Maternal Heart Disease During Pregnancy

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Circulatory changes occurring during pregnancy alter the clinical manifestations of cardiac disease [1], the therapeutic options, and the pharmacokinetics of administered drugs [2]. The influence of therapy on both the mother and the fetus needs to be considered in any given situation. To manage patients with significant cardiac disease during pregnancy, cardiologists, obstetricians and anesthesiologists have to communicate well and coordinate therapy.

Circulatory Changes During Normal Pregnancy

Cardiac output (the product of heart rate and stroke volume) increases by 30-50% during normal pregnancy. There is approximately a 20% rise in cardiac output by the eighth week of gestation and peak cardiac output is achieved by 20-24 weeks and is usually maintained until term [3] although it may decline [4]. Mean heart rate during pregnancy is higher than in the non-pregnant state averaging 10-20 bpm faster at term. Most of this increase in heart rate occurs by the eighth week of pregnancy [5-7]. Systemic vascular resistance declines during pregnancy - the majority of the decline occurring by the eighth week of gestation[8,9] Early in pregnancy there are decreases in both systolic and diastolic blood pressures [8, 9] which continue through the middle trimester with a gradual rise in blood pressure towards term. There is a greater fall in diastolic pressure than systolic pressure early in pregnancy resulting in an increased pulse pressure. Arterial pressures return to near non-pregnant levels before term. Because resting cardiac output is increased, exercise-induced maximum cardiac output is reached at a lower work level in the pregnant woman. As pregnancy advances, there is a gradual increase in resting oxygen consumption. Serial echocardiography of normal pregnant women reveals that there is a mild, significant increase in the dimension of all cardiac chambers during pregnancy which is more pronounced on the right side of the heart [10]. Furthermore, there is normally a progressive increase in the prevalence of physiologic tricuspid and pulmonary regurgitation as well as the development of trivial, transient mitral regurgitation. Aortic regurgitation is not normally detected at any stage of pregnancy [10].

Red blood cell mass increases progressively throughout pregnancy by 30-40%. Plasma volume also begins to increase early and continues throughout the second trimester by 22-65%. The increases in red blood cell mass parallel the increases in plasma volume but the plasma volume changes are of greater magnitude which results in "the physiologic anemia of pregnancy". Alterations in blood volume correlate directly with the number of fetuses in multiple pregnancies, age, parity, placental weight and fetal weight [11]. The time course of the changes in blood volume differ from the changes in cardiac output. During the first trimester, the increases in cardiac output, plasma

volume, and extra cellular fluid volume are associated with increases in renal plasma flow, glomerular filtration rate and an increase in total body water and exchangeable sodium from 500-900 mEq [5]. The changes in total body water and exchangeable sodium are associated with an activation of the renin-angiotensin system and lowering of osmotic thresholds for vasopressin release and thirst stimulation. Thus, there is a fall in plasma sodium and plasma osmolality, and clinical edema is found in up to 80% of healthy pregnant women.

The volume of distribution for some drugs increases during pregnancy because of increases in maternal total body water and gain in fatty tissue from 10-30 weeks. The increase in maternal glomerular filtration rate that occurs during pregnancy increases the rate of elimination of drugs excreted by the kidneys. Concomitantly, maternal hepatic enzyme activity appears to decrease. Last, delayed gastric motility and emptying may enhance or delay maternal drug absorption from the gastro intestinal tract. Any drug entering the maternal blood stream should be considered capable of crossing the placenta, and therefore reaching the fetus, unless information to the contrary exists. After implantation, most drugs pass freely to the embryo and concentration is generally lower than those measured simultaneously in the mother. Because the blood-brain barrier to diffusion is not developed in the fetus until the last half of pregnancy, the fetal central nervous system may be particularly susceptible to pharmacologic agents.

During normal labor and delivery, the circulatory changes depend to some extent on the method of delivery, the maternal posture, the type of sedation and anesthesia. With each uterine contraction during labor some studies have demonstrated an augmentation in heart rate whereas others have suggested that no important change occurs [12-15]. Systolic and diastolic blood pressures and mean arterial pressure rise, during labor, with each uterine contraction. With a normal vaginal delivery in a lightly sedated, unanesthetized mother, during major uterine contractions the mean arterial pressure rises by approximately 10% and concurrently 300-500 mls of blood are expressed into the maternal circulation, augmenting venous return, stroke volume and cardiac output. Circulating catecholamines are increased during labor and delivery [16]. At the onset of labor, oxygen consumption increases 3-fold with each uterine contraction, and by the end of the second stage, the average rate of oxygen consumption has doubled [3] .

The immediate post partem hemodynamics depend on the type of sedation and anesthesia, the amount of blood loss, and the mode of delivery. Immediately after delivery there is usually a marked increase in intravascular volume [17,18] in part due to the sudden release of inferior vena cava obstruction. Pain-induced tachycardia and the increase in intravascular volume are associated with a transient increase in cardiac output. Heart rate also changes rapidly immediately after delivery and usually decreases by 10-20

beats per minute. Over the 4-6 weeks after delivery heart rate, blood volume, cardiac output, and left ventricular diameter and thickness return to non-pregnant levels.

Symptoms and Signs of Normal Pregnancy

During normal pregnancy fatigue, reduced exercise tolerance, and dyspnea at lower levels of exertion are all common [19]. There is a hyperdynamic circulation with an increased heart rate and a wider pulse pressure. The auscultatory findings of gestation develop during the first half of pregnancy and disappear within a week or two following delivery. The first heart sound (mitral and tricuspid valve closure) increases in intensity during pregnancy and the splitting of the two components of the sound may become more exaggerated due to early closure of the mitral valve. (This may reflect hyperkinesis of the left ventricle as well as the increase circulating blood volume). The second heart sound remains constant in character until the last trimester when there is some narrowing of physiologic splitting of the aortic and pulmonic components [20]. A third heart sound is a frequent finding during normal pregnancy occurring in up to 80% of patients and does not usually signify a pathologic condition . Fourth heart sounds [20] and diastolic murmurs are not features of normal pregnancy and, if found, should alert clinician to the possibility of cardiac dysfunction. Systolic murmurs are very common during pregnancy occurring in over 90% of patients and are usually heard in early to mid systole. Most of these murmurs represent flow murmurs across the aortic and pulmonic valves. Patients who have mitral valve prolapse or the click murmur syndrome demonstrate decreases in the intensity of both the murmur and the click with advancing pregnancy [21]. Other extra cardiac noises include supraclavicular murmurs originating from the brachiocephalic arteries [1], venous hums originating from the jugular veins, and continuous or systolic murmurs heard over the breast. Peripheral edema is found in 80% of pregnant women and basal lungs rales which clear with coughing are common. During normal pregnancy there is a rise in triglycerides, LDL cholesterol and HDL cholesterol. HDL levels begin to fall at 24 weeks, triglycerides fall to baseline at the time of delivery and LDL cholesterol remains elevated for some weeks after delivery [22].

Prognosis of Cardiac Conditions During Pregnancy

The prevalence of cardiovascular disorders in pregnant patients is relatively low but certain cardiovascular diseases continue to be associated with a high maternal and fetal mortality, e.g. pulmonary hypertension. Based on physiology of a normal pregnancy cardiac conditions can be divided broadly into those that are "well tolerated" and those that are "poorly tolerated" during pregnancy.

WELL TOLERATED	POORLY TOLERATED
Asymptomatic lesions	Patient breathless at rest
Valve regurgitation: AR and MR (mild to moderate)	Valve stenosis : MS, AS
Left-to-right shunt without pulmonary hypertension	
Pulmonary valve stenosis	Right-to-left shunt : Eisenmenger's
Idiopathic hypertrophic subaortic stenosis (Mild to moderate)	Primary pulmonary hypertension
	Marfan syndrome
	Myocardial Infarction

If careful attention is paid to the symptomatic status of patients and to accurate non invasive cardiac diagnosis, the likelihood of successful outcome of pregnancy can usually be assessed with confidence. Careful history taking, physical exam, electrocardiography, two dimensional echocardiography and Holter monitoring, if necessary, will usually result in accurate assessment. Two-dimensional echocardiography has obviated the need for cardiac catheterization in most patients.

General Management

Even in patients with mild symptoms and cardiac disease during pregnancy daily periods of rest are recommended. Additionally, a balanced diet, mild to moderate sodium restriction (if appropriate), and prompt diagnosis and treatment of intercurrent infections are vital. Pathological anemia should be promptly treated. Of most importance in the general management of patients with cardiac disease in pregnancy are joint consultations with the attending obstetrician, and cardiologist at intervals appropriate for the cardiac condition and careful planning near the end of pregnancy in collaboration with Anesthesiologists [1, 23, 24].

Valvular Heart Disease

In patients with mild cardiac symptoms, the mild or moderate regurgitant valvular lesions, such as mitral regurgitation and aortic regurgitation, are usually well tolerated if the patient maintains sinus rhythm because the reduced peripheral vascular resistance (or afterload) of pregnancy tends to diminish the degree of regurgitation. Obviously, in patients with significant symptoms or major degrees of valvular regurgitation, the hemodynamic changes of pregnancy may impose an excessive load.

In contrast, the stenotic aortic and mitral valvular lesions tend to be poorly tolerated during pregnancy. The severity of the fixed stenoses is accentuated by the increases in cardiac output and heart rate during pregnancy.

Mitral Stenosis

Mitral stenosis is the most common, important rheumatic lesion encountered during pregnancy. The symptoms of mitral stenosis (breathlessness on exertion, orthopnea or nocturnal dyspnea) are accentuated by the increased cardiac output and heart rate associated with pregnancy and this may be the first time that such patients develop symptoms. If a patient who is in sinus rhythm with mitral stenosis has symptoms, despite diuretic therapy, in the first trimester of pregnancy, it is unlikely that the patient and/or fetus will tolerate the lesion hemodynamically through pregnancy, labor, delivery and the puerperium. The onset of atrial fibrillation in the pregnant patient with mitral stenosis should be considered a medical emergency because acute pulmonary edema and cardiac decompensation can rapidly ensue. Other modes of presentation include systemic emboli, hemoptysis and rarely infective endocarditis.

In the evaluation of pregnant patients with mitral stenosis, a careful history, physical examination, and 2-D echocardiography aid in assessing the severity of the problem and the likely outcome. Medical management includes careful, frequent observations through pregnancy and particular vigilance in the first three days following delivery.

While routine use of diuretics for edema of pregnancy is not advised if diuretic therapy is needed, a loop diuretic such as furosemide is often used. **Furosemide** crosses the placenta, resulting in similar maternal and fetal levels, and increased fetal urine production has been observed [25]. After the first trimester, furosemide has been used for the treatment of edema, hypertension, and toxemia during pregnancy without causing fetal or newborn adverse effects [25,26]. Neo-natal thrombocytopenia has not been reported for furosemide. Furosemide is excreted into breast milk, and no adverse effects in nursing infants have been reported.

The new onset of arrhythmias, such as atrial fibrillation or supraventricular tachycardia, should be regarded as a medical emergency in pregnant patients with significant mitral stenosis. Although digitalis may be appropriate for controlling the ventricular response, the onset of acute pulmonary edema may ensue rapidly if the ventricular rate is not controlled promptly or sinus rhythm regained. Therefore, for rapid atrial fibrillation associated with symptoms, prompt cardioversion is recommended. The efficacy and safety of such an approach have been demonstrated [3].

Digoxin has been used for both maternal and fetal indications during all stages of gestation without causing fetal harm. Pregnancy may be associated with increased levels of digoxin-like substances in the blood, which can cause errors in the measurement of serum levels by radioimmunoassay [27]. There have been no reports linking digitalis glycosides with congenital defects. The fetal/maternal serum digoxin concentration ratio varies from 0.5 - 1.0. Digoxin is excreted into breast milk, and the digoxin milk/plasma ratios have varied from 0.6 - 0.9 [28]. Although these amounts in breast milk seem high, they represent small amounts of digoxin as a result of maternal protein binding. No adverse effects in nursing infants have been reported, and the American Academy of Pediatrics considers digoxin to be compatible with breast feeding [29].

Procainamide has been used for the termination and prophylaxis of atrial (and ventricular) tachyarrhythmias. Use of procainamide during pregnancy has not been linked to congenital abnormalities or other adverse fetal effects [30,31]. Procainamide and its' metabolite, N-acetyl procainamide accumulate in breast milk [32], but procainamide is considered to be compatible with breast feeding [29]. The long-term effects of exposure of the nursing infant to procainamide are unknown with regard to development of anti nuclear antibodies and lupus-like syndrome.

Quinidine has been used in pregnancy for more than 50 years. Quinidine crosses the placenta and achieves fetal serum levels similar to maternal levels. Neonatal thrombocytopenia has been reported after maternal use of Quinidine [29]. The use of quinidine during pregnancy has been classified as relatively safe for the fetus [33, 34]. In therapeutic doses, oxytocic properties of quinidine have been rarely observed, but high doses can produce this effect and may result in abortion. Quinidine is excreted into breast milk but is considered to be compatible with breast feeding [29].

With severe mitral valve stenosis, there is a pregnancy-related mortality of up to 5%. Labor, delivery, and especially the immediate post partem period appear to be the times of greatest risk. In patients with Class 3 or 4 symptoms, a rise in pulmonary capillary wedge pressure of approximately 10 mm/Hg may be anticipated [35] immediately post-partum. Clark et al, recommend

that such patients should have oxygen administration in labor in the recumbent position; a pulmonary artery wedge catheter should be placed to monitor hemodynamics during early labor induction, and reduction of pulmonary capillary wedge pressures to approximately 14 mm/Hg is a desired goal [35]. They recommend epidural anesthesia in the active phase of labor, careful monitoring in the puerperium, and use of Caesarean section for obstetric indications only.

PERIPARTUM HEMODYNAMICS OF MITRAL STENOSIS

	1st Stage	2nd Stage	Post Partum	
			1-15 mins	18-24 hrs
PCWP (mmHg)	21	14	24*	11

* $p < 0.01$ Clark SL, et al. Am J Obstet Gyn 152 : 984,1985

For patients with significant mitral stenosis and more than Class II symptomatology in the first trimester of pregnancy, consideration should be given to surgical intervention or mitral balloon valvuloplasty in appropriate candidates. Mitral balloon valvuloplasty has been used successfully in appropriate candidates [29, 36, 37]. Open or closed [38] mitral valvotomy or replacement during cardiopulmonary bypass can be conducted relatively safely during pregnancy [38-41].

Maternal aortic stenosis in pregnancy is usually due to a congenital defect of the valve. Recent reports suggest that with careful monitoring a successful maternal and fetal outcome can be achieved [42] and that if necessary palliative aortic valve balloon dilatation during pregnancy can be accomplished successfully [43]. Aortic valve surgery can also be performed with minimal risk to the mother but fetal loss is a problem [41].

Pregnancy in patients with prosthetic heart valves is hazardous to the mother and to the fetus [44-47] particularly because of the need for continuous anticoagulation in most patients. Recent data [48] suggest that biological prostheses (porcine valves) in women of 35 years, or less, (mean age = 23 years) did not structurally deteriorate because of pregnancy and offered the opportunity for uncomplicated pregnancies and normal children.

Although bacteremia occurs in a small percentage of women during normal labor and delivery, infective endocarditis is a rare complication [48-50]. The American Heart Association Committee on **Prevention of Bacterial**

Endocarditis [51] recommends prophylaxis for patients with certain cardiac conditions.

Cardiac Conditions	Dental or Surgical Procedures
Prosthetic cardiac valves	Urethral catheterization (if urinary infection present)
Previous bacterial endocarditis Most congenital cardiac malformations	Vaginal hysterectomy Vaginal delivery in the presence of infection
Valve dysfunction	
Hypertrophic cardiomyopathy Mitral valve prolapse with regurgitation	

Certain dental and surgical procedures are more likely to initiate the bacteremia that results in endocarditis and these include dental procedures known to induce gingival or mucosal bleeding (including professional cleaning), urethral catheterization if urinary tract infection is present, vaginal hysterectomy and vaginal delivery in the presence of infection.

Endocarditis prophylaxis not recommended ≠:

Cesarean section

Urethral catheterization, D & C, uncomplicated vaginal delivery, therapeutic abortion, sterilization procedures or insertion or removal of intrauterine devices - **in absence of infection.**

≠ In patients who have prosthetic heart valves, prior endocarditis, surgically constructed shunts or conduits physicians may choose to administer prophylactic antibiotics even for low risk procedures that involve the lower respiratory, genitourinary or gastrointestinal tracts.

Endocarditis prophylaxis is <u>not recommended</u> for urethral catheterization, dilatation and curettage, uncomplicated vaginal delivery, therapeutic abortion, sterilization procedures or insertion or removal of intrauterine devices <u>in the absence of infection</u>.

<u>Anticoagulants</u>

In patients with rheumatic mitral valve disease (and associated paroxysmal or chronic atrial fibrillation), women with heart valve prostheses, and women who need prophylaxis to prevent recurrent pulmonary thromboembolism anticoagulant therapy may be needed during pregnancy [52, 53].

Warfarin crosses the placenta and is teratogenic; its use during the first trimester of pregnancy carries a significant risk to the fetus. Exposure in the sixth to ninth weeks of gestation may produce the fetal Warfarin syndrome (nasal hypoplasia due to failure to development of the nasal septum and stippled epiphyses), resulting in depression of the bridge of the nose and neonatal respiratory distress from upper airway obstruction. In addition, central nervous system abnormalities including microcephaly, optic atrophy and hydrocephalus can occur [54]. Spontaneous abortions, stillbirths, and neonatal deaths may also occur. In general, the use of warfarin is to be avoided, especially between the sixth and twelfth gestational weeks. Mothers taking full-dose warfarin therapy can breast feed without altering the clotting mechanisms in their infants [55]. The American Academy of Pediatrics classified Warfarin and Dicumarol to be compatible with breast feeding [29], however, it considers phenindione to be contraindicated because of the risk of hemorrhage in the infant. If the patient is fully anticoagulated with warfarin at the onset of labor, fresh-frozen plasma is usually administered. Warfarin can be restarted on the first post partem day, and usually heparin and warfarin are overlapped for 3 to 5 days when full-dose anticoagulation is required.

The complications of **heparin** therapy during pregnancy include hemorrhage, thrombocytopenia, and symptomless bone loss (osteopenia) that has been reported in more than 1/3 of heparin-treated pregnant women [56]. Transient heparin-induced thrombocytopenia may occur in up to 10% of patients [57]. In rare instances, anti-platelet immunoglobulin antibodies are associated with heparin-induced thrombocytopenia-thrombosis. This serious complication can be associated with significant mortality and appears to occur more frequently with beef lung-derived heparin. Clinically important thrombocytopenia, with or without associated thrombosis, is unusual.

Most authors believe that heparin appears to have major advantages over oral anticoagulants as the treatment of choice during pregnancy [53]. The administration of heparin on an ambulatory basis is feasible [58]. Subcutaneous heparin is usually initiated in doses between 10,000-20,000 units every 12 hours and is regulated by obtaining a six hour post-injection aPTT, which should be 1.5 - 2.0 times higher than the control value for most patients. However, if patients have prosthetic heart valves, some authors suggest a minimum level of twice the control value [59]. Monitoring of high-dose subcutaneous heparin therapy can be achieved on an outpatient basis with a finger stick PTT machine. In addition to intermittent subcutaneous administration of heparin, other options for administration include long-term ambulatory subcutaneous infusion [60] and permanent venous access via Hickman catheter [61]. Heparin injections are discontinued at the onset of labor and are usually resumed twelve hours after a normal vaginal delivery.

There is interest in the use of heparin fragments of low molecular weight that are produced by enzymatic or chemical hydrolysis of longer chains of natural heparin and appear to exert a significant anticoagulant action with possibly reduced risk of bleeding and osteoporosis [62-65]. In 41 pregnancies of women with a history of acute or prior thromboembolic events, antiphospholipid syndrome or active lupus disease low-molecular-weight heparin (enoxaparin) was self administered subcutaneously by a once daily injection of 40 mg in most patients safely, effectively and with excellent tolerance during labor, delivery and immediate post partum period. No heparin induced thrombocytopenia or injection site side effects were reported. No excessive intrapartum bleeding was noted with vaginal or abdominal deliveries [66].

Heparin is not excreted into breast milk owing to its high molecular weight (15,000) therefore, the mother may breast-feed her child safely while receiving full-dose heparin therapy.

Acute Myocardial Infarction

Acute myocardial infarction occurring during pregnancy is a rare (incidence 0.01 percent) but potentially lethal event for both mother and fetus, particularly when it occurs in the third trimester or peripartum period [67]. The particularly poor prognosis of patients suffering a myocardial infarction late in pregnancy is attributable to the increased hemodynamic demands on the heart in the latter half of pregnancy and during labor, delivery and the puerperium. The overall maternal mortality rate may be up to 30%, with the greatest mortality occurring in those patients sustaining acute myocardial infarction late in pregnancy. Post partem acute myocardial infarction is also associated with a high mortality rate [68]. Fetal outcome is generally dependent on maternal outcome; 2/3 of fetal deaths occur simultaneously with the demise of the mother. Occurrence of pregnancy after a myocardial infarction is rare . If myocardial function is not severely compromised and stress testing is satisfactory a restful pregnancy, with close supervision, is likely to result in a successful outcome [69].

Almost all women who have a myocardial infarction before the age of 40 have either insulin requiring diabetes mellitus [70], hypertension, hyperlipidemia or a positive family history and in the absence of these, the possibility of cocaine use should always be considered as an etiological factor [71]. Spontaneous coronary artery dissection is a rare entity, usually reported in women, which occurs one third of the time during pregnancy or the puerperium and presents as sudden death or an unstable coronary syndrome. The left anterior descending coronary artery is usually involved. If the initial event is survived long term survival is possible [72-74] .

When a clinician is asked to evaluate a patient in the peri-partum period to decide whether or not acute myocardial infarction has occurred it is important to know that during normal vaginal deliveries total creatine phosphokinase and MBCK increase markedly reaching a peak of 2-4 x baseline levels 24 hours post-partum [75] Evolving electrocardiographic changes coupled with echocardiographic evidence of regional wall motion abnormalities are essential in making a diagnosis of acute myocardial infarction during this period. Any management plan requires close consultation between the Cardiologist, Obstetric Service and Anesthesiologist coordinate and plan an elective labor or provide optimal management of an unexpected premature labor. Strategy needs to be developed to provide a greater chance of prompt and effective rescue of the fetus in the event of sudden maternal demise. The patient should be cared for in an Intensive Care Unit capable of providing continuous maternal and fetal monitoring along with a complete obstetric service. Initial therapy should include rest, oxygen, pain relief with intravenous morphine and prophylactic use of subcutaneous low-dose heparin to prevent formation of deep venous thrombosis. If two dimensional echocardiography demonstrates a significant area of left ventricular anterior dyskinesia and/or a definite left ventricular mural thrombus then full dose heparin may be used. This is discontinued at the onset of labor and reversal may be required before delivery.

A recent review of the use of **thrombolytic** agents during pregnancy for venous thrombosis, pulmonary embolism and thrombosed prosthetic heart valves suggests a maternal mortality of 1-2%; fetal mortality of 6% and hemorrhagic complications in 8% [76]. **Thrombolytic** agents such as streptokinase and urokinase have been used in pregnancy but have been associated with significant bleeding, premature labor and incoordinate uterine contractions [77, 78]. Such risks may outweigh any potential benefits. Streptokinase has been used in the treatment of deep venous thrombosis during pregnancy in the second and third trimesters without fetal complications [77]. Urokinase has also been used in a pregnant woman (28 weeks gestation) for treatment of hemodynamically significant pulmonary emboli; a healthy term infant was delivered two months after initiation of therapy [79]. Minimal amounts of streptokinase cross the placenta, and although fibrinolytic effects in the fetus do not ensue, streptokinase antibodies do cross to the fetus. No association between the use of streptokinase and the development of congenital defects has been reported.

Successful percutaneous transluminal coronary angioplasty has been achieved during pregnancy [67, 80] as has insertion of intra-coronary stents [81] If operative revascularization on an elective basis is deemed necessary, the rate of maternal mortality from present-day cardio pulmonary bypass during pregnancy is similar to that of the overall population undergoing cardio pulmonary bypass (2-4%) and fetal loss is relatively low (less than 10%) [41]. Antianginal therapy with nitrates and beta blockers can be used.

Nitroglycerin has been used during pregnancy and hypertensive patients without adverse effects on the fetus [82]. Diltiazem has been used to treat myocardial ischemia during human pregnancy without adverse effects [83] but some toxic effects in the embryo and fetus have been observed in experimental animals. Verapamil has been used successfully as an antiarrhythmic agent for fetal and maternal supraventricular arrhythmias. As in non pregnant patients intravenous verapamil can result in hypotension [33]. Both verapamil and diltiazem are excreted in breast milk but the American Academy of Pediatrics considers them to be compatible with breast feeding.

Peripartum Cardiomyopathy

Peripartum cardiomyopathy is a rare, poorly understood condition that presents as heart failure with a dilated cardiomyopathy in the last month of pregnancy or in the first six months post partum. There is absence of an obvious cause for the heart failure; and there is absence of demonstrable heart disease before the last month of pregnancy. Echocardiography should reveal impaired left ventricular systolic function and usually shows generalized cardiac dilation often involving the left ventricle and left atrium more than the right sided chambers [84]. The mortality can be as high as 30% with an initial period of high risk. Longitudinal studies have suggested that some patients can rapidly return to normal and that the initial severity of left ventricular dysfunction is not necessarily predictive of long-term functional outcome [85]. Persistence of cardiac dysfunction beyond 6-12 months often indicates a long-term problem although recovery of left ventricular function can be seen later than this. No study has clearly identified a distinct cause of this disease and antemortem biopsy specimens usually show non-specific findings.

Prolonged bed rest has been thought by some authors to facilitate recovery [86]. In addition routine therapy for dilated cardiomyopathy including digitalization, diuretics, sodium restriction and anti coagulation is recommended. Afterload reduction with agents such as hydralazine and captopril is suggested. **Hydralazine hydrochloride** has been widely used for many years in pregnancy without adverse maternal or fetal effects [87]. Its use has not been linked to congenital defects although it readily crosses the placenta. A number of studies alone, or in combination, with other hypertensive agents, have shown that it is relatively safe for the fetus [88]. It's use in pregnancy has been linked to a lupus-like syndrome [89]. It is excreted in breast milk in which it occurs in low concentration but the American Academy of Pediatrics considers hydralazine to be compatible with breast feeding [29].

Because of toxicity identified in animal studies, the National Institute of Health recommended (1984) that **captopril** be avoided during pregnancy [90,

91]. However, the use of captopril limited to the first trimester does not appear to represent a significant risk to the fetus. Exposure after this time has been associated with teratogenesity and toxic effects in the fetus in newborn animals. Although captopril is excreted in breast milk in low concentrations, the American Academy of Pediatrics considers captopril compatible with breast feeding [29].

In patients with peripartum cardiomyopathy who continue to have refractory heart failure despite aggressive medical management including intra aortic balloon counter pulsation, therapy with orthotopic cardiac transplantation remains an option in qualified patients [84]. Some patients may safely undergo pregnancy when left ventricular function has "recovered" but contractile reserve may be impaired in such patients [84] and caution is required when rendering an opinion on the outcome of future pregnancies.

Primary or Secondary Pulmonary Hypertension

Patients with primary or secondary pulmonary hypertension or pulmonary hypertension secondary to other causes (e.g. Eisenmenger's Syndrome: patients with large intracardiac defects that allow free communication between the systemic and pulmonary circulations and who have predominantly right to left shunting secondary to fixed and markedly elevated pulmonary vascular resistance) should avoid pregnancy because of the high maternal and fetal mortality rates. With pregnancy, and the usual maternal hemodynamic alterations (increased cardiac output and a major fall in systemic vascular resistance) patients with Eisenmenger's Syndrome have more right to left shunting and experience deeper cyanosis, a reduced systemic arterial oxygen saturation and a rise in hematocrit. This is one of the few cardiac conditions for which sterilization may be recommended because pregnancy is poorly tolerated and the maternal mortality rate is high [92]. If termination of pregnancy is not feasible or is declined, supportive measures must include avoidance of operative procedures and hypotension, hypovolemia, and thromboembolic phenomena. Gleicher and colleagues recommend hospitalization and prolonged bed rest, anticoagulation of patients from mid pregnancy, non induced labor, administration of high concentrations of oxygen during labor, epidural anesthesia, and vaginal delivery (non induced) with elective low forceps to shorten the second stage of labor. Despite these active measures, the maternal mortality rate may remain substantial in the first week after delivery [92]. It is possible that a multidisciplinary team approach to the management of such patients from the middle of pregnancy, with pre-partum hospitalization, oxygen therapy, anticoagulation with heparin and a controlled vaginal delivery utilizing epidural anesthesia may result in a successful outcome [93,94] .

Primary pulmonary hypertension is also associated with a high maternal mortality rate and the frequency of spontaneous abortions and of neonatal

deaths is high. Both tubal ligation and pregnancy terminations are indicated. If the patient elects to continue with pregnancy, bed rest should be enforced, and anticoagulation instituted [95]. Adequate oxygenation with careful hemodynamic monitoring is undertaken during labor and delivery. In primary pulmonary hypertension, oral calcium channel blockers have been shown to have a modest effect in patients with some preservation of pulmonary vasoreactivity [96].

The Marfan Syndrome

In patients with the Marfan Syndrome and minimal cardiovascular involvement pregnancy may be tolerated without serious problems [97-99]. Women with mild aortic dilation and no evidence of valvular regurgitation have a small risk of dissection and monitoring with serial echocardiograms every eight to twelve weeks may be appropriate [99, 100] However women who have moderate or severe cardiovascular dysfunction may be at considerable risk during pregnancy. Aortic dissection during pregnancy occurs most frequently during the third trimester and first post partem month and most dissections have occurred in women with aortic regurgitation or evidence of marked aortic root enlargement [101]. There is a relatively small risk of aortic dissection during pregnancy provided the patient is asymptomatic, the aortic root diameter is less than 40 mm and there is no significant valvular dysfunction [101]. Nevertheless, patients should be observed at a "high risk" clinic. It is recommended that women with the Marfan Syndrome who are considering pregnancy have expert genetic counseling, and a clinical cardiac assessment, including echocardiography, should be performed to determine whether aortic root dilation or valvular dysfunction exists.

Beta blockers are given to virtually all patients with the Marfan Syndrome, even during pregnancy, because it is thought that they will reduce the rate of aortic dilation and the risk of complications [102]. Certainly, it is thought that the maternal advantages of beta blockers far outweigh their potential adverse effects on the fetus. It should be understood that even in patients with a normal aortic root and no evidence of valvular dysfunction, the presence of the Marfan Syndrome alone can predispose a patient to a poor outcome with morbid or fatal events [103].

Cardiac Arrhythmias

The most common arrhythmias during pregnancy include premature atrial and ventricular beats, re-entrant supraventricular tachyarrhythmias, and occasional tachyarrhythmias associated with the Wolff-Parkinson-White Syndrome [104, 105]. In patients with normal cardiac function, there is

usually no need to treat asymptomatic or mildly symptomatic patients with ventricular or supraventricular premature beats. The history of caffeine use, alcohol use, or other precipitants of arrhythmias should be sought (e.g. sympathomimetic amine inhalers for asthma). Interestingly, there are reports of increased incidence of paroxysmal supraventricular tachyarrhythmias during pregnancy [104-107]. If vagal maneuvers are ineffective, patients may be treated with digitalis, beta blocking agents, adenosine or intravenous verapamil. **Adenosine** was first used in human pregnancy in a patient with a recurrent narrow complex tachycardia and reported in 1991 [108]. Other reports have since described the use of adenosine to treat maternal supraventricular tachycardia [109-111]. No adverse effects attributable to adenosine in the fetus or newborn have been reported in any of these cases. Occasionally, cardioversion may be needed to achieve sinus rhythm.

Ventricular tachycardia can occur in pregnant patients and has been reported in the absence of detectable organic disease [112]. Therapy with **lidocaine** is used acutely, and subsequent recurrence is prevented with beta blocking drugs, procainamide or quinidine. The majority of information on lidocaine in pregnancy comes from its use as a local anesthetic during labor and delivery. The drug rapidly crosses the placenta to the fetus, appearing in the fetal circulation within minutes after administration to the mother. It may produce central nervous system depression in the newborn with high serum levels. However, lidocaine is the treatment of choice for ventricular arrhythmias. Small amounts of lidocaine are excreted in breast milk, but the American Academy of Pediatrics considers lidocaine to be compatible with breast feeding [29].

Cardiopulmonary Resuscitation

In the event of cardiopulmonary resuscitation during pregnancy, the main objective before the onset of fetal viability (approximately the 24th week of gestation) is to resuscitate the mother. After this stage of pregnancy, consideration has to be given to delivery of the fetus, which is usually expedited by emergency Caesarean section within 5-15 minutes if cardiopulmonary resuscitation is unsuccessful [113]. If a cardiac arrest occurs in a pregnant woman standard resuscitative protocols should be followed without modification [114,115]. To minimize the effects of the gravid uterus on venous return and cardiac output a wedge (a pillow) should be placed under the right abdominal flank and hip to displace the uterus to the left [114,115].

	Placental transfer	Risk Factor	Fetal Effects	Breast Feed
Adenosine	?	C_M	No adverse effects reported.	No data.
Amiodarone	Yes	C	Hypothyroidism, premature birth, hypotonia, large fontanelle.	No
Atenolol	Yes	C_M	Low birth weight.	Yes
Captopril	Yes	D_M	Teratogenic when use in second and third trimesters producing renal defects and hypocalvaria (perhaps due to fetal hypotension and decreased renal blood flow).	Yes
Digitalis	Yes	C	Low birth weight	Yes
Diltiazem	Yes	C_M	No adequate human studies.	Yes
Enalapril	Yes	D_M	Teratogenic when use in second and third trimesters producing renal defects and hypocalvaria (perhaps due to fetal hypotension and decreased renal blood flow).	Yes
Furosemide	Yes	C_M	Decreased Na^+, K^+, glucose.	Yes
Heparin	No	C	Abortion	Yes
Hydralazine	Yes	C_M	Thrombocytopenia, acute distress.	Yes
Hydrochlorothiazide	Yes	D	Decreased Na^+, K^+, glucose.	Yes.Can suppress lactation
Isoproterenol	?	C	Tachycardia.No adequate human studies.	No data.
Labetolol	Yes	C_M	No adequate human studies.	Yes
Lidocaine	Yes	C	Bradycardia and CNS toxicity (keep maternal blood levels < 4μg/mL).	No data
Metoprolol	Yes	B_M	No obvious risk - no long term data.	Yes
Mexilitine	Yes	C_M	Bradycardia, small infants, low APGAR, hypoglycemia.	Yes
Nifedipine	Yes	C_M	No adequate human studies.Use with care.	Yes
Nitroglycerin	?	C_M	No adequate human studies.	No data.
Procainamide	Yes	C_M	None	Yes
Propranolol	Yes	C_M	Growth retardation,prematurity, hypoglycemia, bradycardia, respiratory depression.	Yes
Quinidine	Yes	C	Thrombocytopenia.	Yes
Sodium Nitroprusside	Yes	C	Potentially toxic.No adequate human studies.	No
Streptokinase	Yes	C	No adequate human studies.	No data.
Verapamil	Yes	C_M	No adequate human studies.	Yes
Warfarin	Yes	D	Abortion, hemorrhage.	Yes

Data mainly from Reference [2]. Risk factors : Category B: Either animal-reproduction studies have not demonstrated a fetal risk but there are no controlled studies in pregnant women or animal-reproduction studies have shown an adverse effect (other than a decrease in fertility) that was not confirmed in controlled studies in women in the first trimester(and there is no evidence of a risk in later trimesters). Category C : Either studies in animals have revealed adverse effects on the fetus and there are no controlled studies in pregnant women or studies in women and animals are not available. Drugs should only be given if the potential benefit justifies the potential risk to the fetus. Category D: There is positive evidence of human fetal risk, but the benefits from use in pregnant women may be acceptable despite the risk (e.g. if the drug is needed in a life-threatening situation for a serious disease for which safer drugs cannot be used or are ineffective). If the manufacturer has rated the risk of the drug in the professional literature the subscript m is used i.e. C_M.

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