agents with beta-mimetic effects should not be used in women with MS so as to prevent tachycardia-mediated increase in left atrial pressure. Atosiban, an oxytocin antagonist, is an alternative agent. Antibiotic prophylaxis is not recommended in women with native valve disease (32). Women with severe stenotic lesions usually benefit from post-partum monitoring in a coronary care or step-down unit for at least 24 h for close management of their volume status.

MITRAL STENOSIS. Rheumatic MS is the most common valve lesion in women of childbearing age. There is often some associated mitral regurgitation (MR). During pregnancy, increases in heart rate, CO, red blood cell mass, and plasma volume can lead to increased left atrial pressures and cardiac decompensation. Some women with rheumatic MS will present with symptoms for the first time during pregnancy due to these hemodynamic changes. The most common cardiac complications during pregnancy are declines in functional capacity, atrial arrhythmias, such as atrial fibrillation, and pulmonary edema (28,33,34). Complications are related to the severity of MS and to baseline NYHA functional class (28,33,35,36). Pregnancy outcomes from 2 large North American centers reported rates of pulmonary edema in pregnant women with mild, moderate, and severe MS of between 11% and 24%, 34% and 61%, and 56% and 78%, respectively (28,33,37). Rates of atrial arrhythmias in pregnant women with mild, moderate, and severe MS ranged between 0% and 7%, 10% and 22%, and 33%, respectively. Atrial arrhythmias and HF often occur in the third trimester, when the hemodynamic changes of pregnancy are most pronounced (28). Complications also occur at the time of labor and delivery or within the first week postpartum. Women with atrial fibrillation are at risk for stroke and transient ischemic events. Although maternal mortality in the setting of MS is very rare in developed countries, it is reported in underdeveloped and developing countries (36,38). Fetal and neonatal complications are also increased in women with MS, with high rates of pre-term delivery, intrauterine growth restriction, low birth weight, and fetal deaths (28,33). Women who develop symptoms should receive beta-blockers to lengthen diastolic filling time and decrease left atrial pressure (39). Pulmonary edema should be treated with intravenous beta-blockers and diuretic agents. Women who develop atrial fibrillation should be fully anticoagulated and sinus rhythm should be restored when possible (6).

Women who are refractory to medical therapy may be considered for percutaneous mitral balloon valvuloplasty. Many case reports and case series of mitral balloon valvuloplasty outcomes during pregnancy have been published. Generally, percutaneous mitral balloon valvuloplasty is associated with improvements in the mitral valve area and mitral valve gradients (40–42). However, worsening MR, atrial fibrillation, thromboembolism, and cardiac tamponade have been described (40). Mitral valve surgery may be considered in women who are not candidates for balloon valvuloplasty. As with aortic valve surgery, a major concern regarding cardiopulmonary bypass during pregnancy is related to fetal mortality; therefore, valve surgery is only considered if other therapies have failed because it is associated with a significant fetal mortality risk of 20% to 30% (28–30).

MITRAL REGURGITATION. Rheumatic heart disease, CHD, and mitral valve prolapse are the most common causes of MR in women of childbearing age. The decrease in peripheral vascular resistance and BP during pregnancy are thought to be the reason that asymptomatic women with mild, moderate, and even severe MR with normal LV size and systolic function tend to do well during pregnancy. However, the increased plasma volume and CO may lead to HF or arrhythmias in pregnancy in women with severe MR, especially in those with significant ventricular dilation or dysfunction.

AORTIC STENOSIS. In North America, AS is most commonly due to bicuspid aortic valve disease. Bicuspid valve disease may be associated with aortic root dilation or coarctation of the aorta, and these may confer additional pregnancy risks. Less frequently, AS is secondary to rheumatic heart disease. The increased CO of pregnancy may be poorly tolerated in the setting of a fixed outflow obstruction. At the time of labor and delivery, relief of inferior vena cava compression, autotransfusions from the contracting uterus, and excessive intravenous fluid administration may also be poorly tolerated. Women with mild or moderate AS often do well, whereas women with severe AS can develop angina, tachyarrhythmias, and pulmonary edema (27,33,41). In 1 large North American series, maternal cardiac complications occurred in approximately 10% of pregnant women with severe AS (27), but higher rates have been reported, with HF occurring in 42% of pregnancies in women with AS in 1 small series (33). Maternal mortality is rare (<1%) in contemporary pregnancy series (27,33,41). Pregnancies in women

with significant AS are associated with high rates of pre-term delivery, low birth weight, and fetal death (27,33,41). Transmission of CHD to offspring is 10% in the setting of left-sided outflow tract obstruction, and therefore, fetal echocardiography should be offered to women with bicuspid valve disease.

Women who develop symptoms during pregnancy should be admitted for bed rest. Pulmonary edema should be treated with diuretic agents. Aggressive diuresis, however, can cause hypovolemia, hypotension, and decreased placental perfusion, and should be avoided. Sinus rhythm should be restored in women who develop arrhythmia. Unlike MS, there is no effective medical therapy for AS. For women with persistent symptoms despite bed rest and medical therapy, percutaneous aortic balloon valvuloplasty should be considered if the valve is suitable for the procedure, there is no significant aortic regurgitation, and an experienced team is available to perform the procedure (6,7). Valve surgery should only be considered when pregnant women are refractory to medical therapy and balloon valvuloplasty is not an option. Transcutaneous aortic valve implantation has not yet been reported in pregnant women. The need for valve interventions after pregnancy is more common in women with AS who have been pregnant compared with those who have not been pregnant (27,42). The mechanism for these high rates of valve intervention after pregnancy is not known.

AORTIC REGURGITATION. Similar to AS, the most common cause of aortic regurgitation (AR) in young women is bicuspid aortic valve disease. Less commonly, women have an aortopathy with a dilated aorta, or have residual AR after a valvuloplasty or endocarditis. The increased plasma volume and CO of pregnancy can lead to complications in women who have severe AR with LV systolic dysfunction. Women with AR and preserved LV size and systolic function usually do well during pregnancy. Women who develop complications should receive medical therapy for HF or arrhythmias.

PULMONARY REGURGITATION. Pulmonary regurgitation (PR) is most commonly seen in young women after tetralogy of Fallot repair. Less commonly, severe PR is present after valvuloplasty for pulmonary stenosis (PS). Some women with tetralogy of Fallot have mixed PR and right ventricular outflow tract obstruction. The increase in plasma volume and CO during pregnancy can result in right-sided HF in women with severe PR, particularly in those women with pre-existing right ventricular dilation and dysfunction. In the BACH and the ZAHARA risk scores, PR is a predictor of adverse outcomes during pregnancy (16,17). A number of groups have reported on pregnancy outcomes in women with PR, with variable rates of HF and arrhythmias (43–45). In general, women with normal right ventricular function do well during pregnancy. However, women with severe PR and right ventricular systolic dysfunction or hypertrophy and those with branch pulmonary artery stenosis are at higher risk for developing right HF (45). Transmission of heart disease to offspring is approximately 3% to 5%.

PULMONARY STENOSIS. In young women, isolated PS is mostly secondary to congenital pulmonary valve abnormalities. Even in women with severe PS, cardiac complications during pregnancy are very rare (14,46–48). Noncardiac complications have been reported in women with PS, including hypertensive-related disorders, premature deliveries, and thromboembolic complications (46).

TRICUSPID REGURGITATION. Isolated tricuspid valve disease in young women is rare. Causes of tricuspid regurgitation in young women include congenital cardiac lesions, such as Ebstein anomaly, rheumatic heart disease, and endocarditis. Most women with tricuspid regurgitation, including those with Ebstein anomaly, tolerate the hemodynamic changes of pregnancy well (49). However, in the setting of congenitally corrected transposition of the great arteries or the atrial switch operations for complete transposition of the great arteries (Mustard or Senning operation), the tricuspid valve is the systemic atrioventricular valve. In adults, this valve is commonly regurgitant and is associated with subaortic ventricular dilation and dysfunction. This group of women is at higher risk for pregnancy complications (50). In the ZAHARA study, systemic atrioventricular valve regurgitation was a predictor of complications during pregnancy (17).

PROSTHETIC HEART VALVES

Pregnancy in women with prosthetic heart valves (PHVs) has been shown to be associated with a substantial risk of morbidity and even mortality (51,52). The choice between a bioprosthetic heart valve (BPHV) and a mechanical prosthetic heart valve (MPHV) in women of childbearing age is difficult. The use of BPHVs in young women is often recommended (53) because of a lower risk of thromboembolism and anticoagulation (AC). The tradeoff, however, is a high risk of structural valve deterioration, which can occur as early as 2 to 3 years after the initial replacement and has been reported in 80% of cases at 10 years and in 90% at 15 years (51). Although not confirmed by some reports, multiple studies have suggested a

pregnancy-related increased incidence of structural valve deterioration in women with BPHVs (51). Because a second valve replacement is almost mandatory in young women who elect to receive a BPHV, the risk of a second and possibly a third cardiac valve operation needs to be taken into account. Although published information does not allow an accurate estimate of the risk of redo valve replacement in young women (54), recent publications in older and higher-risk patients reported early mortality in 4.5% of patients undergoing redo aortic valve surgery (54) and between 4.7% and 7.4% in those undergoing repeat mitral valve replacement (55,56). For mitral and aortic valve replacement, the Society of Thoracic Surgeons cardiac risk calculator for a redo valve surgery in a woman 35 years of age without other risk factors indicates a 1.7% risk of mortality; a 17% and 14% risk of morbidity, respectively; and a 1% risk of stroke.

Transcatheter aortic valve replacement for deteriorated bioprosthetic aortic valve has been increasingly and successfully used in older patients (57). However, no information is available about the safety and durability of such a procedure in young women. Early publications by North et al. (58,59) in 1999 to 2000 reported a superior durability of homograft aortic valves in young women compared with BPHV and an excellent outcome of pregnancy in 34 women. These limited data published by a single group suggested superiority of homograft valves compared with BPHV in women of childbearing age. No further information is available, however, to substantiate these findings, especially when compared with more contemporary BPHV, which may be associated with better long-term durability (60). The Ross procedure, which involves replacing the aortic valve with an autologous pulmonary valve and the pulmonary valve with a homograft, provides important advantages, including an excellent hemodynamic profile and high thromboresistance. For these reasons, this procedure has been considered attractive for aortic valve surgery in young women (61). Outcome data for pregnancy are limited, but appear favorable (26). However, the operation is complex and results are variable (62,63), with relatively high mortality and 15-year reoperation rates. A recent review and meta-analysis reported an early mortality of 3.2% followed by 0.64% per year, and autograft and right ventricular outflow tract deterioration rates of 1.14% and 0.65% per patient year, respectively, in patients >18 years of age (64). A recent study by Stulak et al. (65) reported a broad spectrum of complex reoperations after the Ross procedure in 56 patients with a median age of 26 years, with 2% early mortality and an additional 7% late death rate during a median follow-up of 8 months.

Most MPHVs offer a superior hemodynamic profile compared with BPHVs and excellent durability (66), but are associated with a high risk of thromboembolism and the need for lifelong effective AC. A number of recent reports have provided data on maternal and fetal outcomes in pregnant women with MPHVs. Sillesen et al. (67) used the national patient registry in Denmark and compared cardiac, obstetric, and neonatal adverse outcomes in 155 pregnancies in 79 women with a history of valve replacement (only 6 women with BPHVs) to matched control women. Pregnancy outcomes were corroborated by questionnaires. Mortality was reported in 2 women: the first from HF and the second from post-partum bleeding. A total of 4 thromboembolic complications were reported in 4 women, all with MPHVs treated with unfractionated heparin. There was a significant increase in the rate of miscarriages and pregnancy terminations as well as in post-partum bleeding. The dominant neonatal complication was prematurity; there was more than a 2-fold increase in the incidence of all congenital malformations and an 8% rate of warfarin embryopathy. A second report from Australia published in 2014 (68) described the outcome of 136 pregnancies in 87 women with PHV who gave birth between 2000 and 2011. There were 20 pregnancies in 14 women with MPHVs and 44 pregnancies in 25 women with BPHVs; the type of the PHV was unknown in 72 pregnancies in 48 women. There was no maternal mortality among women with PHVs, but there was a higher risk of severe maternal morbidity, major maternal cardiovascular events (including HF and stroke), pre-term birth (mostly iatrogenic), and small-for-gestational-age infants. A comparison of a subgroup of 14 pregnancies in women with MPHVs and 38 with BPHVs revealed a comparable rate of major cardiovascular events, but a substantial increased risk of cesarean delivery and planned birth, and a trend for an increased incidence of pre-term birth, small for gestational age, post-partum hemorrhage, and intensive care unit admissions in women with MPHVs. The outcomes of 212 patients with MPHVs included in the ESC's ROPAC were recently reported (52). The data were compared with those of 134 patients with BPHVs and 2,620 patients without PHVs. Maternal mortality was about 1.5% in both groups of patients with PHVs and 0.2% in patients without PHVs ($p = 0.025$). Mechanical valve thrombosis complicated 10 pregnancies in women with MPHVs. Women with MPHVs also had a higher rate of hemorrhagic complications, occurring in 23% of pregnancies compared with 5% of women either

with BPHVs or without PHVs ($p < 0.001$). Freedom from serious adverse events was reported in 78% of women without PHVs, 79% of patients with BPHVs, and only 58% with MPHVs ($p < 0.001$). Fetal outcome was also unfavorably affected in women with MPHVs, with a significantly higher incidence of miscarriage, fetal mortality, and lower birth weight.

In summary, recent published information clearly shows that the presence of MHPV is associated with a significant unfavorable effect on maternal and fetal outcome. Complications are mostly related to the mandatory use and the complexity of the administration of AC during pregnancy. The high incidence of complications of women with MHPVs strongly suggests the need for these patients to be managed in tertiary medical centers with expertise in the management of AC in pregnant women with MPHVs, as well as the importance of a very close follow-up of such patients during pregnancy, labor and delivery, and the post-partum period.

ANTICOAGULATION. The risk of TEs in women with MPHV is significantly increased due to the hypercoagulable state of pregnancy (68). Effective AC is therefore critical, but remains problematic because of the potential maternal and fetal complications associated with various AC regimens, the lack of randomized clinical trials, and inconsistent guideline recommendations. Both experienced physicians and fully informed patients, who understand the risks and benefits associated with the various AC options, should decide upon the AC regimen.

Warfarin is effective for TE prevention in pregnant patients with mechanical valves. Its use during the first 6 to 12 weeks of gestation can, however, be associated with important fetal complications, including warfarin embryopathy (1% to 30%) and miscarriage (15% to 56%). Warfarin risk continues throughout pregnancy, with increased rates of fetal loss and intracranial bleeding (52,67). In addition, warfarin use at time of delivery also mandates a cesarean delivery to prevent fetal bleeding complications, including intracranial bleeding, during vaginal delivery. In addition, long-term sequelae, including increased incidence of minor neurological dysfunction as well as of IQ score below 80, have been reported (68,69). Although a few studies have reported no warfarin-associated fetal toxicity, others have shown an unacceptably high incidence of complications (69,70). Studies on a limited number of patients published by 1 group suggested a significantly reduced rate of fetal complications when therapeutic effects can be achieved with a daily warfarin dose <5 mg (71,72). These data have influenced guideline recommendations to consider a low dose of warfarin as a safe therapeutic option during gestation (6). A recent meta-analysis supported a reduced fetal risk with low-dose warfarin. However, the rate of fetal wastage in this study and others was still high (52,69,70,73,74).

Unfractionated heparin (UFH) does not cross the placenta and therefore offers no direct risk to the fetus. Subcutaneous administration has been associated with a high incidence of TE complication and is not recommended for AC of pregnant women with MPHV (73,75,76).

Similar to UFH, low molecular weight heparin (LMWH) does not cross the placenta and does not have a direct effect on the fetus. However, this drug is superior to UFH in a number of ways, including better bioavailability, longer half-life, more predictable and stable dose response, less bleeding, and a lower risk of heparin-induced thrombocytopenia (68). Although TE complications have been reported in pregnant women with MPHV receiving LMWH, the great majority of these cases have been due to subtherapeutic AC secondary to inappropriate dosing, insufficient monitoring, or poor patient compliance (69). With appropriate patient selection, dose regimen, and careful monitoring, the efficacy and safety of LMWH is probably comparable to that of warfarin (70,77–81). Recent recommendations by the ESC (6) and American College of Cardiology/American Heart Association (7) for AC during pregnancy in women with MPHV are listed in **Table 3**. These recommendations emphasize the importance of careful pre-pregnancy evaluation, close follow-up during pregnancy, and the need for care of pregnant women with MPHV in tertiary care centers with dedicated, multidisciplinary teams that are experienced in the management of such patients. The guidelines suggest that continuation of warfarin during the first trimester is reasonable for women with MPHV if the daily dose required to achieve a therapeutic level is ≤5 mg. This recommendation is debatable due to data showing risk to the fetus, even with a low dose of warfarin (70). Twice-daily subcutaneous LMWH is recommended, with the dose adjusted to achieve an anti-Xa level of 0.8 to 1.2 U/ml 4 to 6 h post-dose. These recommendations did not address important data from a number of studies demonstrating a high incidence of subtherapeutic trough levels of anti-Xa activity, despite what seem to be adequate peak anti-Xa levels (82–85). A recent study by 2 authors of this review analyzed 187 paired (trough and peak) determinations of anti-Xa levels in 30 pregnant patients receiving subcutaneous enoxaparin twice daily (82). Trough anti-Xa levels were subtherapeutic in about 70% of cases with peak anti-Xa levels between 0.7 to 1.0 U/ml and in about 40% of those with peak levels of

1.0 to 1.2 U/ml. These data strongly support routine measurement and maintenance of trough levels in the therapeutic range to ensure adequate AC and prevent complications in pregnant women with MPHV. Table 4 demonstrates the AC protocol used for over 2 decades in pregnant women with MPHV at the University of Southern California, with excellent results. The protocol favors the use of LMWH during the first 35 to 36 weeks of gestation in the majority of lower-risk women who can be followed closely (once weekly), followed by intravenous, in-hospital administration of UFH until parturition. Because of the lack of information with use of LMWH in high-risk patients, especially those with old-generation MPHVs, and/or prior thromboembolic complications on LMWH, warfarin, or higher-intensity LMWH dosing (trough anti-Xa levels >0.7 IU/ml) is recommended.

PROSTHETIC VALVE THROMBOSIS. Valve thrombosis is a life-threatening complication in pregnant women with MPHV and is more likely to occur in patients with older-generation mechanical prostheses (Björk-Shiley, Starr-Edwards) and with valves in the mitral or tricuspid positions (51). Recent guidelines recommend thrombolysis as a first-line treatment or heparin in cases with small, nonobstructive thrombi and in those cases where thrombolysis is contraindicated (86–88). Özkan et al. (89) from Turkey published the largest series of cases of prosthetic valve thrombosis (PVT) in pregnancy in 2013. These investigators reported PVT in 25 pregnancies, all of them involving the mitral valve. A total of 50% of the PVT episodes occurred during the first trimester, 14% during the second trimester, and 36% in the third trimester. The clinical presentation was mostly dyspnea or palpitations, and 1 patient presented with a transient ischemic attack. A total of 15 patients had been using warfarin and 10 used LMWH during the pregnancy. Poor compliance with warfarin or subtherapeutic antifactor Xa levels or INR were present in 93% of the cases. All patients were treated with low-dose thrombolytic therapy (tissue-type plasminogen activator 25 mg without bolus, given up to 1 h, if needed; mean dose 48 ± 29 mg), which resulted in complete thrombolysis in all cases. One patient had placental hemorrhage with pre-term live birth at 30 weeks, and another patient had minor bleeding. These results are significantly better than the results of previous reports on full-dose thrombolysis given to 32 pregnancies with 38 episodes of PVT. These studies reported thrombolytic success in 76% of the cases, but maternal mortality and major complications in 10% and 14%, respectively, and fetal/neonatal mortality in 28%.

TABLE 3 Guideline-Recommended Anticoagulation for Pregnant Patients With a Mechanical Prosthetic Heart Valve

American Heart Association/American College of Cardiology 2013 (7)

Class I
1. Therapeutic anticoagulation with frequent monitoring is recommended for all pregnant patients with a mechanical prosthesis (Level of Evidence: B).
2. Warfarin is recommended in pregnant patients with a mechanical prosthesis to achieve therapeutic INR in the second and third trimesters (Level of Evidence: B).
3. Discontinuation of warfarin with initiation of intravenous UFH (with an aPTT >2× control) is recommended before planned vaginal delivery in pregnant patients with a mechanical prosthesis (Level of Evidence: C).
4. Low-dose aspirin (75–100 mg) once per day is recommended for pregnant patients in the second and third trimesters with either a mechanical prosthesis or bioprosthesis (Level of Evidence: C).

Class IIa
1. Continuation of warfarin during the first trimester is reasonable for pregnant patients with a mechanical prosthesis if the dose of warfarin to achieve a therapeutic INR is ≤5 mg/day, after full discussion with the patient about risks and benefits (Level of Evidence: B)*
2. Dose-adjusted LMWH at least twice per day (with a target anti-Xa level of 0.8 U/ml to 1.2 U/ml, 4 to 6 h post-dose) during the first trimester is reasonable for pregnant patients with a mechanical prosthesis if the dose of warfarin is >5 mg/day to achieve a therapeutic INR (Level of Evidence: B)*
3. Dose-adjusted continuous intravenous UFH (with an aPTT at least 2× control) during the first trimester is reasonable for pregnant patients with a mechanical prosthesis if the dose of warfarin is >5 mg/day to achieve a therapeutic INR (Level of Evidence: B)*

European Society of Cardiology 2011 (6)

Class I C
- OACs are recommended during the second and third trimesters until the 36th week.
- Change of anticoagulation regimen during pregnancy should be implemented in hospital.
- If delivery starts while on OACs, cesarean delivery is indicated.
- OAC should be discontinued and dose-adjusted UFH (aPTT 2× control) or adjusted-dose LMWH (target anti-Xa level 4–6 h post-dose 0.8–1.2 U/ml) started at the 36th week of gestation.
- In pregnant women managed with LMWH, the post-dose anti-Xa level should be assessed weekly.*
- LMWH should be replaced by intravenous UFH at least 36 h before planned delivery. UFH should be continued until 4–6 h before planned delivery and restarted 4–6 h after delivery if there are no bleeding complications.
- Immediate echocardiography is indicated in women with mechanical valves presenting with dyspnea and/or an embolic event.

Class IIa C
- Continuation of OACs should be considered during the first trimester if the warfarin dose required for therapeutic anticoagulation is <5 mg/day (or phenprocoumon <3 mg/day or acenocoumarol <2 mg/day), after patient information and consent.*
- Discontinuation of OACs between weeks 6 and 12 and replacement by adjusted dose UFH (aPTT >2× control in high-risk patients applied as intravenous infusion) or LMWH twice daily (with dose adjustment according to weight and anti-Xa level 4–6 h post-dose 0.8–1.2 U/ml) should be considered in patients with a required warfarin dose >5 mg/day (or phenprocoumon >3 mg/day or acenocoumarol >2 mg/day).*

Class IIb C
- Discontinuation of OACs between weeks 6 and 12, and replacement by UFH or LMWH under strict dose control (as described earlier), may be considered on an individual basis in patients with a warfarin dose required for therapeutic anticoagulation >5 mg/day (or phenprocoumon >3 mg/day or acenocoumarol >2 mg/day).*
- Continuation of OACs may be considered between weeks 6 and 12 in patients with a warfarin dose required for therapeutic anticoagulation >5 mg/day (or phenprocoumon <3 mg/day or acenocoumarol <2 mg/day).*

Class III C
- LMWH should be avoided unless anti-Xa levels are monitored.

*See text for discussion of limitations of these recommendations.

aPTT = activated partial thromboplastin time; INR = international normalized ratio; LMWH = low molecular weight heparin; OAC = oral anticoagulant; UFH = unfractionated heparin.

The recent American Heart Association/American College of Cardiology guidelines recommend a transesophageal echocardiogram to diagnose PVT, assess the hemodynamic severity and follow resolution of valve dysfunction, and evaluate the thrombus size

TABLE 4 USC Protocol for Anticoagulation Therapy of Women With MPHV During Pregnancy

Higher Risk: Old-Generation MPHV in Mitral and Aortic Position, MPHV in Tricuspid Position, History of TE on LMWH
Warfarin (INR 2.5–3.5) for 36 weeks, followed by IV UFH (aPTT >2.5) to parturition + ASA 81–100 mg/day. OR LMWH SC Q12 h (trough anti-Xa ≥0.7 IU/ml, peak anti-Xa <1.5 IU/ml) for 12 weeks, followed by warfarin (INR: 2.5–3.5) to 36 weeks then UFH IV (aPTT >2.5) to parturition + ASA 81–100 mg/day.
Lower Risk: New-Generation MPHV in Mitral and Aortic Positions
LMWH SC Q12 h (trough anti-Xa ≥0.6 IU/ml, peak anti-Xa <1.5 IU/ml) for 36 weeks, followed by IV UFH (aPTT >2.5) to parturition.

ASA = acetylsalicylic acid; IV = intravenous; MPHV = mechanical prosthetic heart valve; Q = every; SC = subcutaneous; TE = thromboembolism; UFH = unfractionated heparin; USC = University of Southern California; other abbreviations as in Table 3.

and valve motion (86). Valve motion can be assessed by fluoroscopy, although, because of radiation risk, echocardiographic assessment is preferred in pregnancy. Thrombolytic therapy (TT) was defined as reasonable in PVT of recent onset (<14 days) with NYHA functional class I to II symptoms and a small thrombus (<0.8 cm^2), as well as in cases of thrombosed right-sided PHV. Administration of TT in pregnancy is associated with potential hemorrhagic complications that need to be taken into account, especially before or after the delivery. Emergency valve surgery is recommended by the guidelines for nonpregnant patients with thrombosed left-sided PHV with NYHA functional III to IV symptoms and in patients with embolization or a large thrombus (>0.8 cm^2). However, cardiopulmonary surgery during pregnancy is associated with high fetal mortality (20% to 30%) and morbidity (premature delivery and growth retardation), and an increased rate of maternal mortality. These complications are further increased in patients requiring urgent surgery (31,90–92).

PREGNANCY-ASSOCIATED ACUTE MYOCARDIAL INFARCTION

There is a 3-fold increase in the incidence of acute myocardial infarction (AMI) during pregnancy and the peripartum period (PP) compared to that seen in nonpregnant women of similar age (93). Most recent nationwide inpatient samples for pregnancy-related discharges showed an incidence of 1 in 16,000 deliveries (94). Myocardial infarction related to pregnancy occurs in all ages, but the majority of women are

TABLE 5 Fetal Safety of Cardiac Drugs During Pregnancy and Lactation*

Drug	Clinical Experience	Risk Category	Potential Side Effects	Breastfeeding
Morphine sulfate	Limited	C	Neonatal respiratory depression when given shortly before delivery.	Only a trace amount in milk, considered compatible with breastfeeding.
Organic nitrates	Limited	B	Maternal hypotension and reduced uterine perfusion.	No data available.
BBs	Considerable with metoprolol tartrate and atenolol.	Metoprolol C Atenolol D	Fetal bradycardia, hypoglycemia, hyperbilirubinemia, apnea at birth, fetal growth retardation (more with atenolol). Nonselective BB can facilitate uterine activity.	All BBs accumulate in greater concentration in breast milk; however, the total amount is small.
Nondihydropyridine calcium-channel blockers	Limited	Diltiazem C Verapamil C	Diltiazem may be teratogenic.	Compatible with breastfeeding.
Aspirin	Extensive		High dose: increased maternal and fetal bleeding, premature closure of PDA, IUGR, teratogenic effects, increased perinatal mortality. Low dose: <150 mg/day is safe.	Caution suggested
Clopidogrel	Anecdotal	B	Not known	Not recommended
GP IIb/IIIa	Anecdotal	B	Not known	Not recommended
ACEi/ARBs	Moderate	C	Contraindicated due to fetotoxic effect. Oligohydramnios, anuria, IUGR, prematurity, body malformations, limb contractures, PDA, pulmonary hypoplasia, RDS, neonatal hypotension anuria, and death.	Both captopril and enalapril are compatible with breastfeeding.
Statins	Limited	X	Inhibits synthesis of mevalonic acid, which may play a role in DNA replication.	Women on statins should not breastfeed.
UFH and LMWH	Extensive	C	Drugs do not cross the placental barrier	Not excreted into breast milk.

*Data from Roth and Elkayam (93) and Briggs et al. (102).

ACEi = angiotensin-converting enzyme inhibitors; ARB = angiotensin-receptor blocker; BB = beta-blocker; DNA = deoxyribonucleic acid; GP = glycoprotein; IUGR = intrauterine growth restriction; PDA = patent ductus arteriosus; RDS = respiratory distress syndrome; other abbreviations as in Table 3.

older than 30 years of age. There is also a relatively high incidence of traditional risk factors for coronary artery disease, despite the young age, including hyperlipidemia, hypertension, obesity, and diabetes (93). In addition, pre-eclampsia and eclampsia have been suggested as additional risk factors (94).

CORONARY ANATOMY. A recent report (95) of coronary anatomy studied in 132 women with pregnancy-associated acute myocardial infarction (PAMI) showed coronary dissection in 43% of the patients, atherosclerosis in 27%, clot without evidence of atherosclerosis in 17%, normal anatomy in 9%, spasm in 2%, and Takotsubo cardiomyopathy in 2%. These data show that, in contrast to the general population in whom atherosclerotic disease is the cause of AMI in the great majority of cases, spontaneous coronary artery dissection (SCAD) is the most common mechanism of PAMI, especially in late pregnancy or the early post-partum period (PP). Coronary dissection mostly involves the left anterior descending artery and left main segment, and often affects more than 1 coronary artery (95). Proposed mechanisms for the high incidence of SCAD related to pregnancy have been hormonally-mediated arterial structural changes, with a loss of normal corrugation of elastic fibers and a decrease in acid mucopolysaccharide ground substance, which may lead to cystic medial necrosis and lack of structural support of the vasa vasorum in the media-adventitia border. This lack of support may lead to rupture and intramural hematoma.

Coronary thrombosis without atherosclerosis, which has been described in as high as 17% of cases, is most likely related to the hypercoagulable state of pregnancy. Normal coronary artery anatomy, which has been described in about 10% of women with coronary thrombosis, may be due to transient spasm or missed SCAD (96).

Pregnancy-associated myocardial infarction presents in the majority of cases as ST-segment elevation myocardial infarction (STEMI), and has been reported to involve the anterior wall in 70% to 80% of patients. As a result, there was a significant reduction of LV ejection fraction (>40%) in >50% of cases, and a high incidence of HF, cardiogenic shock, and ventricular arrhythmias (95). Maternal mortality was reported in 3 recent trials to be between 5% and 7% (95), a rate 2- to 3-fold higher than that reported in women with AMI who were <55 years of age (97). Fetal mortality was reported in the most recent study to be 5%, and was mostly associated with maternal mortality (95).

DIAGNOSIS. Diagnostic criteria are similar to those used in nonpregnant patients and are mainly on the basis of symptoms, ECG changes, and biomarkers. It should be noted, however, that induction of anesthesia for a cesarean section might be associated with ST-segment depression mimicking myocardial ischemia (93). An increase in creatine kinase-MB level of nearly 100% can be seen within 30 min after normal delivery, and continues to rise, reaching a maximum at 24 h. One should, therefore, rely on troponin levels that show only a small increase after the delivery, with the exception of women with hypertension or pre-eclampsia.

The use of radiation during pregnancy should be minimized if possible. Cardiac catheterization and interventional procedures may result in fetal exposure of <1 rad. Although termination of pregnancy is not recommended for fetal exposure to <5 rad, it should be considered if the dose is >10 rad (98).

TREATMENT. The management plan for PAMI should follow usual guideline recommendations, but also needs to be influenced by fetal safety. If at all possible, treatment should take place in an intensive care unit that can also provide comprehensive obstetric services, with a plan in place for urgent delivery of a viable fetus if maternal deterioration occurs.

Primary percutaneous coronary intervention is standard care in nonpregnant patients with an STEMI and in unstable patients with non-NSTEMI, and should also be recommended to pregnant women with similar presentations. At the same time, however, a recent publication by Elkayam et al. (95) demonstrated a high incidence of iatrogenic coronary dissection as a result of coronary contrast injections or coronary interventions. These complications resulted in catastrophic consequences, leading to emergency surgery, use of mechanical support, and mortality. For this reason, a noninvasive approach to stable women with non-STEMI is preferred. When coronary angiography is performed, the procedure should be done cautiously with the use of a nonselective injection to assess for left main dissection, avoiding deep catheter intubation, and using the minimum number of low-pressure contrast injections to minimize the risk of dissection (95). Use of intracoronary devices, including balloons, stents, suction devices, intravascular ultrasound, and fractional flow reserve pressure guidewires, should be reserved for cases where the potential benefit outweighs the increased risk (95). CT coronary angiography may provide a safer method to obtain anatomic information, but it is also associated with hazards related to fetal radiation and a need to use high doses of a beta-blocker for appropriate heart rate reduction.

The conservative approach seems advisable in stable patients with SCAD. This recommendation is

supported by reports of spontaneous healing in the majority of such patients (99). For unstable patients or those with involvement of the left main coronary artery, bypass surgery is preferred. Percutaneous coronary interventions for SCAD have been associated with high rates of technical failure and an increased risk of extending the dissection and requiring emergency surgery (100,101). Surgical revascularization has been successful in most reported nonpregnant patients (99,100). A recent publication (95) reported surgery in 30 patients with PAMI, 23 of them for SCAD. Surgery was performed during pregnancy in 11 cases and during the PP in the rest of the patients, and was associated with no maternal mortality and with only 1 fetal loss.

THROMBOLYTIC THERAPY. The information available regarding TT for PAMI is limited, and this therapy is considered relatively contraindicated in pregnancy. Most available information, which is related to use in patients with stroke, PVT, pulmonary embolism, or deep vein thrombosis, suggests that placental transfer of both streptokinase and tissue-type plasminogen activator is too low to affect the baby. Although maternal outcomes were favorable in most cases, occasional complications, including pre-term delivery, fetal loss, spontaneous abortion, abruption of the placenta, and major bleeding complications, have been reported. Because many women with PAMI have SCAD or normal coronary anatomy, a blinded use of TT is not recommended (93,95).

DRUG THERAPY. Only limited information is available regarding the fetal safety of most drugs recommended in the nonpregnant patient with AMI. Information on the safety of cardiac drugs is provided in **Table 5** (93,102).

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