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EDITORIAL

Pregnancy and Cardiovascular Disease

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The cardiovascular system undergoes significant changes during pregnancy to adapt to and accommodate the increased metabolic demands of the fetus and the mother.[1-5] These adaptations produce an important hemodynamic burden on patients with underlying heart disease, and confer an increase in morbidity and mortality. Furthermore, pregnancy may cause specific cardiovascular disorders, which can impose a risk to the pregnant woman and to her fetus. It is estimated that in the western world 0.2-4% of all pregnancies are complicated by cardiovascular diseases (CVD).[4] This risk is in the ascending order as the age of first pregnancy is increasing and as the number of cardiovascular risk factors is rising (e.g. smoking, hypercholesterolemia, diabetes, hypertension, obesity). During pregnancy, the most frequent cardiovascular events relate to hypertension (6–8%). On the other hand, in the western world, the most frequent CVD present during pregnancy is congenital heart disease-CHD (circa 75%),[4,6,7] while rheumatic heart disease predominates in the other countries (circa 70%) and CHD is seen in ~15%. In pregnant women with heart disease, maternal death is estimated around 1% but it varies depending on the underlying CVD; neonatal complications occur in 20–28% and neonatal mortality ranges between 1% and 4%. In general, CVDs are the most common cause of maternal death during pregnancy in the Western industrialized world.[4] Thus, women of child-bearing age with CVD or cardiovascular risk factors should be counseled and managed early by an interdisciplinary team of gynecologists, cardiologists, and, when necessary, cardiothoracic surgeons.[1,4,8]

To meet the metabolic demands of mother and fetus, cardiac output increases 1 L/min at 8 weeks' gestation, representing >50% of the total change seen, which culminates in an increase of cardiac output of 30-50% during normal pregnancy, maintained until term.[9,10] Cardiac output increases primarily because of stroke volume rather than heart rate, at least in early pregnancy, while later the heart rate also increases. By 8 weeks' gestation, systemic vascular resistance has fallen to 70% of its preconceptional value. The majority of the pregnancy-induced changes in these parameters occur during the embryonic period. Plasma volume has increased by ~40% at 24 weeks of gestation. Blood pressure falls mainly due to vasodilation, primarily conferred by nitric oxide and relaxin, affecting both systolic and diastolic components. In the third trimester, diastolic pressure gradually rises and may normalize to baseline values at term. Another important aspect of the cardiovascular status in pregnancy relates to hemostatic changes, which lead to hypercoagulability via an increase in concentration of coagulation factors, fibrinogen, and

platelet adhesiveness, and a concomitant diminution of endogenous fibrinolysis. In addition, mechanical obstruction to venous return by the enlarged uterus can cause stasis which enhances the thromboembolic risk.[4] During labor and delivery, particularly when the uterus is contracting, a further increase occurs in cardiac output, oxygen consumption and blood pressure; these hemodynamic changes are influenced by the mode of delivery.[10] Cardiac output is also increased during the early postpartum period as additional blood reaches the circulation from the contracting uterus producing a preload increase, rendering at-risk patients susceptible to developing pulmonary edema at this stage. Hemodynamic conditions mostly return to normal within 1–3 days after delivery but in some women this may take up to a week.

Diagnosis of CVD

All diagnostic approaches start with a detailed *history* and a complete *physical examination* which may contribute to rendering a diagnosis or a suspicion of CVD prior to resorting to other more expensive tests.[4] An electrocardiogram (*ECG)* and / or *Holter* monitor may provide further clues for structural and electrical disorders. *Echocardiography*, not involving exposure to radiation, has become the screening method of choice, as well as a most important diagnostic tool during pregnancy for initial diagnosis and follow-up. Transesophageal echocardiography is a semi-invasive method, less often needed, but capable of better studying complex CHD. Exercise testing is important to assess functional capacity, chronotropy and exercise-induced arrhythmias; stress echocardiography and myocardial scintigraphy should be avoided. In patients with known CVD, exercise testing should be performed prior to pregnancy for risk evaluation. Invasive testing and procedures should be avoided, if possible, or used with extra caution and exposure to radiation should be "as low as reasonably achievable" ("ALARA"). Fetal assessment with use of ultrasound is most important. Congenital cardiac malformations can thus be diagnosed as early as the 13th week, with optimal timing between 18-22 weeks.

Interventions in a pregnant woman should be limited to those absolutely necessary with provision for minimal radiation exposure and measures to protect and shield the fetus; best timing would be after the 4th month in the 2nd trimester, when organogenesis is complete, the thyroid still inactive and the uterus still small.

Risk Assessment

Pre-pregnancy risk assessment and counselling is indicated in all women with known or suspected congenital or acquired cardiovascular and aortic disease.[4] The risk of pregnancy depends on the specific type of heart disease and clinical and functional status of the patient. Women with significant CVD should be managed jointly by an obstetrician and an experienced cardiologist. Risk assessment can be based on predictors that have been identified in studies that included large populations with a variety of CVD. Several risk scores have been developed based on these predictors, of which the CARPREG risk score (Toronto group risk score) is most widely known and used. This risk score has been validated in several studies and appears valuable to predict maternal risk, although overestimation can occur.[4] The *CARPREG risk score* includes acquired and congenital heart disease and comprises 4 items, each receiving 1 point: prior arrhythmias or cardiac event, New York heart Association (NYHA) functional class >II or cyanosis, left heart obstruction, and systemic ventricular dysfunction (ejection fraction < 40%).[11] With 0 points, the risk is estimated at 5%; with 1 point it rises to 27%; and with >1 points the risk is prohibitive at 75%. The *ZAHARA I risk score* is more comprehensive, albeit it relates to congenital heart disease only, and enlists 8 items to consider: prior arrhythmias, NYHA functional class >II, left heart obstruction, cardiac medication before pregnancy, systemic atrioventricular (AV) valve regurgitation, pulmonary AV valve regurgitation, mechanical valve prosthesis, and cyanotic heart disease.[12] Details of this scoring system can be viewed in Table 1.

Table 1. ZAHARA Prediction Score

Predictors	Points		Total Points	Risk
Prior arrhythmias	**1.5**		**0**	**2.9%**
NYHA class ≥II	**0.75**		**0.5-1.5**	**7.5%**
Left heart obstruction (PG >50 mmHg or AVA <1 cm^2)	**2.5**		**1.51-2.50**	**17.5%**
Cardiac medication before pregnancy	**1.5**		**2.51-3.50**	**43.1%**
Systemic AV valve regurgitation	**0.75**		**>3.51**	**70%**
Pulmonary AV valve regurgitation	**0.75**			
Mechanical valve prosthesis	**4.5**			
Cyanotic heart disease (corrected / uncorrected)	**1.0**			

AV = atrioventricular; AVA = aortic valve area; NYHA = New York Heart Association; PG = peak gradients

However, the European Task Force recommends that maternal risk assessment should be performed according to the *modified World Health Organization (WHO) risk classification* (Table 2).[4] This risk classification includes the underlying maternal heart disease and specifies contraindications for pregnancy that are not incorporated

in the CARPREG and ZAHARA risk scores. Women in ***WHO class I*** have a very low risk requiring limited cardiology follow-up. Those in ***WHO class II*** are at low or moderate risk, and need follow-up every trimester. For women in ***WHO class III***, there is a high risk of complications, and frequent, monthly or bimonthly, cardiology and obstetric follow-up is advised. Women in ***WHO class IV*** should be advised against pregnancy but, if they become pregnant and will not consider termination, close (e.g. monthly) follow-up will be needed. In pregnant women with heart disease, as mentioned earlier, neonatal complications occur in 20–28% and neonatal mortality ranges between 1% and 4%. Maternal predictors of neonatal events include: baseline NYHA class >II or cyanosis; maternal left heart obstruction; smoking during pregnancy; multiple gestation; use of oral anticoagulants during pregnancy, and; mechanical valve prosthesis.[4]

Table 2. Modified World Health Organization (WHO) Risk Classification

Class	Risk	Conditions
I	No detectable ↑ risk of maternal mortality & no/mild ↑ in morbidity	• Uncomplicated, small or mild: √ pulmonary stenosis; √ PDA; √ MVP • Successfully repaired simple lesions (ASD or VSD, PDA, anomalous pulmonary venous drainage). • Atrial or ventricular ectopic beats, isolated
II	Small ↑ risk of maternal mortality or moderate ↑ in morbidity	• Unoperated ASD or VSD • Repaired tetralogy of Fallot • Most arrhythmias
		WHO II–III (depending on individual) • Mild LV impairment • Hypertrophic CM • Native or tissue VHD not considered WHO I or IV • Marfan syndrome without aortic dilatation • Aorta <45 mm in aortic disease associated with bicuspid aortic valve • Repaired coarctation
III	Significantly ↑ risk of maternal mortality or severe morbidity. Expert counselling required. If pregnancy is decided upon, intensive specialist cardiac & obstetric monitoring needed throughout pregnancy, childbirth, & puerperium	• Mechanical valve • Systemic RV • Fontan circulation • Cyanotic heart disease (unrepaired) • Other complex CHD • Aortic dilatation 40–45 mm in Marfan syndrome • Aortic dilatation 45–50 mm in aortic disease associated with bicuspid aortic valve
IV	Extremely ↑ risk of maternal mortality or severe morbidity; ***pregnancy contraindicated***. If pregnancy occurs termination should be discussed. If pregnancy continues, care as for class III.	• Pulmonary arterial hypertension of any cause • Severe systemic ventricular dysfunction (LVEF <30%, NYHA III–IV) • Previous peripartum CM with any residual impairment of LV function • Severe MS, severe symptomatic AS • Marfan syndrome with aorta dilated >45 mm • Aortic dilatation >50 mm in aortic disease associated with bicuspid AoV • Native severe coarctation

AS = aortic stenosis; AoV = aortic valve; ASD = atrial septal defect; CHD = congenital heart disease; CM = cardiomyopathy; LV = left ventri-cle(-ular); LVEF = left ventricular ejection fraction; MS = mitral stenosis; MVP = mitral valve prolapse; NYHA = New York Heart Association; PDA = patent ductus arteriosus; RV = right ventricle; VHD = valvular heart disease; VSD = ventricular septal defect

Pregnancy Complications and CVD

Epidemiological and other studies indicate that in women presenting with severe preeclampsia, functional, biochemical, and familial cardiovascular risk markers may contribute to later development of CVD. Recurrent abortion may be a potential risk factor for CVD in this patient population.[13,14] In a significant number of women with a history of severe preeclampsia and spontaneous recurrent abortions, endothelial dysfunction may be present, as characterized by a lower endothelium-mediated vasodilatation and lower blood nitrites. It is suggested that endothelial dysfunction may be a triggering mechanism for both preeclampsia and recurrent abortions, as well as a risk for future development of CVD.[14] Based on these findings, an exciting hypothesis has been put forth that interventions to correct the endothelial dysfunction early in pregnancy may help prevent obstetric complications emanating from placentation-related disorders and also may finally ameliorate the cardiovascular risk later in life. It has been reported that supplementation with L-arginine during pregnancy may confer significant improvement of the reproductive outcome in women with endothelial dysfunction diagnosed preconceptionally or in early pregnancy.[14,15]

Gestational dysglycemia, even in its milder forms, identifies a group of women who are at increased risk not only for type 2 diabetes mellitus but also for an earlier age of onset of CVD.[16] Furthermore, much of that risk, expressed as dysglycemia, metabolic syndrome, and altered vascular physiology, may become evident in the first few months postpartum. Identifying a dysglycemic pregnancy and hence a population of women at increased subsequent cardiometabolic risk enables clinicians to modify such conditions and thus attenuate adverse long-

term outcomes, particularly cardiovascular risk, by targeted intervention. Future research may identify and validate potential useful postpartum screening tools and biomarkers of subsequent vascular risk, including altered endothelial responsiveness, which may be evident before diabetes, metabolic syndrome, or cardiovascular events emerge.[16]

In a recent study, among women pregnant at least once, a cohort of women was identified with miscarriages or stillbirths.[17] Among 1,031,279 such women followed for an average of 15 years per woman, 2798 myocardial infarctions (MIs), 4053 strokes, and 1269 cases of renovascular hypertension were detected. Women with stillbirths had 2.7, 1.7, and 2.4 times the rates of MI, strokes, and renovascular hypertension, respectively, as women with no stillbirths. Compared with women with no miscarriages, women with miscarriages had 1.13, 1.16, and 1.20 times the rates of these same outcomes, respectively; more miscarriages increased these rates significantly. Associations were strongest in younger women (<35 years). The authors concluded that pregnancy losses were associated with subsequent risks of MI, strokes, and renovascular hypertension, conditions linked to atherosclerosis, making pregnancy loss a possible candidate risk factor for atherosclerotic disease in women, with possible inflammatory processes being the common denominator.[17]

In another case-control study, in a Dutch population, it was found that women with pregnancies complicated by preeclampsia or intrauterine growth restriction and their mothers have high-risk cardiovascular profiles with higher glucose levels, prevalence of hypertension, and larger waist circumferences compared with women with uncomplicated pregnancies and their mothers.[18] The authors concluded that vascular-related pregnancy complications may confer higher risk for future development of CVD. According to the AVON study in a prospective cohort of 3416 British women, pregnancy was an important opportunity for early identification of women at increased risk of CVD later in life.[19] Specifically, in that study hypertensive disorders of pregnancy and pregnancy diabetes mellitus were independently associated with an increased calculated 10-year CVD risk. Preeclampsia appeared to be a better predictor of future CVD because it was associated with a wider range of cardiovascular risk factors.[19] Similar were the findings of a case-control study, whereby in a cohort of 325 women with hypertension in pregnancy, mortality from ischemic heart disease was more common in these hypertensive women (24.3%) compared with 629 normotensive women (14.6%; relative risk-RR 1.66).[20] Cerebrovascular event deaths occurred in 9.5% of cases and in 6.5% of controls (RR 1.46). Survival times were shorter on average by 3-9 years as a consequence of CVD. The authors concluded that there was an increased risk of death from ischemic heart disease and cerebrovascular events over long-term follow-up among women who suffered from hypertension in pregnancy.

However, the results of a Norwegian population-based study (HUNT), indicated that cardiovascular risk factors that are present before a hypertensive pregnancy are more important determinants of subsequent cardiovascular risk factors than the hypertensive pregnancy itself.[21] Specifically, the study assessed whether the increased risk that preeclampsia and hypertension confer later in life can be attributed to factors that operate in pregnancy or to prepregnancy risk factors that are shared by both disorders. Among 3225 women with a singleton birth, those who experienced preeclampsia or gestational hypertension in pregnancy had significantly higher levels of body mass index and systolic and diastolic blood pressures and unfavorable lipids compared with other women. However, after adjustment for prepregnancy measurements, the difference in body mass index was attenuated by >65%, and the difference in blood pressure by circa 50%. In relation to high-density lipoprotein cholesterol and triglycerides, differences between the groups were attenuated by 40% and 72%, respectively. The authors concluded that the positive association of preeclampsia and gestational hypertension with postpregnancy cardiovascular risk factors could be due largely to shared prepregnancy risk factors rather than reflecting a direct influence of the hypertensive disorder in pregnancy.[21]

A study of singleton first births (129,920 deliveries) investigated whether pregnancy complications associated with *low birthweight* were related to risk of subsequent ischemic heart disease in the mother over 15-19 years of follow-up.[22] Maternal risk of admission for ischemic heart disease or death was associated with delivering a baby in the lowest birthweight quintile for gestational age (adjusted hazard ratio-HR 1.9), preterm delivery (HR 1.8), and pre-eclampsia (HR 2.0). The associations were additive; women with all three characteristics had a risk of ischemic heart disease admission or death 7 times greater than the reference category. The authors concluded that complications of pregnancy associated with low birthweight confer an increased risk of subsequent ischemic heart disease in the mother. Common genetic risk factors might explain the link between birthweight and risk of ischemic heart disease in both the individual and the mother.

The incidence of pregnancy-related acute myocardial infarction (MI) is quite low, estimated at 3–10 per

100,000 deliveries.[23,24] However, pregnancy increases the risk of MI by 3–4 fold. In general, the incidence of coronary artery disease and MI is increasing among pregnant women, most likely as a result of the increased frequency of smoking among women. Although MI is rare in pregnancy, when it occurs it is associated with a disproportionately high maternal mortality rate reaching 5–37%. The risk of death from MI increases as pregnancy advances, with a mortality rate in the first and second trimester reported at ~25%, in the third trimester ~40%, and if the MI occurs in the peripartum period, the mortality rate may increase to 50%.[23] Risk factors that predispose to MI are smoking, maternal age, familial hypercholesterolemia, hypertension and diabetes mellitus. Pregnancy is known to be associated with an increased probability of developing hypertension (preeclampsia, eclampsia) or for the worsening of pre-existing hypertension. The diagnosis of MI in pregnancy may be difficult and is challenging for several reasons; due to its rarity, MI may not be considered in a young apparently healthy female, while the physiological alterations of pregnancy may mask or mimic the signs and symptoms of MI, such as dyspnea, palpitations, fatiguability, nausea and heart burn, epigastric or chest pain (attributed to gastro-esophageal reflux), peripheral edema, distended neck veins, and the presence of a third heart sound and ejection systolic murmur.[23]

Pregnancy-associated plasma protein-A (PAPP-A) is one of the circulating proteins in the maternal plasma, which is also present in unstable plaques. Elevated levels of PAPP-A in pregnancy may reflect instability of atherosclerotic plaques. PAPP-A is a new candidate marker of unstable angina and acute MI and may have diagnostic value in unstable angina or acute MI during pregnancy.[23] The utilization of PAPP-A in coronary artery disease in pregnancy may be of particular value in patients with negative troponin testing; PAPP-A seems to be associated with inflammation and might be used to detect plaque instability and rupture before an increase in cardiac troponin is detectable.[23]

A US population-based study assessed the incidence, mortality, and risk factors for pregnancy-related acute MI.[25] The incidence of MI was estimated at 6.2 per 100 000 deliveries with a mortality of 5.1% (44/859). The odds of acute MI were 30-fold higher for women aged $\geq$40 years than for women <20 years of age. Important risk factors for pregnancy-related acute MI included hypertension (odds ratio - OR 21.7), thrombophilia (OR 25.6), diabetes mellitus (OR 3.6), smoking (OR 8.4), transfusion (OR 5.1), postpartum infection (OR 3.2), and age $\geq$30 years. The authors concluded that although acute MI is a rare event in women of reproductive age, pregnancy increases the risk 3- to 4-fold.[25]

Some of the risk factors and/or mechanisms for pregnancy-related acute MI may be unique to pregnancy. Coronary artery dissection is a rare cause of acute MI; however, in one series, this mechanism involved 20% of women who had recently delivered.[26] Postpartum degeneration of the ground substance of the connective tissue in the intima and media of the coronary arteries has been proposed as a mechanism.[27] In another series, findings of coronary artery anatomy in 68 of 125 cases of pregnancy-related acute MI revealed coronary artery dissection in 16%, coronary thrombus without atherosclerotic disease in 21%, normal coronaries in 29%, and atherosclerosis with or without intracoronary thrombus in 43% of the cases.[28] In contrast, the majority of cases of acute MI outside of pregnancy are due to coronary thrombosis overlying a ruptured atherosclerotic plaque.

Finally, women with an implantable cardioverter defibrillator (ICD) device who become pregnant do not have any additional risk apart from that conferred from their underlying heart disease and the presence of the device does not seem to pose any extra risk to the fetus.[29]

Management of Coronary Heart Disease During Pregnancy

Beta-1 selective beta-blockers are the drugs of choice for coronary heart disease during pregnancy.[4] Nitrates can also be used in symptomatic patients. Antiplatelet therapy with aspirin as secondary prevention is controversial, due to the increased risk of hemorrhage. However, it should be administered in case of percutaneous coronary intervention (PCI) and stenting and also following MI. Data on use of clopidogrel remain insufficient. Angiotensin converting enzyme (ACE) inhibitors and statins are not considered safe. For the management of acute MI, coronary angiography with possible PCI is preferable to thrombolysis, particularly when spontaneous dissection of the coronary arteries is suspected. Bare stents should be used where possible. Great caution should be exercised during the first trimester, when meticulous risk/benefit analysis is warranted, due to the potential harm to the fetus. Thrombolytics are probably not teratogenic, as these drugs do not generally cross the placental barrier; however, they confer an increased risk of bleeding.

Peri-Partum Cardiomyopathy (CM)

Heart failure associated with pregnancy has been described in women with a distinct type of cardiomyopathy, designated as peri-partum or pregnancy-associated cardiomyopathy (CM). Initially considered to occur during the last gestational month and first 5 months

after delivery, later data indicate that women may present with CM earlier during pregnancy.[30] A potential detrimental effect of subsequent pregnancy on the outcome of these patients has been reported and thus the advice is to avoid subsequent pregnancies. The disease can affect women of various ethnic backgrounds at any age but it appears more common in women >30 years of age. A strong association of the disease with gestational hypertension and twin pregnancy has been noted and thus the suspicion should be higher in these women. Severe left ventricular dysfunction has been noted upon diagnosis of the disease, albeit it normalizes in more than half of the patients, especially in women with a left ventricular (LV) ejection fraction (LVEF) >30% at the time of diagnosis. Early recognition of peri-partum CM is important as it may lead to timely initiation of anticongestive and supportive therapy, and better care and outcome of this life-threatening condition. With the recent discovery of a possible key role of oxidative stress and the generation of a cardiotoxic subfragment of prolactin in the pathophysiology of peripartum CM, pharmacological blockade of prolactin with use of bromocriptine may offer a novel approach for a disease-specific therapy.[31,32]

Exercise in Pregnancy

In 2002, the American College of Obstetricians and Gynecologists published exercise guidelines for pregnancy, which suggested that in the absence of medical or obstetric complications, 30 minutes or more of moderate exercise a day on most, if not all, days of the week is recommended for pregnant women.[33] Recent research has determined that increasing physical activity energy expenditure to a minimum of 16 metabolic equivalent task (MET) hours per week, or preferably 28 MET hours per week, and increasing exercise intensity to ≥60% of heart rate reserve during pregnancy, reduces the risk of gestational diabetes mellitus and perhaps hypertensive disorders of pregnancy (i.e. gestational hypertension and pre-eclampsia) compared with less vigorous exercise.[34] To achieve this more rigorous exercise program, one could walk at 3.2 km per hour for 11.2 hours per week (2.5 METs, light intensity), or preferably exercise on a stationary bicycle for 4.7 hours per week (~6-7 METs, vigorous intensity).[34] Light muscle strengthening performed over the second and third trimester of pregnancy has minimal effects on a newborn infant's body size and overall health.

Pregnancy in Women with Structural Heart Disease

In 2007, the European Registry on Pregnancy and Heart disease was initiated by the European Society of Cardiology enrolling pregnant women with valvular, congenital or ischemic heart disease, or cardiomyopathy (CM). Recent data from this registry of 1321 pregnant women with most patients being in NYHA class I (72%), indicated that congenital heart disease (66%) was most prevalent; other structural heart disease included valvular disease in 25%, CM in 7%, and ischemic heart disease in 2%.[7] Maternal death was at 1%, compared with 0.007% in the normal population. Highest maternal mortality was found in patients with CM (2.4%). During pregnancy, there were 338 hospitalizations (26%), mostly for heart failure (n=133). Caesarean section was performed in 41%. Fetal mortality was 1.7% and neonatal mortality 0.6%, both higher than in the normal population (0.35% and 0.4% respectively). In centers of developing countries, maternal and fetal mortality was higher than in developed countries (3.9 vs. 0.6%, $P < 0.001$ and 6.5 vs. 0.9% $P < 0.001$). The authors concluded that the majority of patients can safely complete pregnancy and delivery as long as adequate pre-pregnancy evaluation & specialized high-quality care during pregnancy and delivery are available. Pregnancy outcomes were markedly worse in patients with CM and in developing countries.

The adverse effect and prognosis that CM confers in pregnant women was also confirmed in a study of 36 pregnancies in 32 women with dilated CM.[35] A total of 39% (14 of 36) of the pregnancies were complicated by at least 1 maternal cardiac event. Moderate or severe LV dysfunction and/or NYHA functional class III or IV ($p = 0.003$) were the main determinants of adverse maternal cardiac outcomes during pregnancy; 16-month event-free survival was worse in pregnant women compared with nonpregnant women ($28 \pm 11\%$ vs. $83 \pm 10\%$, $p = 0.02$). The adverse neonatal event rate was highest among women with obstetric and cardiac risk factors (43%). The authors concluded that in pregnant women with dilated CM the risk of adverse cardiac events is significant; pre-pregnancy characteristics can identify women at the highest risk. Pregnancy seems to have a short-term negative impact on the clinical course in women with dilated CM.

Pregnancy in Women with Congenital Heart Disease

A special group of patients are those with congenital heart disease (CHD) reaching child bearing age and wishing to pursue pregnancy.[6,36-38] Progress in diagnosis and management of CHD over the years has improved the long-term outcome of these patients and rendered possible this scenario.[6,38] However, pregnancy, as outlined above, imposes a circulatory burden, mainly due to volume overload, having an impact on a healthy mother and, of course, an even greater risk on a mother with CHD placing both the mother and the fetus at great

risk. In this setting the risk of pregnancy varies according with the underlying disease and the clinical condition of the mother.[38] It thus becomes imperative to have a risk assessment performed before pregnancy. Risk scores have been proposed to make this possible (see previous discussion and Tables 1 & 2).

Overall the percentage of cardiac complications during pregnancy in this group is estimated ~11%. The most frequent cardiac complication appears to be the development of heart failure (~5%), with patients with complex CHD (Eisenmenger, other cyanotic CHD, pulmonary atresia with ventricular septal defects) being at highest risk.[38] The second most common problem appears to be cardiac arrhythmias, mostly supraventricular, but also ventricular and occasional bradyarrhythmias. Cardiovascular events (~1 in 50 pregnancies), including death, MI, or stroke may be encountered mainly in patients with Eisenmenger syndrome and those with palliated or uncorrected cyanotic heart disease.

Obstetric complications may include hypertensive disorders (eclampsia) observed with about the same incidence (~9%) as in the general population (8%), and the "hemolysis elevated liver enzymes low platelets" syndrome. Preeclampsia and eclampsia may be more prevalent (13-16%) in patients with transposition of the great vessels, pulmonic stenosis, aortic coarctation, and pulmonary atresia with ventricular septal defects. Thromboembolic events have also been reported in ~2% of pregnancies. With regards to fetal complications, offspring mortality may be ~ 4% (vs 1% in the general population), ascribed in part to the relatively high overall premature birth rate (16%) and the recurrence of CHD, the latter depending on the type of CHD, ranging between 0.6% for the transposition patients and 8% for patients with AV septal defects.[37] Particularly high rates of premature delivery and/or CHD recurrence are observed in patients with Eisenmenger syndrome (~28%).

Guidelines on the Management of CVD During Pregnancy [4, 39]

Recommendations for the management of **congenital heart disease (CHD)**:

- Balloon valvulotomy should be performed before pregnancy to relieve severe *pulmonary valve stenosis* (peak gradient by Doppler >64 mmHg) **(Class I / Level B)**
- *Follow-up* should be individualized: from twice during pregnancy to monthly **(Class I / Level C)**
- Patients with *Ebstein's* anomaly with symptoms of cyanosis and/or heart failure should be treated before pregnancy or advised against pregnancy **(Class I / Level C)**
- In severe *pulmonary regurgitation*, pulmonary valve replacement (bioprosthesis) should be performed before pregnancy in symptomatic women with marked dilatation of the right ventricle (**Class I / Level C)** or considered in asymptomatic women **(Class IIa / Level C)**
- All women with a *bicuspid aortic valve* should undergo imaging of the ascending aorta before pregnancy, and surgery should be considered when the aortic diameter is >50 mm (**Class IIa / Level C**)
- Anticoagulation should be considered during pregnancy in *Fontan* patients (**Class IIa / Level C**)
- In *pulmonary artery hypertension (PAH*), anticoagulation should be considered in patients with suspicion of pulmonary embolism as the cause of or contributor to the PAH (**Class IIa / Level C**)
- In patients already taking drug therapy for PAH before pregnancy, continuation may be considered after informing about the teratogenic effects (**Class IIa/Level C**)
- Women with the following conditions should be advised against pregnancy: pulmonary hypertension; oxygen saturation <85% at rest; patients with transposition of the great vessels (TGA) and a systemic right ventricle with more than moderate impairment of right ventricular function and/or severe tricuspid regurgitation; Fontan patients with depressed ventricular function and/or moderate to severe AV valvular regurgitation or with cyanosis or with protein-losing enteropathy

Recommendations for the management of **aortic disease**:[4,40]

- Women with *Marfan syndrome* or other known aortic disease should be counselled about the risk of aortic dissection during pregnancy and the recurrence risk for the offspring (**Class I / Level C**)
- Imaging of the entire aorta (CT/MRI) should be performed before pregnancy in patients with Marfan syndrome or other known aortic disease (**Class I / Level C**)
- Women with Marfan syndrome and an ascending aorta >45 mm should be treated surgically before pregnancy (**Class I / Level C**)
- In pregnant women with known *aortic dilatation*, (history of) type B dissection or genetic predisposition for dissection, strict blood pressure control is recommended (**Class I / Level C**)
- Repeated echocardiographic imaging every 4–8 weeks should be performed during pregnancy in patients with ascending aorta dilatation (**Class I / Level C)**
- For imaging of pregnant women with dilatation of the distal ascending aorta, aortic arch or descending aorta, MRI (without gadolinium) is recommended (***Class I/Level C*)**
- In women with a bicuspid aortic valve, imaging of the ascending aorta is recommended (**Class I / Level C)**
- In patients with an ascending aorta <40 mm, vaginal delivery is favored (**Class I / Level C**)

● Women with aortic dilatation or (history of) aortic dissection should deliver in a center where cardiothoracic surgery is available (**Class I / Level C**)
● In patients with an ascending aorta >45 mm, caesarean delivery should be considered (**Class I / Level C)**
● Surgical treatment pre-pregnancy should be considered in women with aortic disease associated with a bicuspid aortic valve when the aortic diameter is >50mm (or >27 mm/m^2 BSA) (**Class IIa / Level C**)
● Prophylactic surgery should be considered during pregnancy if the aortic diameter is ≥50 mm and increasing rapidly (**Class IIa / Level C**)
● In Marfan, and other patients with an aorta 40–45 mm, vaginal delivery with epidural anesthesia and expedited second stage should be considered (**Class IIa / Level C**) or alternatively caesarean section may be considered (**Class IIb / Level C**)
● Patients with (or history of) type B dissection should be advised against pregnancy.

Recommendations for the management of **valvular heart disease**:[4,41,42]

Mitral stenosis (MS)

●In patients with symptoms or pulmonary hypertension: restricted activities and β1-selective blockers (**Class I / Level B)**
● Diuretics when congestive symptoms persist despite β-blockers (**Class I / Level B)**
● Patients with severe MS should undergo intervention before pregnancy (**Class I / Level C)**
● Anticoagulation in the case of atrial fibrillation (AF), left atrial thrombosis, or prior embolism (**Class I / Level C)**
● Percutaneous mitral commissurotomy should be considered in pregnant patients with severe symptoms or systolic pulmonary artery pressure >50 mmHg despite medical therapy (**Class IIa / Level C)**

Aortic stenosis (AS)

● Patients with severe AS should undergo intervention pre-pregnancy if: they are symptomatic (**Class I / Level B);** or LV dysfunction (LVEF <50%) is present (**Class I / Level C)**
● Asymptomatic patients with severe AS should undergo intervention pre-pregnancy when they develop symptoms during exercise testing (**Class I / Level C)**
● Asymptomatic patients with severe AS should be considered for intervention pre-pregnancy when a fall in blood pressure below baseline during exercise testing occurs (**Class IIa / Level C)**

Regurgitant lesions

● Patients with severe aortic or mitral regurgitation and symptoms or impaired ventricular function or ventricular dilatation should be treated surgically pre-pregnancy (**Class I / Level C)**
● Medical therapy is recommended in pregnant women with regurgitant lesions when symptoms occur (**Class I / Level C)**

Mechanical valves [4, 42]

● Oral anticoagulants (OACs) are recommended during the second and third trimesters until the 36th week (**Class I / Level C)**
● Change of anticoagulation regimen during pregnancy should be done in hospital (**Class I / Level C)**
● If delivery starts while on OACs, caesarean delivery is indicated (**Class I / Level C)**
● OAC should be discontinued and dose-adjusted unfractionated heparin (UFH) (a PTT ≥2× control) or adjusted-dose low-molecular-weight heparin (LMWH) (target anti-Xa level 4–6 hours post-dose 0.8-1.2 U/mL) started at the 36th week of gestation (**Class I / Level C)**
● In pregnant women managed with LMWH, the post-dose anti-Xa level should be assessed weekly (**Class I / Level C)**
● LMWH should be replaced by IV UFH at least 36 hours before planned delivery. UFH should be continued until 4–6 hours before planned delivery and restarted 4–6 hours after delivery if there are no bleeding complications (**Class I / Level C)**
● Immediate echocardiography is indicated in women with mechanical valves presenting with dyspnea and/or an embolic event (**Class I / Level 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 (**Class IIa / Level C)**
● Discontinuation of OAC between weeks 6 - 12 and replacement by adjusted-dose UFH (a PTT ≥2× control; in high risk patients applied as IV infusion) or LMWH bid (with dose adjustment according to weight and target anti-Xa level 4–6 h post-dose 0.8–1.2 U/mL) should be considered in patients with a warfarin dose required of >5 mg/d (or phenprocoumon >3 mg/d or acenocoumarol >2mg/d) (**Class IIa / Level C)**
● Discontinuation of OACs between weeks 6 - 12 and replacement by UFH or LMWH under strict dose control (as described above) may be considered on an individual basis in patients with warfarin dose required for therapeutic anticoagulation <5 mg/d (or phenprocoumon <3 mg/d or acenocoumarol <2 mg/d) (**Class IIb / Level C)**
● Continuation of OACs may be considered between weeks 6 - 12 in patients with a warfarin dose required for therapeutic anticoagulation >5 mg/d (or phenprocoumon >3 mg/d or acenocoumarol >2 mg/d) (**Class IIb / Level C)**

● LMWH should be avoided, unless anti-Xa levels are monitored

Recommendations for the management of **coronary artery disease**

● ECG and troponin levels should be performed in the case of chest pain in a pregnant woman (**Class I / Level C)**
● Coronary angioplasty is the preferred reperfusion therapy for ST-elevation MI (STEMI) during pregnancy (**Class I / Level C)**
● A conservative management should be considered for non ST-elevation acute coronary syndrome (ACS) without risk criteria (**Class IIa / Level C)**
● An invasive management should be considered for non ST-elevation ACS with risk criteria (including non-STEMI) (**Class IIa / Level C)**

Recommendations for the management of **cardiomyopathies (CM) and heart failure**

● Anticoagulation is recommended in patients with intracardiac thrombus detected by imaging or with evidence of systemic embolism (**Class I / Level A)**
● Women with heart failure during pregnancy should be treated according to current guidelines for non-pregnant patients, respecting contraindications for some drugs in pregnancy (**Class I / Level B)**
● Women with dilated CM (DCM) should be informed about the risk of deterioration of the condition during gestation and peripartum (**Class I / Level C)**
● In patients with a past history or family history of sudden death close surveillance with prompt investigation is recommended if symptoms of palpitations or presyncope are reported (**Class I / Level C)**
● Therapeutic anticoagulation with LMWH or vitamin K antagonists according to stage of pregnancy is recommended for patients with atrial fibrillation (AF) (**Class I / Level C)**
● Delivery should be performed with β-blocker protection in women with hypertrophic CM (HCM) (**Class IIa / Level C)**
● β-blockers should be considered in all patients with HCM and more than mild LV outflow tract obstruction or maximal wall thickness >15mm to prevent sudden pulmonary congestion (**Class IIa / Level C)**
● In HCM, cardioversion should be considered for persistent AF (**Class IIa / Level C)**
● Due to high metabolic demands of lactation and breastfeeding, preventing lactation may be considered in peri-partum CM (**Class IIb / Level C)**
● Subsequent pregnancy is not recommended if LVEF does not normalize in women with peripartum CM

Medications for Pregnant Women with Heart Failure[39]

β-blockers: can be used during pregnancy; require close fetal monitoring for growth retardation; beta-1 selective antagonists preferred to avoid potential increased uterine tone and decreased uterine perfusion
Digoxin: may be used if volume overload symptoms persist despite vasodilator and diuretic therapy
Diuretics: may be used, but with caution regarding excessive volume contraction leading to reduced placental perfusion
Hydralazine: may be used for management of heart failure symptoms or elevated blood pressure
Nitrates: may be used to treat decompensated heart failure in pregnancy

Recommendations for the management of **arrhythmias**

Management of supraventricular tachycardia (SVT)

● For acute conversion of paroxysmal SVT, vagal maneuver followed by IV ***adenosine*** is recommended (**Class I / Level C)**
● Immediate electrical cardioversion is recommended for acute treatment of any tachycardia with hemodynamic instability (**Class I / Level C)**
● For long-term management of SVT oral ***digoxin*** or ***metoprolol***/***propranolol*** is recommended (**Class I/Level C)**
● For acute conversion of paroxysmal SVT, IV metoprolol or propranolol should be considered (**Class IIa / Level C)**
● For long-term management of SVT, oral sotalol or flecainide should be considered if digoxin or a β-blocking agent fails (**Class IIa / Level C)**
● For acute conversion of paroxysmal SVT, IV verapamil may be considered (**Class IIb / Level C)**
● For long-term management of SVT, oral propafenone, or procainamide may be considered as a last option if other suggested agents fail and before amiodarone is used (**Class IIb / Level C)**
● For long-term management of SVT, oral verapamil may be considered for rate regulation if the other AV nodal-blocking agents fail (**Class IIb / Level C)**
● Atenolol should not be used for any arrhythmia

Management of ventricular tachycardia (VT)

● The implantation of an ICD, if clinically indicated, is recommended prior to pregnancy but is also recommended whenever indicated, during pregnancy (**Class I / Level C)**
● For long-term management of the congenital long QT syndrome, ***β-blocking agents*** are recommended during pregnancy and also postpartum when they have a major benefit (**Class I / Level C)**

● For long-term management of idiopathic sustained VT, oral metoprolol, propranolol or verapamil is recommended (**Class I / Level C)**

● Immediate electrical cardioversion of VT is recommended for sustained, unstable, and stable VT (**Class I / Level C)**

● For acute conversion of VT that is sustained, hemodynamically stable, and monomorphic, IV sotalol or procainamide should be considered (**Class IIa / Level C)**

● Implantation of permanent pacemakers or ICDs (preferably single chamber) should be considered with echocardiographical guidance, especially if the fetus is beyond 8 weeks gestation (**Class IIa / Level C)**

● For acute conversion of VT that is sustained, monomorphic, hemodynamically unstable, refractory to electrical cardioversion or not responding to other drugs, IV amiodarone should be considered (**Class IIa / Level C)**

● For long-term management of idiopathic sustained VT, oral sotalol, flecainide, propafenone should be considered if other drugs fail (**Class IIa / Level C)**

● Catheter ablation may be considered in the case of drug-refractory and poorly tolerated tachycardias (**Class IIb / Level C)**

Recommendations for the management of **Hypertension**

● Non-pharmacological management for pregnant women with systolic blood pressure (SBP) of 140-150 mmHg or diastolic blood pressure (DBP) of 90-99 mmHg is recommended (**Class I / Level C)**

● In women with gestational hypertension or pre-existing hypertension superimposed by gestational hypertension or with hypertension and subclinical organ damage or symptoms at any time during pregnancy, initiation of drug treatment is recommended at a blood pressure (BP) of 140/90 mmHg. In any other circumstances, initiation of drug treatment is recommended if SBP ≥150 mmHg or DBP ≥95 mmHg (**Class I / Level C)**

● SBP ≥170 mmHg or DBP ≥110 mmHg in a pregnant woman is an emergency, and hospitalization is recommended (**Class I / Level C)**

● Induction of delivery is recommended in gestational hypertension with proteinuria with adverse conditions such as visual disturbances, coagulation abnormalities, or fetal distress (**Class I / Level C)**

● In pre-eclampsia associated with pulmonary edema, nitroglycerin given as an IV infusion, is recommended (**Class I / Level C)**

● In severe hypertension, drug treatment with IV labetalol or oral methyldopa or nifedipine is recommended (**Class I / Level C)**

● Women with pre-existing hypertension should be considered to continue their current medication except for ACE inhibitors, angiotensin receptor blockers (ARBs), and direct renin inhibitors under close BP-monitoring (**Class IIa / Level C)**

Recent **hypertension** guidelines are in accordance with the above recommendations regarding hypertension management of pregnant women.[43] It is indicated that the antihypertensive drugs to be used in pregnant hypertensive women may include *methyldopa, labetalol* and *nifedipine* as the only calcium antagonist really tested in pregnancy. Beta-blockers (implicated for fetal growth retardation if given in early pregnancy) and diuretics (in pre-existing reduction of plasma volume) should be used with caution. All agents involved in the renin-angiotensin system (ACE inhibitors, ARBs, renin inhibitors) should be avoided. In emergency situations, such as during pre-eclampsia, IV labetalol is the drug of choice; IV sodium nitroprusside or nitroglycerin may be another option.[42]

Recommendations for the prevention and management of **venous thrombo-embolism** (VTE) in pregnancy and puerperium

● In all women who are pregnant or consider pregnancy, assessment of risk factors for VTE is recommended (**Class I / Level C)**

● Mothers should be informed about the signs and symptoms of VTE in pregnancy and the necessity to contact the physicians if they occur (**Class I / Level C)**

● High risk patients should receive antenatal prophylaxis with LMWH as well as post-partum for the duration of 6 weeks (**Class I / Level C)**

● In intermediate risk patients post-partum prophylaxis with LMWH should be given for at least 7 days or longer, if >3 risk factors persist (**Class I / Level C)**

● In low risk patients early mobilization and avoidance of dehydration is recommended (**Class I / Level C)**

● Graduated compression stockings are recommended antepartum and post-partum in all women at high risk (**Class I / Level C)**

● D-Dimer measurement and compression ultrasonography is recommended in patients with suspected VTE during pregnancy (**Class I / Level C)**

● For treatment of acute VTE during pregnancy, UFH is recommended in high-risk and LMWH in non-high risk patients (**Class I / Level C)**

● Graduated compression stockings should be considered in women with intermediate risk during pregnancy and post-partum (**Class IIa / Level C)**

●In intermediate risk patients, antenatal prophylaxis with LMWH should be considered (**Class IIa / Level C)**

● Routine screening for thrombophilia should not be performed

CONCLUSION

Cardiovascular disease (CVD) is the leading cause of maternal death and keeps rising. Pre-pregnancy diagnosis is most important. Women with pre-existing CVD should receive pre-pregnancy counselling to reduce morbidity and mortality; effective and safe contraceptive measures remain of paramount importance in patients with known CVD to avoid unplanned pregnancies. As ischemic heart disease increases in pregnancy, greater attention needs to be paid to risk factors in this group. Clinicians should have a low threshold for investigating any women complaining of chest pain and in particular if requiring significant analgesia. Recent advances have led to improved survival and function in patients with congenital heart disease (CHD) and to an increase in the number of women reaching child-bearing age. As experience in managing these patients during pregnancy has grown, the majority of patients with CHD can expect to get through pregnancy and delivery with acceptably low risk for complications. High-risk pregnancies should be managed in specializing centers by an experienced multidisciplinary team. Risk assessment tools are useful in determining the risk of women with CVD in pregnancy. Cardiac societies' specific guidelines need to be adhered to.

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